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Electrophilic Cyclisations of 3-Arylpenta-1,4-diyn-3-ols for the Synthesis of Heterocycles

A Thesis Submitted to the University of Huddersfield in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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The University of Huddersfield

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Abstract

This project was concerned with investigating the electrophilic cyclisation reactions of 3-phenylpenta-1,4-diyn-3-ols possessing either an *ortho*-*N*-linked- or an *ortho*-*S*-linked- sulfonamide function. Cyclisations of both series of sulfonamides meditated by alkynophilic initiators [e.g. I_2, ICl, AgOAc or $In(OTf)_3$] provided access to novel functionalised heterocycles.
Thus, addition of methyl 2-(arenesulfonamido)benzoates to alkynyllithium reagents furnished 3-[(2-arenesulfonamido)phenyl]penta-1,4-diyn-3-ols in which the alkyne termini possess identical substituents. Dialkynols having unsymmetrical alkyne terminal groups have been obtained from the addition of an alkynyllithium reagent or HC≡CMgBr to 3-aryl-1-(2-tosylamidophenyl)prop-2-yn-1-ones. The *ortho*-*S*-linked sulfonamides have been accessed directly from *N*-substituted saccharins that readily add alkynyllithiums to provide 3-(2-sulfamoylphenyl)penta-1,4-diyn-3-ols in good yields.

Desilylation (5M NaOH in MeOH) of 1,5-bis(trimethylsilyl)-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol also triggered cyclisation *via* a 5-*exo*-*dig* pathway and gave a quantitative yield of 3-ethynyl-2-methylene-1-tosylindolin-3-ol. However, when both silyl functions were replaced with either a propyl- or a phenyl- group, cyclisation to the 1-tosylindolin-3-ol did not occur with base. A quantitative yield of 3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl(1-phenyl)methanol was obtained from treatment of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol with AgOAc in MeCN. The analogous reaction with 6-(2-tosylamidophenyl)undeca-4,7-diyn-6-ol, provided 1-[3-(pent-1-yn-1-yl]-1-tosyl-1*H*-indol-2-yl)butan-1-ol, together with smaller amounts of (*E*)-2-but-1-en-1-yl-3-pentyn-1-yl-1-tosyl-1*H*-indole and 4-pentyn-1-yl-2-propylquinoline. It was found that when 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols possessed bulky groups on the alkyne units, the reaction followed an alternative course giving access to the (*Z*)-2-benzylidene-, (*Z*)-2-(2,2-dimethylpropylidene)- and (*Z*)-2-(trimethylsilylmethylene)- derivatives of 3-alkynyl-1-tosylindolin-3-ols. Mechanisms to account for these outcomes have been proposed. Contrasting behavior was observed from the $In(OTf)_3$-mediated cyclisation of 1,5-diphenyl-3-(2-tosylaminophenyl)penta-1,4-diyn-3-ol, which promoted an unexpected and remarkable cascade pathway leading to 2,4-diphenyl-1-tosyl-4,5-dihydrofuro[2,3-*c*]quinoline, albeit in moderate yield.

Attempted iodocyclisation (ICl in MeCN) of 1,5-diphenyl-3-[2-(*N*-methylsulfamoyl)phenyl]penta-1,4-diyn-3-ol resulted only in cyclodehydration to give the novel 3,3-bis(phenylethynyl)-2-methyl-1,2-benzisothiazole 1,1-dioxide. However, application of these conditions to 1,5-diphenyl-3-[2-(*N*-*p*-tolylsulfamoyl)phenyl]penta-1,4-diyn-3-ol provided a novel derivative of the unusual 1,2-benzisothiazolo[2,3-*a*]quinoline system that was characterised by X-ray crystallography; the

corresponding 2-aryl-3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxide was also formed. The latter also underwent iodocyclisation to give the 1,2-benzisothiazolo[2,3-*a*]quinolines. It was established that the 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides could be generated most efficiently by treatment of the 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols with $In(OTf)_3$ in DCM.

Iodocyclisation (ICl in MeCN) of 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols having symmetrical alkyne substituents afforded novel 4-alkynyl-3-iodoquinolines. However, the unsymmetrically-substituted pentadiynols cyclised less efficiently to give, in some cases, mixtures of regioisomeric 3-iodoquinolines. The cyclisation of 1-(4-methoxyphenyl)-5-phenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol regiospecifically generated 3-iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline, as anticipated.

Silver-catalysed cyclisation (AgOAc in MeCN) of 3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols proceeds stereoselectively to (*Z*)-3-alkylidene-4-alkynyl-2-aryl- and (*Z*)-4-alkynyl-2-aryl-3-arylidene-1,2-benzothiazin-4-ol 1,1-dioxides *via* a 6-*endo-dig* pathway in good to excellent yields, constituting a new approach to this ring system. Two of the pentadiynols also furnished 1,2-benzothiazepine 1,1-dioxides derived *via* a 7-*endo-dig* ring closure. Mechanisms for the formation of these novel compounds are proposed.

With a range of heterocycles to hand some were subjected to functionalisation or annulation reactions. Of note is the Pd-mediated domino-amination-hydroamination of 4-alkynyl-3-iodoquinolines with a range of primary amines. This approach was exploited to access novel 2,3,4-trisubstituted pyrrolo[2,3-*c*]quinolines, analogues of the biologically active Marinoquinolines. However, in some instances the hydroamination step was suppressed and the major or exclusive product was a 4-alkynyl-3-amino-2-arylquinoline.

Suzuki-Miyaura couplings to 4-alkynyl-2-iodo-3-arylquinolines and efforts to effect iodocyclisations of the products are also described.

Guide to the Referencing System

The referencing system employed in this thesis is that devised by Katritzky and utilised in *Advances in Heterocyclic Chemistry*, and the annual reviews *Progress in Heterocyclic Chemistry* and also for the major reference works *Comprehensive Heterocyclic Chemistry* Pergamon Press, Oxford 1984 and *Comprehensive Heterocyclic Chemistry* II and III, Elsevier, Oxford 1996 and 2008 respectively.

This system is used in place of numerical references and allows the reader to extract the reference directly from the text. The references are given in the format [NNLLNN] where the initial numbers denote the year in which the citation was published, the letters indicate the journal, book or patent from which the citation has originated, and the final numbers refer to the page number. For journals which publish more than one volume per year, the volume number is given in parentheses after the journal code. Less common journals, new journals and books are assigned the code MI.

Contents

List of Figures

List of Tables

Abbreviations

Abbreviation	Meaning
δ	Chemical Shift (ppm)
Δ	Heat
app.	Apparent
Aq.	Aqueous
Ar	Aryl
b	Broad
Bn	benzyl
Boc	*tert*-Butoxycarbonyl
b.p.	Boiling Point
cm^{-1}	Wavenumbers
COSY	Correlated Spectroscopy
CSA	Camphorsulfonic acid
d	Doublet
DBAD	Bis(1,1-dimethylethyl)azodicarboxylate
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of Doublets
DIPA	Diisopropylamine
DMEDA	*N,N'*-Dimethylethylenediamine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dt	Doublet of Triplets
equiv.	Equivalents
ESI	Electrospray Ionisation
FT-IR	Fourier Transform Infrared
FVP	Flash Vacuum Pyrolysis
HMBC	Heteroatom Multiple Bond Coherence Spectroscopy
HMPA	Hexamethylphosphoramide

HRMS	High Resolution Mass Spectrometry
HSQC	Heteroatom Single Quantum Coherence Spectroscopy
J	Coupling Constant (Hz)
m	Multiplet
m.p.	Melting Point
MOM	Methoxymethyl acetal
NMP	*N*-Methylpyrrolidin-2-one
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
q	Quartet
r.t.	Room Temperature
s	Singlet
sep	Septet
sxt	Sextet
t	Triplet
TFA	Trifluoroacetic acid
TfOH	Triflic acid
TLC	Thin Layer Chromatography
tolyl	4-MeC_6H_4
tosyl	4-Toluenesulfonyl
Ts	4-Toluenesulfonyl

Chapter 1

Introduction

Chapter 1 Introduction

1.1 Natural Occurrence, Applications and Synthesis of Quinolines

Bark from the Cinchona tree (*Cinchona officinalis*) has been known to exhibit anti-malarial activity since around 1600. Pure cinchonine and quinine were first isolated from the bark of *Cinchona officinalis* in 1820 by Pelletier and Caventou. Quinoline was first isolated by Runge (1834) from coal tar, later Gerhardt (1842) isolated quinoline from cinchonine [67MI1].

Within the natural world quinolines are a very important class of heterocycle. The quinoline skeleton is ubiquitous in natural products especially, alkaloids [10MI1], as well as pharmaceuticals [10COB347], electrically conducting materials, dyes and agrochemicals. Some examples of important quinoline-containing compounds are shown in Figure 1.1.

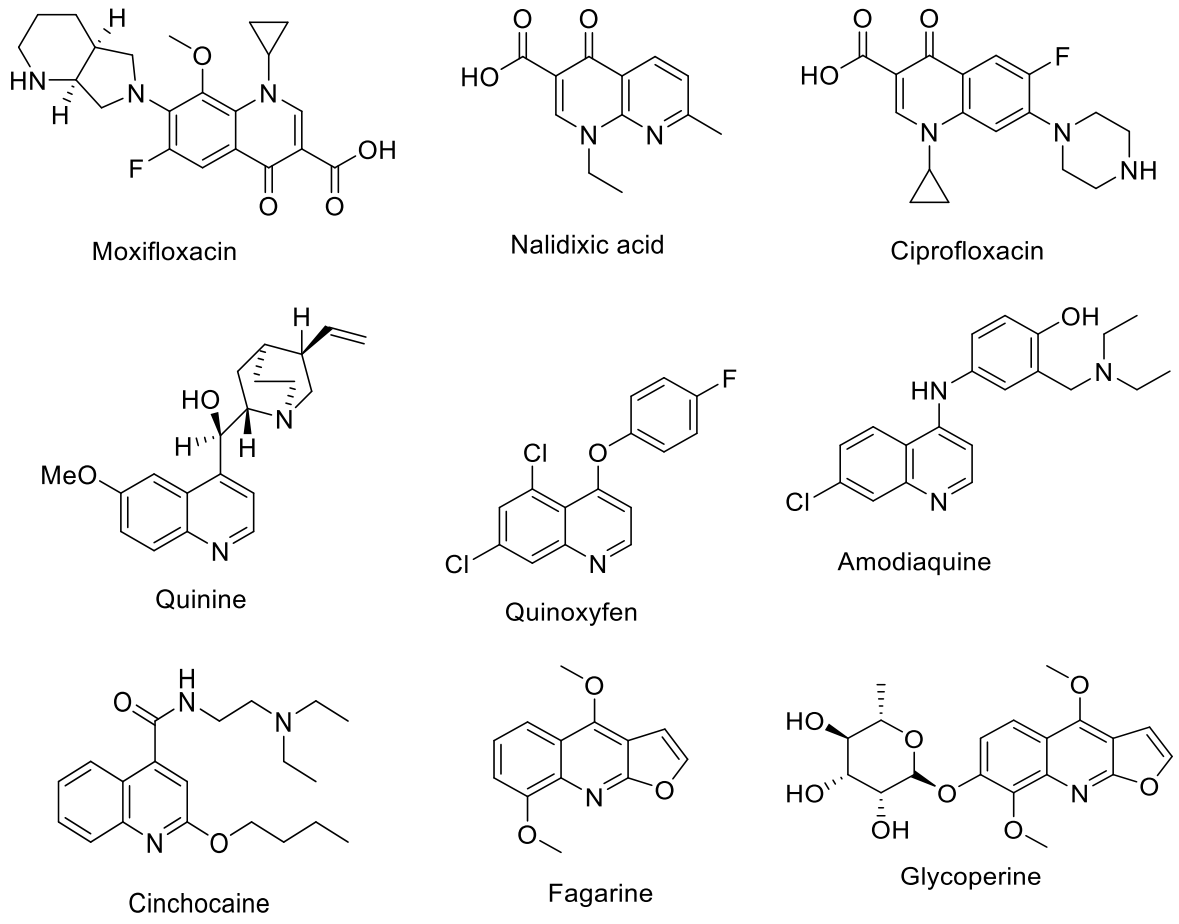
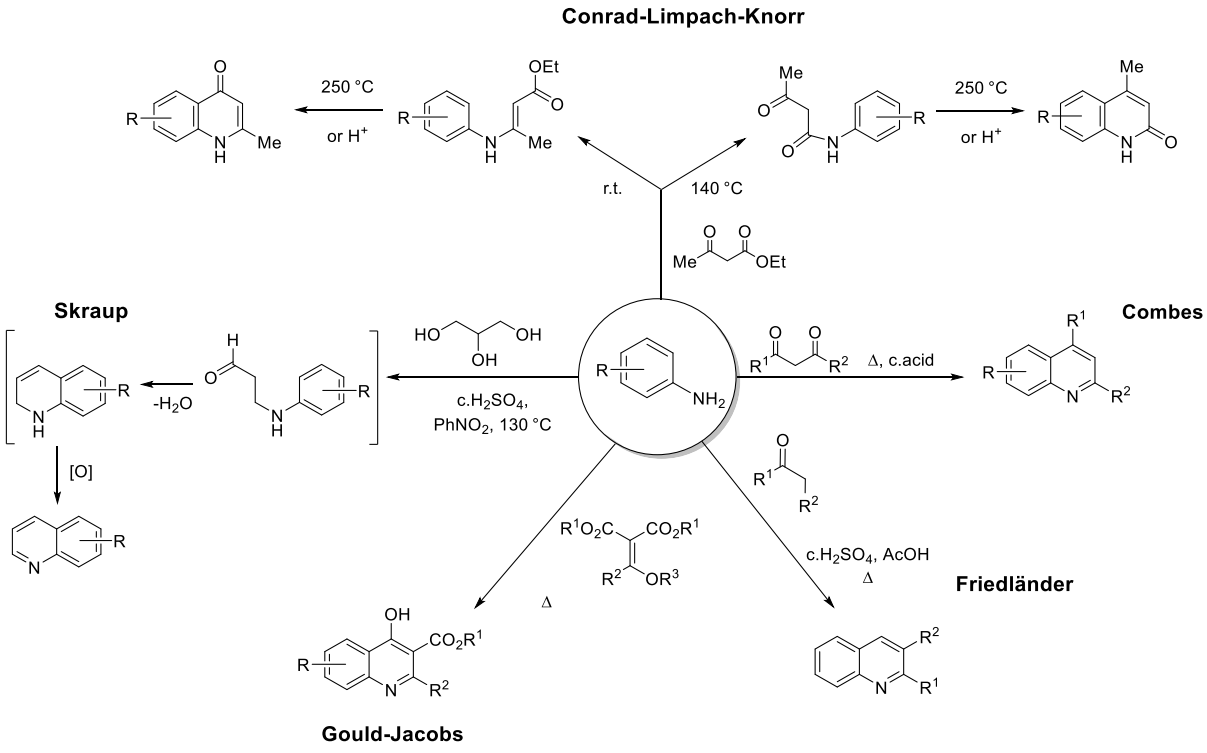


Figure 1.1 Quinoline derivative examples

Consequently, much attention has been paid to the synthesis of quinoline derivatives. There are a plethora of ways by which the quinoline ring can be constructed. Some classical

examples being; Conrad-Limpach-Knorr, Combes, Friedländer, Gould-Jacobs and Skraup syntheses (Scheme 1.1). All of the important routes rely upon construction of the heterocyclic ring onto a benzene (aniline) derivative [03MI1, 10MI2]. With extensive reviews relating to quinoline synthesis, structure and reactivity available in all the editions of *Comprehensive Heterocyclic Chemistry* [synthesis: 84CHEC-I(2)395, 96CHEC-II(5)167, 08CHEC-III(7)217; structure: 84CHEC-I(2)99, 96CHEC-II(5)1, 08CHEC-III(7)1; reactivity: 84CHEC-I(2)165, 84CHEC-I(2)315, 96CHEC-II(5)37, 96CHEC-II(5)91, 08CHEC-III(7)41, 08CHEC-III(7)101]. Reviews in the literature are also summarised yearly (1991 – present) in *Progress in Heterocyclic Chemistry*.



Scheme 1.1

1.2 Natural Occurrence, Applications and Synthesis of Indoles

Indole and its derivatives are prevalent throughout both the plant and animal kingdom and indoles is therefore classed as a privileged structure [10COB347], some examples include; dyes like indigo, amino acids (tryptophan), hormones (indole-3-acetic acid), and skatole (3-methylindole) which is found in citrus oils and widely used within fragrances. Possibly the most useful application of the Fischer indole synthesis is its use in the synthesis of the neurotransmitter serotonin, and its derivatives which act as agonists of serotonin.

Derivatives of serotonin have been used as pharmaceuticals, for example Sumatriptan is used to treat migraines. A few more examples of important indoles are shown in Figure 1.2 below. Extensive reviews relating to indole synthesis, structure and reactivity have been summarised in *Comprehensive Heterocyclic Chemistry* [synthesis: 84CHEC-I(4)313, 96CHEC-II(2)119, 08CHEC-III(3)269; structure: 84CHEC-I(4)155, 96CHEC-II(2)1, 08CHEC-III(3)1; reactivity: 84CHEC-I(4)39, 84CHEC-I(4)201, 96CHEC-II(2)39, 08CHEC-III(3)45]. Developments in the literature are also summarised yearly (1991 – present) in *Progress in Heterocyclic Chemistry*.

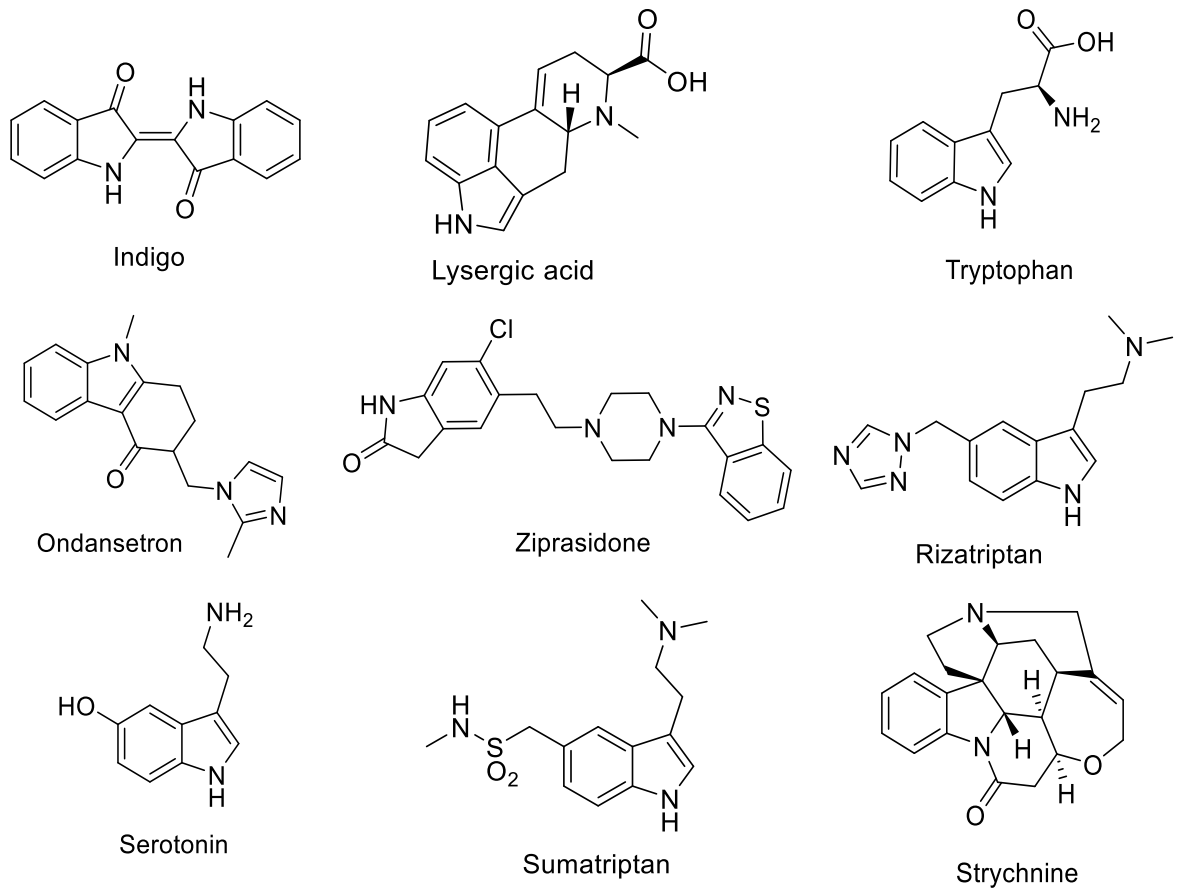
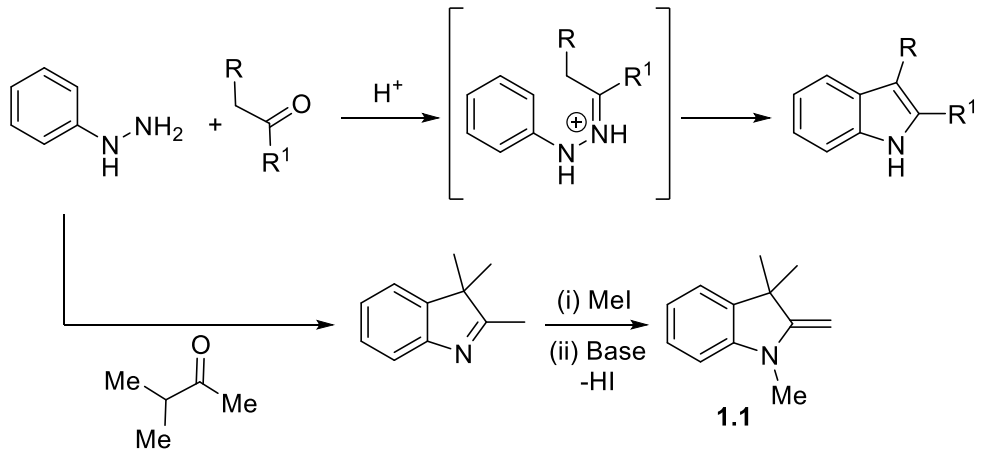


Figure 1.2 Indole derivative examples

The Fischer indole synthesis has been the most important method for the preparation of substituted indoles since its discovery in 1883. Fischer and Jourdan treated pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride, which resulted in the formation of 1-methylindole-2-carboxylic acid [1883MI2241]. The general reaction conditions for the

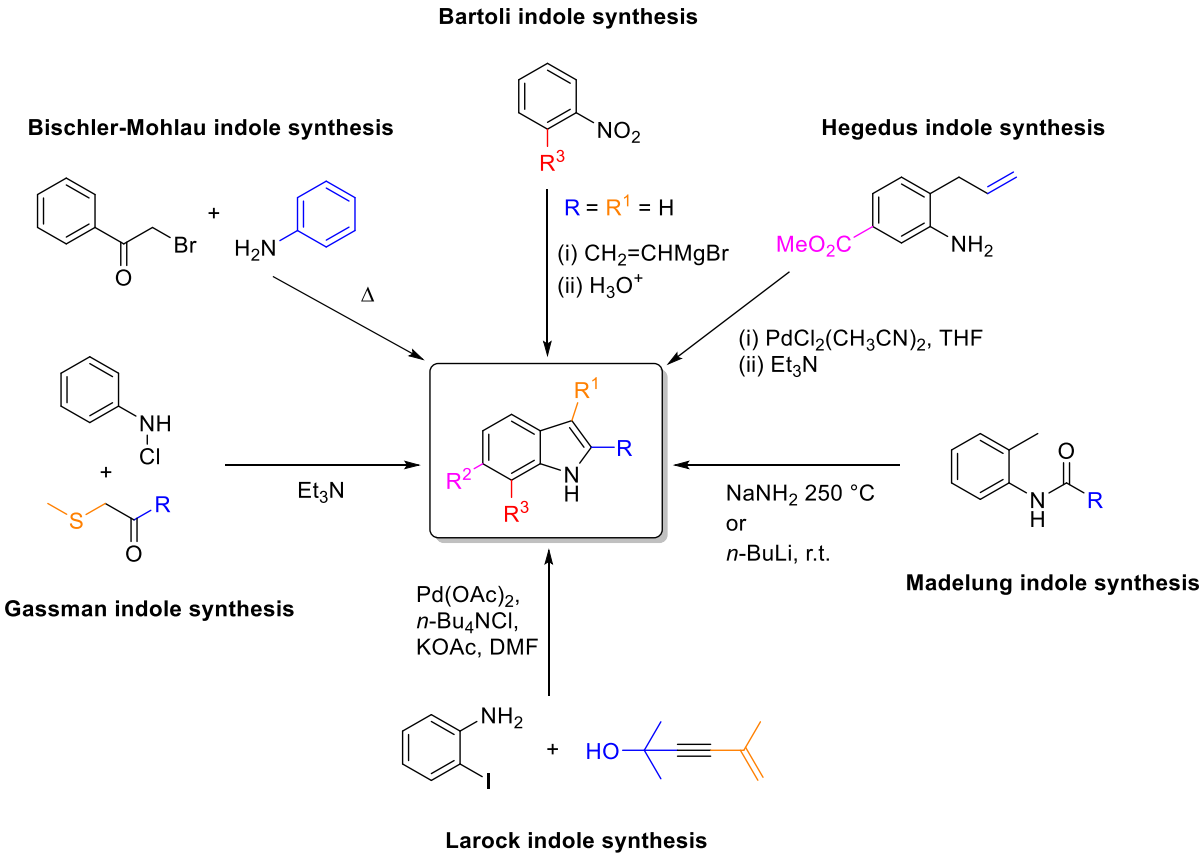
Fischer indole synthesis involve the heating of arylhydrazines with an α-methylene ketone or an aliphatic aldehyde in the presence of an acid (Scheme 1.2) [06CRV2875].

Another widely used application of the Fischer indole synthesis is in the synthesis of the so-called Fischer base (1,3,3-trimethyl-2-methyleneindoline) (**1.1**, Scheme 1.2), which has been utilised extensively in industry for the synthesis of cyanine dyes and photochromic compounds [16JST426, 17DP481, 17JMC5111]. Fischer base is obtained *via* the reaction of $PhNHNH_2$ with 3-methylbutan-2-one followed by alkylation of the resulting 2,3,3-trimethyl-3*H*-indole. Alternatively indolisation of 3-methylbutan-2-one with $PhN(Me)NH_2$ affords the product directly.



Scheme 1.2

There are a plethora of indole syntheses that allow access to variously substituted derivatives, a selection of examples are provided by the Bartoli indole synthesis, the Bischler-Möhlau indole synthesis, Hegedus, Larock, Gassman and the Madelung synthesis (Scheme 1.3) [03MI1, 16MI39].



Scheme 1.3

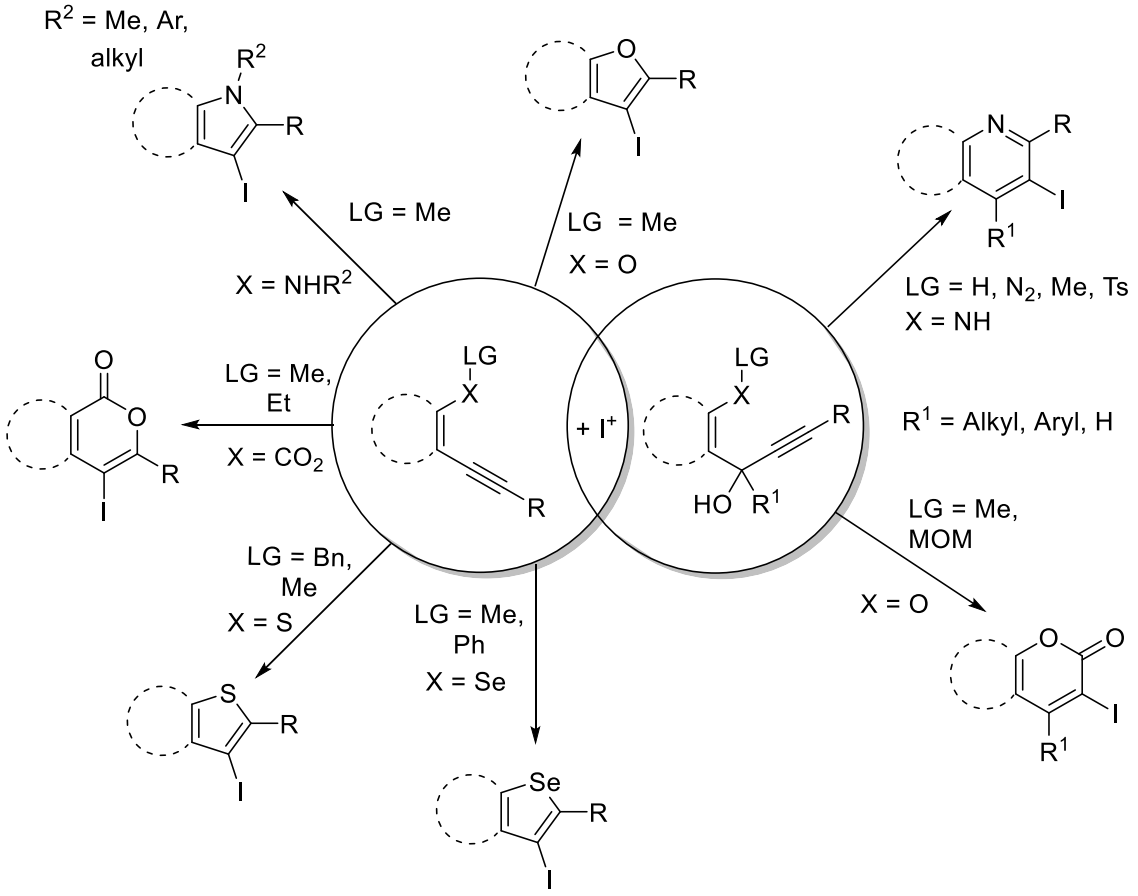
1.3 Heterocycles *via* Electrophilic Cyclisations

Both alkenes and alkynes possessing a pendant nucleophilic function can, providing the necessary stereochemical requirements are fulfilled, cyclise upon treatment with an electrophilic initiator. This process has been developed as a means to access a wide range of heterocycles and application to functionalised alkynes has been extensively exploited. The most useful electrophilic initiators are selected from halogen or positive halogen sources. Of these elemental iodine or iodine-containing reagents have been widely employed i.e. I_2, NIS, ICl or, less commonly, bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4, Barluenga's reagent). The uses of these reagents in electrophilic cyclisations leading to novel heterocyclic compounds has been reviewed [11CRV2937, 15S1961, 16OBC7639]. Some examples of these iodocyclisation reactions are shown in Scheme 1.4. Electrophilic iodocyclisation reactions have been used for the construction of highly functionalized pyrroles, indoles, furans, thiophenes, selenophenes, pyridines, quinolines, benzo[*b*] furans and the review literature details many examples [11CRV2937, 15S1961, 16CC853,

16OBC7639]. Additional examples relating to the construction of indoles [17OL6744], quinolines [17JOC4625] and quinoline annulation to generate thieno[2,3-*b*]quinolines [18OBC245] are noteworthy.

All the reactions depicted in Scheme 1.4 proceed *via* initial iodination of the triple bond to generate a bridged iodonium ion. Subsequent attack by an adjacent nucleophile facilitates cyclisation, most commonly *via* a 5-*exo*-*dig* or 6-*endo*-*dig* pathway. These mechanisms are considered in more detail in the following chapters.

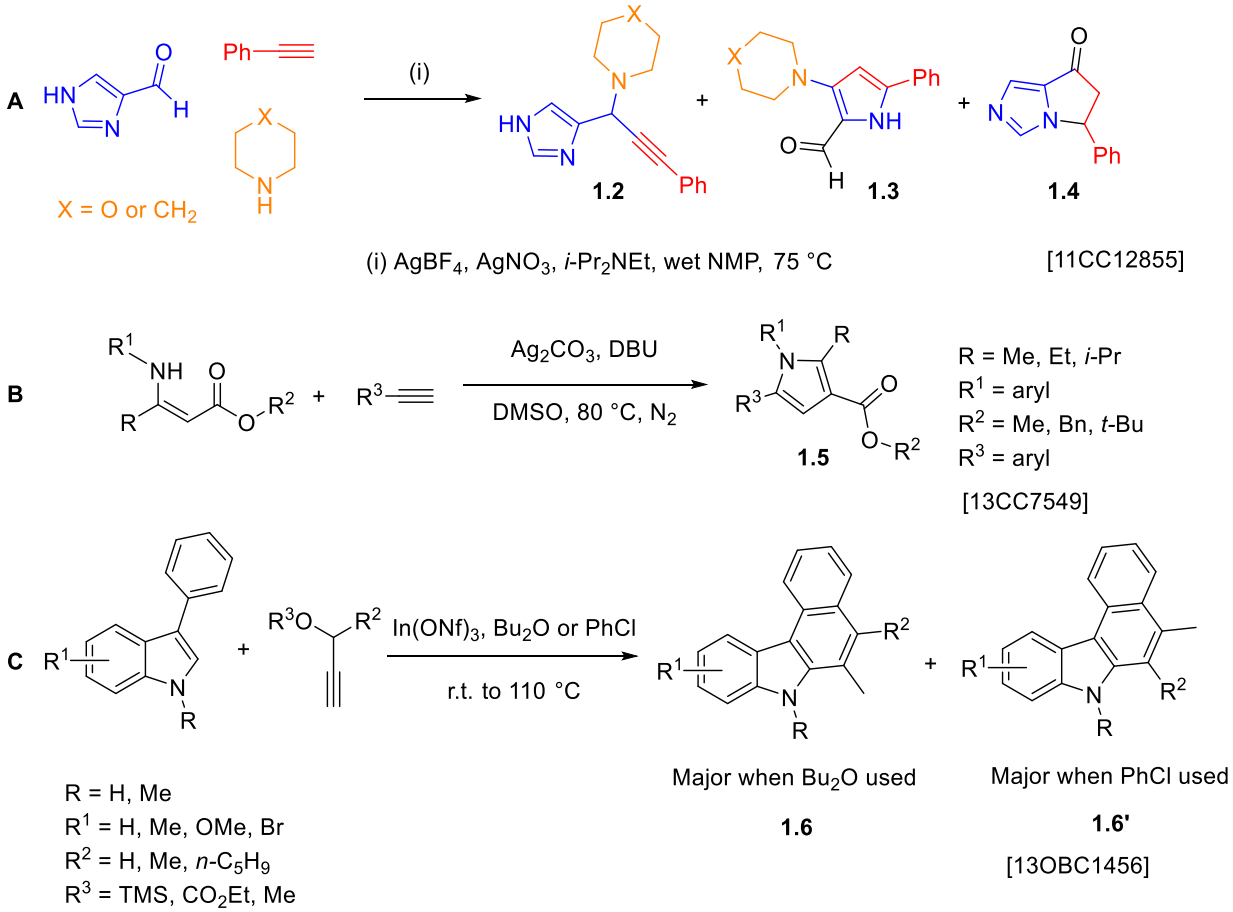
These electrophilic cyclisations often proceed with incorporation of an iodo-substituent into the ring. Thus, heterocycles with an iodine substituent allows for further structural modifications and access to structurally complex compounds. In addition, the halogen atom can sometimes enhance the bioactivity [10T1177].



Scheme 1.4

Metal-containing Lewis acid catalysts are developing as powerful reagents to effect the cyclisation of alkynes, as many can be used in tandem reactions to both couple a terminal

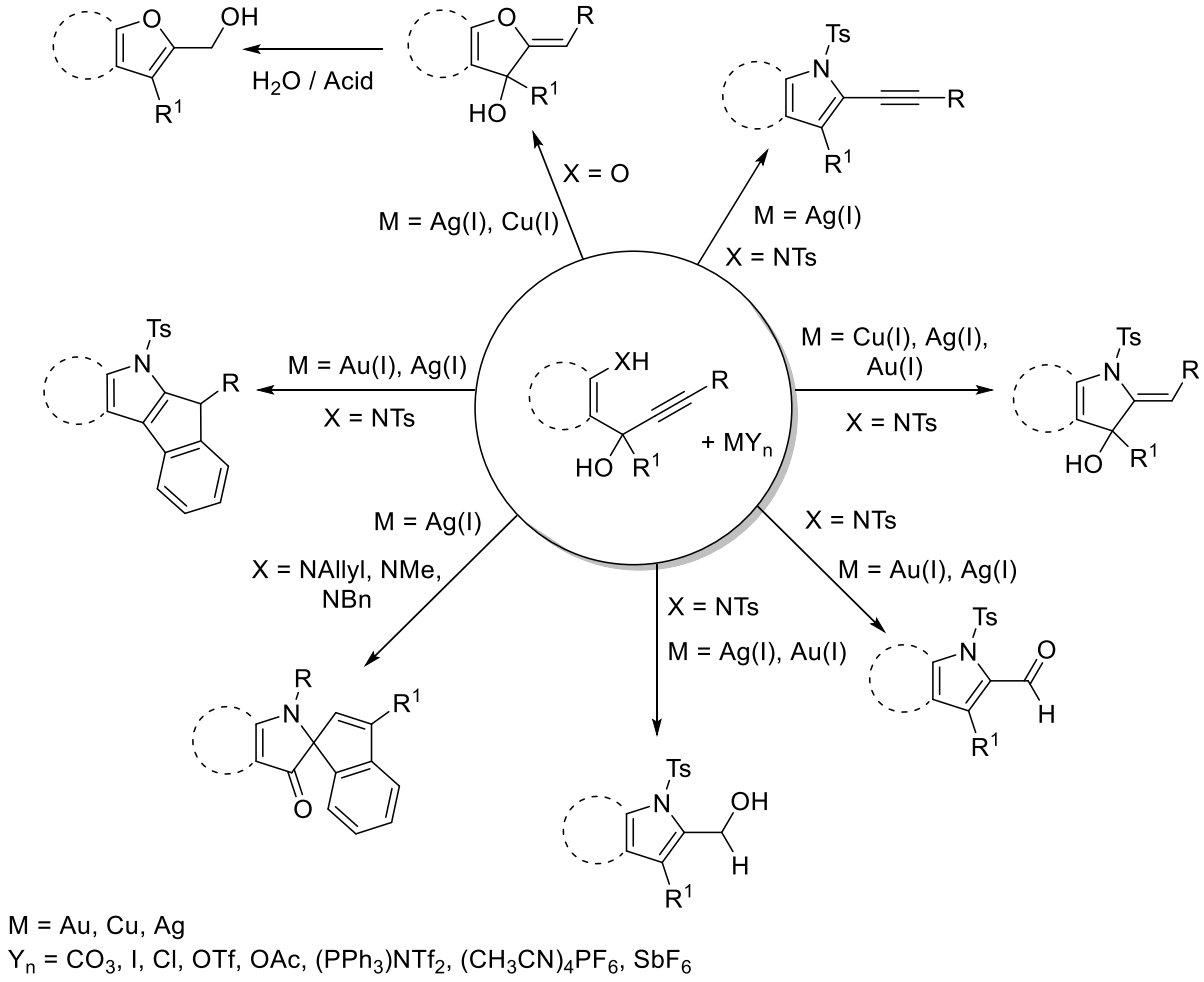
alkyne to the starting material *in situ* and then to induce cyclisation (in most cases a domino oxidative cross-coupling electrophilic cyclisation) Scheme 1.5 [08CRV3174, 11CC12855, 11CRV1780, 13CC7549, 13OBC1456]. For example, silver(I) was employed to catalyse the A3 reaction of 4-imidazolecarboxaldehyde, phenylacetylene and a secondary amine to obtain alkyne **1.2,** the pyrrole **1.3** and ketone **1.4** (**A**, Scheme 1.5) [11CC12855]. Another silver-mediated oxidative cross-coupling and cyclisation reaction made use of a β-enamino ester and arylacetylenes affording substituted pyrroles **1.5** (**B**, Scheme 1.5) in varying yields (37 – 84%) [13CC7549]. Tsuchimoto and co-workers employed In(III) to activate phenylindole derivatives to addition of propargyl ethers, subsequent *in situ* cyclisation afforded 6-methyl-7*H*-benzo[*c*]carbazoles **1.6** and **1.6'** (**C**, Scheme 1.5) [13OBC1456].



Scheme 1.5

A range of alkynol substrates and solvents are tolerated (Scheme 1.6) for the metal-catalysed cyclisation, reviews of catalytic activation have been published [16CC853, 18MI31129]. Metal containing Lewis acid catalysts most relevant to the present project, which have also been reviewed are; Ag(I) [15CSR8124], In(III) [03S633, 07S1, 04T1959] Au(I)

and Au(III) [07CC333]. The mechanisms of the reactions shown in Scheme 1.6 will be discussed in subsequent chapters in the context of results from the present study.

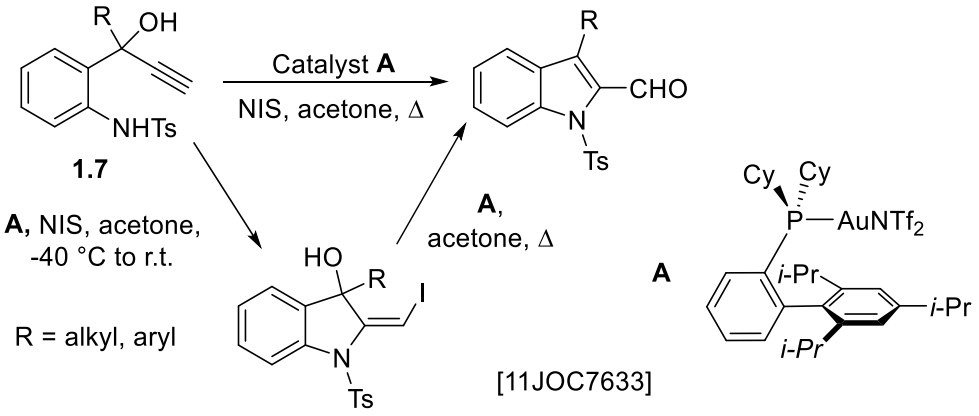


Scheme 1.6

1.4 Electrophilic Cyclisations for the Synthesis of Indoles and Fused-Ring Derivatives

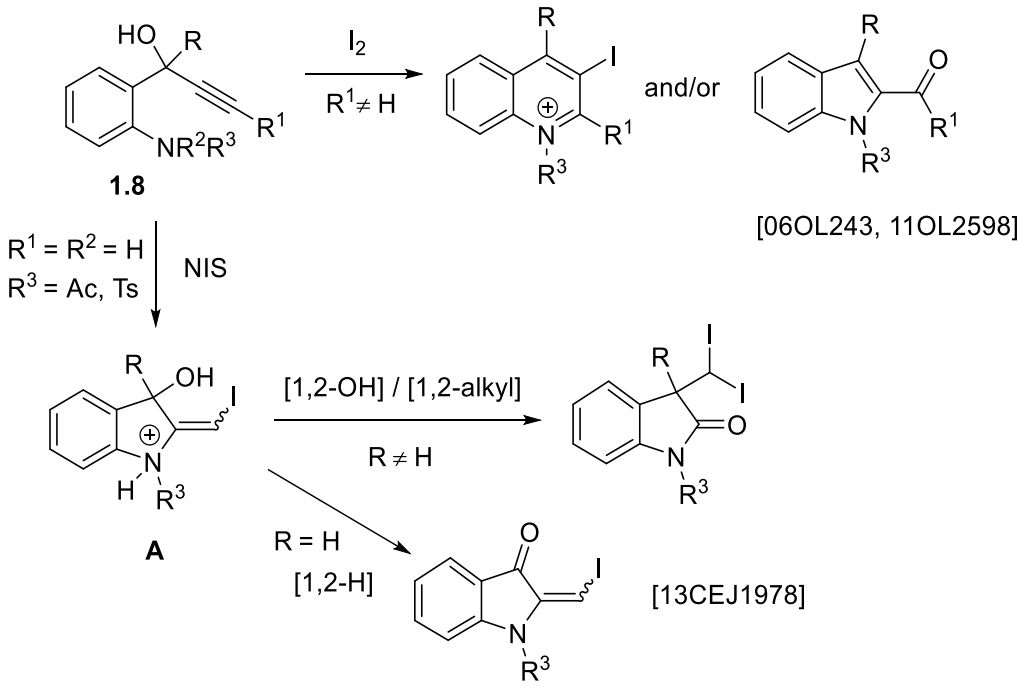
1.4.1 From 1-(2-Aminophenyl)- or 1-[2-(Alk)oxyphenyl]-prop-2-yn-1-ol Derivatives

Chan and co-workers used a gold(I) catalyst to cyclise the propargylic alcohol **1.7** and effect iodination with NIS in acetone to produce 1*H*-indole-2-carbaldehydes. It was found that by keeping the mixture at a low temperature (-40 °C) the reaction could be halted at the iododeauration step (Scheme 1.7) [11JOC7633].



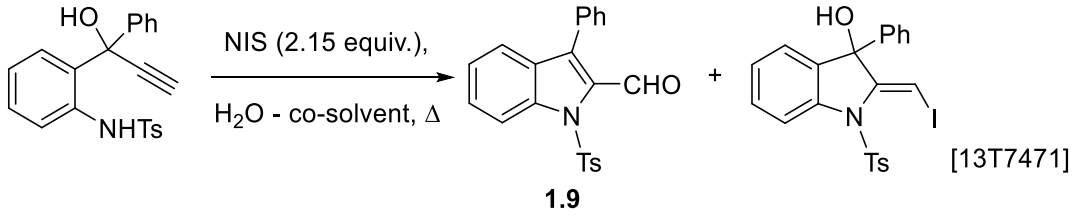
Scheme 1.7

Subsequent work showed that when $R^1 \neq H$ in 1-(2-anilinyl)prop-2-yn-1-ols **1.8,** treatment with molecular iodine affords a mixture of 3-iodoquinolinium salts and 2-acyl-1*H*-indoles (Scheme 1.8) [06OL243, 11OL2598]. When the alkynols (**1.8**) were treated with NIS the course of the reaction is controlled by the nature of the R group, and two routes can operate. When NIS was used to trigger the cyclisation of the nitrogen nucleophile to the alkyne, intermediate **A** was formed. Thus, if R ≠ H then **A** was susceptible to an hydroxyl group shift followed by alkyl migration and oxidation to afford 3-(diiodomethyl)indolin-2-ones. However in **A** R = H a 1,2-hydride shift and oxidation of the secondary carbinol centre resulted in formation of 2-(iodomethylene)indolin-3-one (Scheme 1.8) [13CEJ1978].



Scheme 1.8

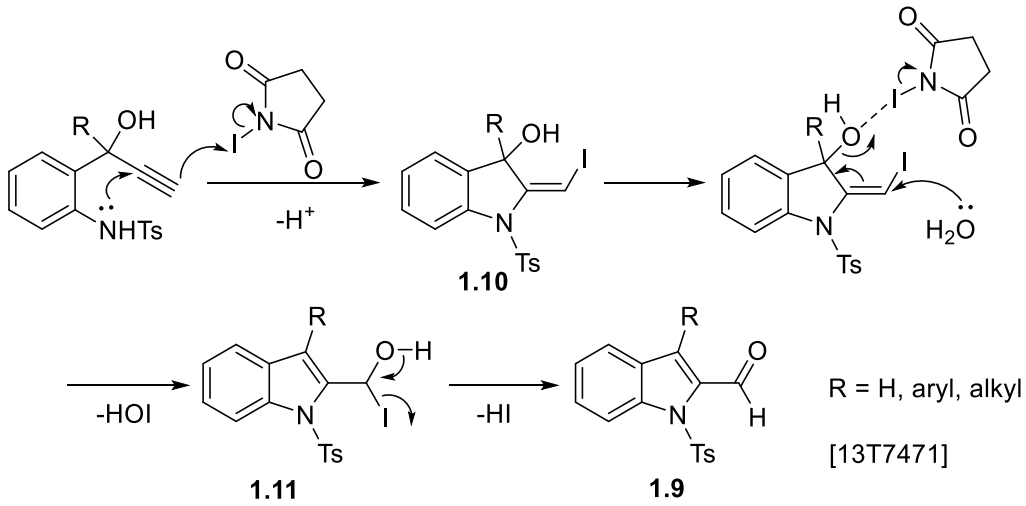
In a further extension of the reactions in Scheme 1.8, it was found that when non-distilled solvents were used the yield of indole-2-carbaldehyde was increased. This led to the optimisation of solvents in which H_2O – acetone (6:1 v/v) and 2.15 equiv. of NIS was used, affording the highest yields of **1.9** (Scheme 1.9) [13T7471].



1.9

Scheme 1.9

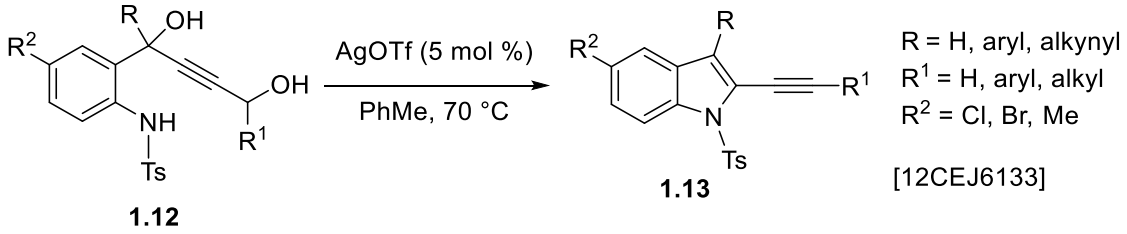
A suggested mechanism for the formation of indole-2-carbaldehyde **1.9** involves an initial iodocyclisation to the 2-(iodomethylene)-indolin-3-ol **1.10.** Co-ordination to the alcohol by another molecule of NIS facilitates dehydration, nucleophilic substitution of the activated species by H_2O generating **1.11**, the loss of HI then generates **1.9** (Scheme 1.10).



1.11 **1.9**

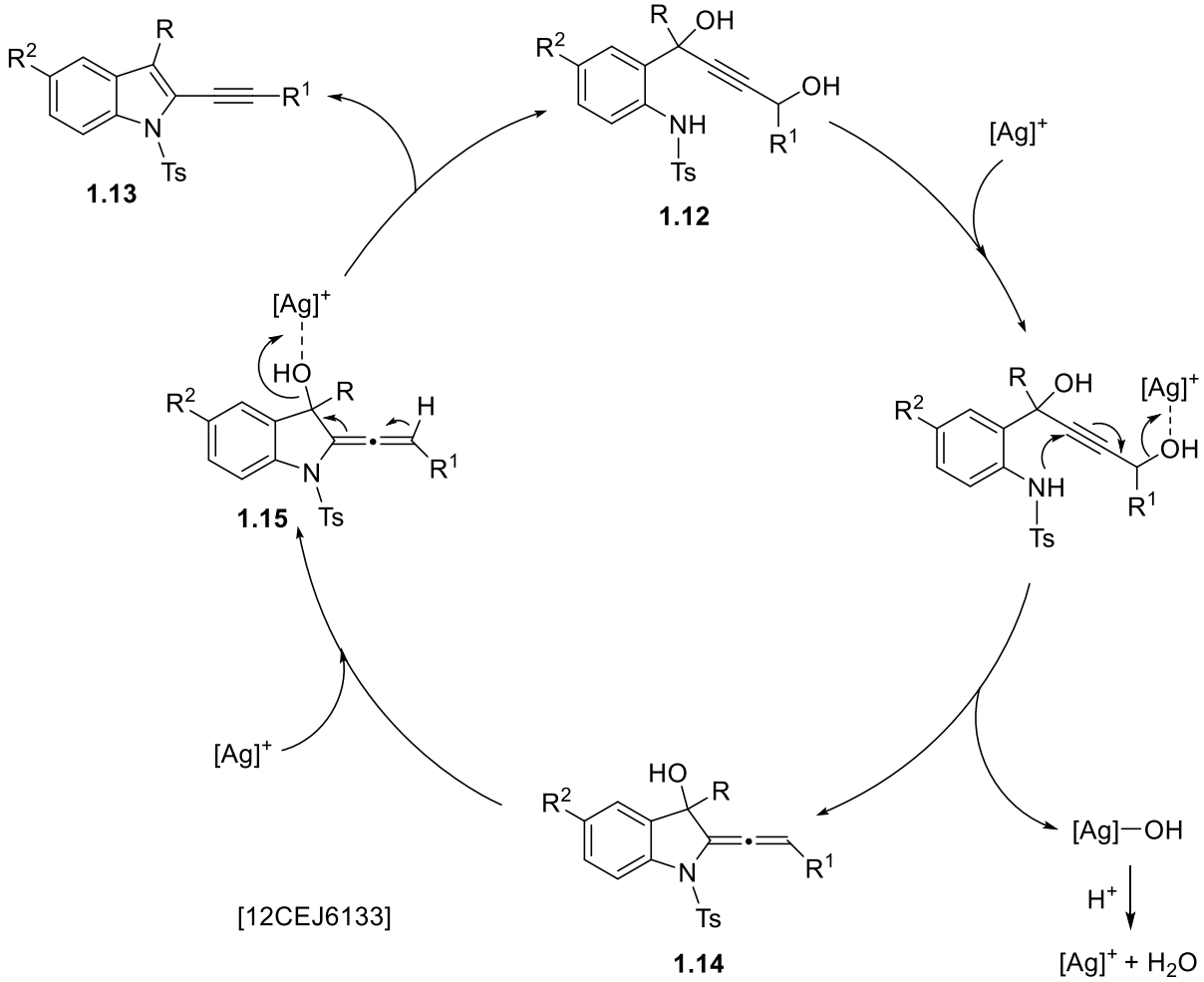
Scheme 1.10

Chan *et al.* found that Ag(I) salts catalysed the cyclisation of 1-[(2-tosylamido)aryl]but-2-yne-1,4-ols **1.12**, affording 2-alkynylindoles **1.13** in fair to excellent yields 38 – 94 % (Scheme 1.11) [12CEJ6133].



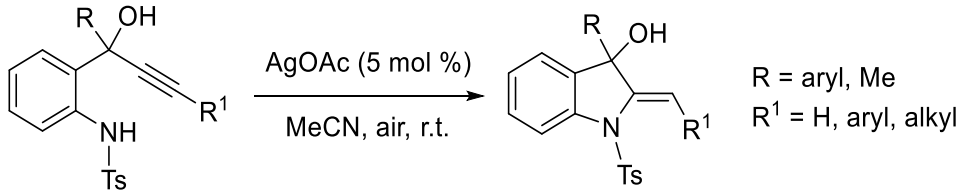
Scheme 1.11

A suggested mechanism for the formation **1.13** is *via* allene **1.14**. Silver(I) co-ordination of the alcohol promotes the deprotonation of **1.15**, followed by elimination of [Ag]-OH which on protonolysis regenerates the catalyst and a molecule of water (Scheme 1.12) [12CEJ6133].



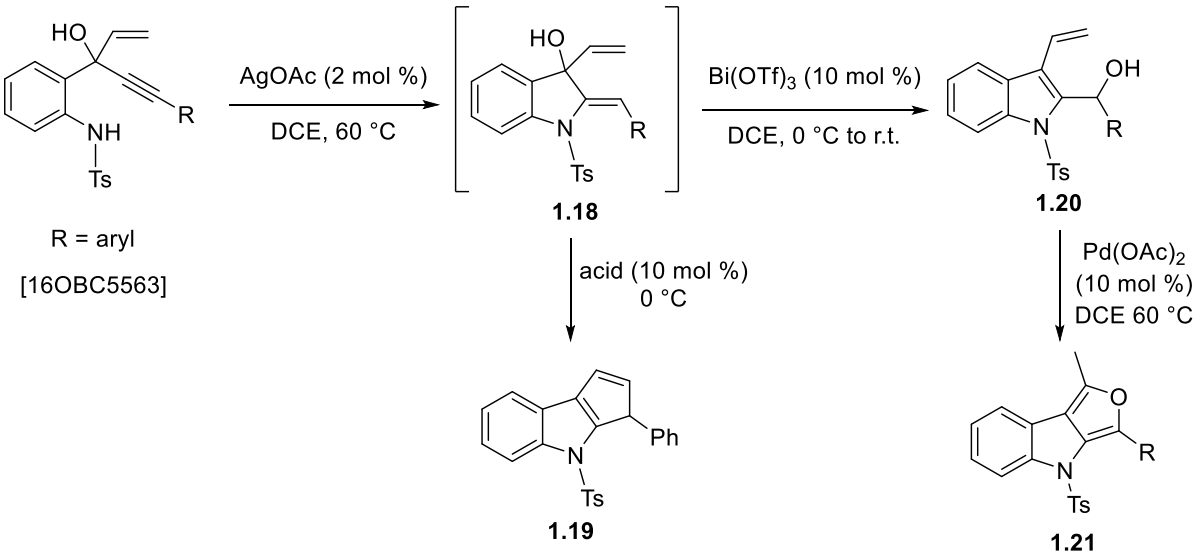
Scheme 1.12

1-[2-(Tosylamino)phenyl]prop-2-yn-1-ols **1.16** were cyclised (5-*exo*-*dig*) upon treatment with AgOAc in acetonitrile, when R^1 = H a Fischer base-like structure was produced (Scheme 1.2, **1.1**). (*Z*)-2-Methylene-1-sulfonylindolin-3-ols **1.17** were also obtained from a range of alkyl and/or aryl substituents (Scheme 1.13). However when the nitrogen protecting group was replaced with an acetyl or a Boc function, the cyclisation did not proceed and resulted only in quantitative recovery of starting material [12JOC7166].



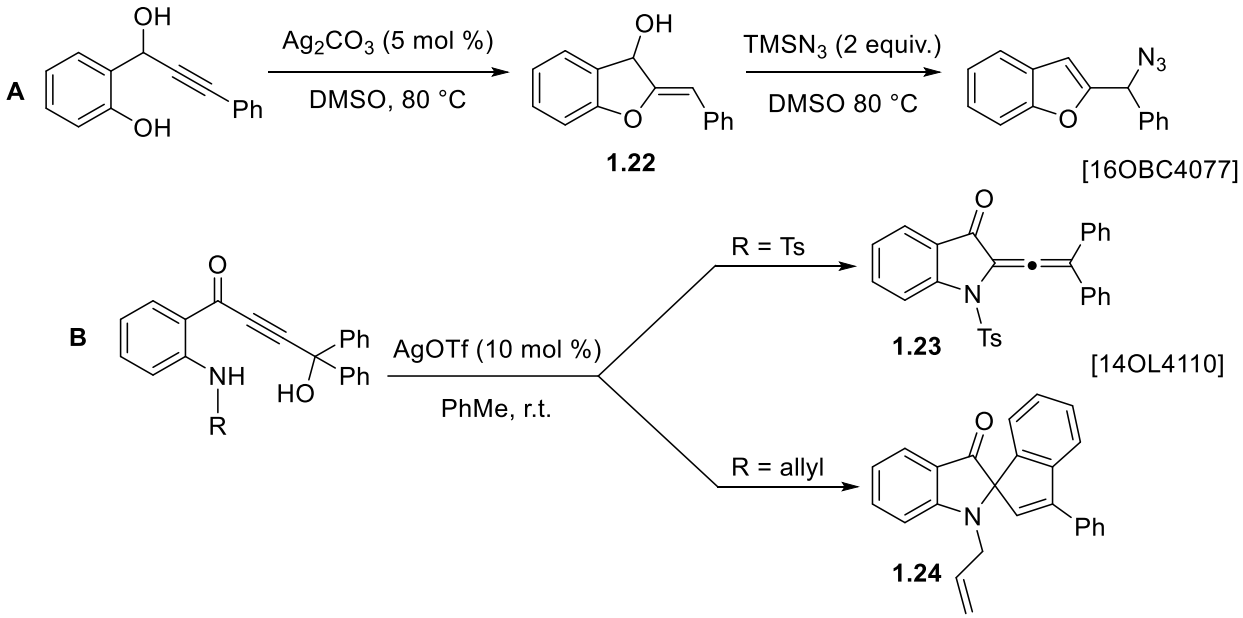
Scheme 1.13

Ramasastry and co-workers used silver(I) acetate along with other Lewis acids and Brønsted acids in a relay system, *via* **1.18,** to generate cyclopenta[*b*]indoles **1.19** – when a protic acid was used (CSA, *p*-TsOH or TfOH). However, in the presence of $Bi(OTf)_3$ the intermediate 3-vinylindolin-3-ol **1.18** underwent rearrangement with concomitant aromatisation to afford indole **1.20**. Treatment of the latter with $Pd(OAc)_2$ promoted oxidative cyclisation to the furo[3,4-*b*]indoles **1.21** (Scheme 1.14) [16OBC5563].



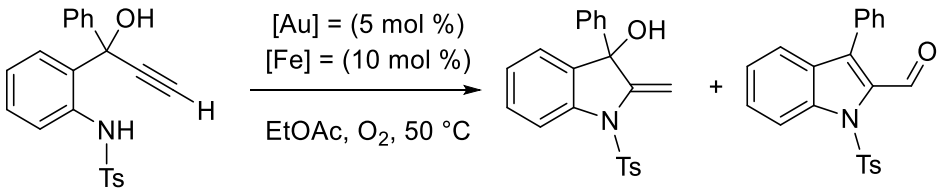
Scheme 1.14

Reddy *et al.* used silver(I) carbonate to cyclise 2-hydroxyphenyl propargyl alcohols to the dihydrobenzofuran-3-ol e.g. **1.22**, which was then subjected to treatment with $TMSN_3$ to afford 2-(α-azidobenzyl)benzofuran (**A**, Scheme 1.15). It was found that this and related reactions also proceeded in a one-pot sequence to give moderate to high yields of products (52 – 92 %) [16OBC4077]. Another example of silver(I) catalysis for the cyclisation of propargylic alcohols is provided by the ynone-terminated example from Chan and co-workers (**B**, Scheme 1.15). When the substituent on the amine function was a tosyl group, only the allene **1.23** was obtained. However, when the *N*-allyl-protected propargylamines was employed the reaction proceeded to the spirocycle **1.24** in high yields [14OL4110].



Scheme 1.15

Shi and co-workers treated 1-[2-(tosylamino)phenyl]prop-2-yn-1-ol **1.25** with a gold(I) – iron(II) catalyst system to effect cyclisation to **1.26** and **1.27**. However, there was no concern with obtaining good yields of indolines **1.26**, as they were intermediates in the synthesis of indole aldehydes **1.27** (Scheme 1.16). When only the gold(I) catalyst was used only a 13% yield of **1.26** was obtained. None of the indole-2-carbaldehyde **1.27** was formed. This observation was attributed to a slow protodeauration step. However, in the presence of both gold(I) and iron(II) catalysts the yield of **1.27** increased to 78% [15JAC8912].

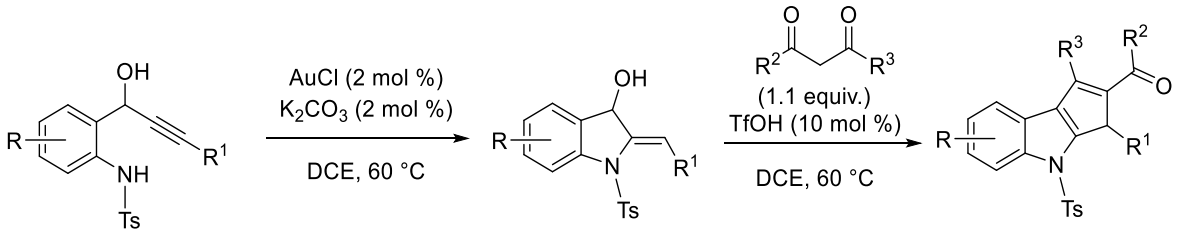


1.25 **1.26** **1.27**

[Au] = ditBuXphosAu(CH_3CN)SbF_6
[Fe] = $FeCl_2$
[15JAC8912]

Scheme 1.16

Ramasastry and Dhiman treated 1-(*N*-tosylaminophenyl)prop-2-yn-1-ols with a gold(I) catalyst in the presence of base, followed by addition of a 1,3-dicarbonyl and triflic acid in a two-step, one pot synthesis of cyclopenta[*b*]indoles. Indoline **1.28** could be isolated when gold(I) and base was used alone. However, TfOH did not facilitate the cyclisation in the absence of AuCl (Scheme 1.17) [15CC557].



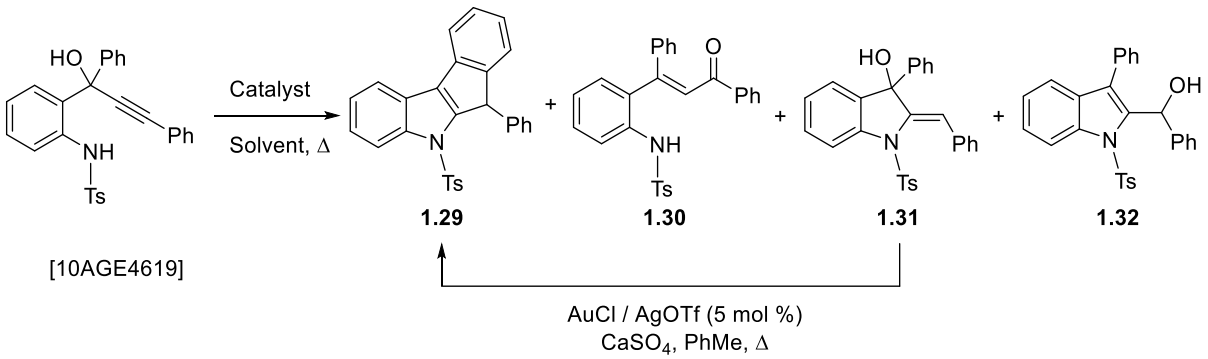
R = H, OMe, CF_3, OTs
R^1 = H, alkyl, aryl
[15CC557]

1.28

R^2 = Me, Ph, NHPh, OEt, CH=CHPh, O*t*Bu
R^3 = Me, Ph, CH_2COPh

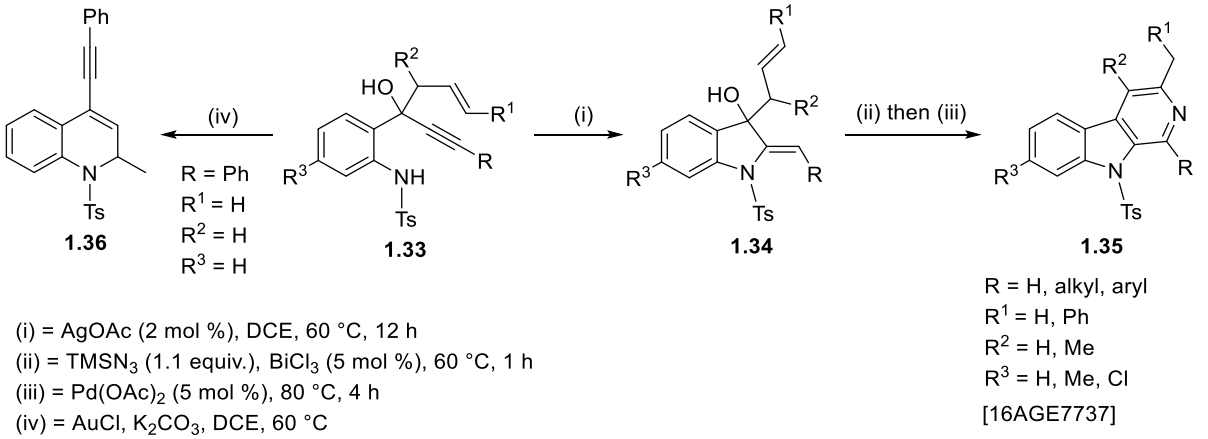
Scheme 1.17

Another example of gold catalysis for the cyclisation of aryl propargyl alcohols is provided by Chan and co-workers (Scheme 1.18). They found that either indole or acyclic structures could be obtained by varying the reaction conditions. Thus gold(I) chloride and an AgOTf co-catalyst with 20 mol % HMPA and $CaSO_4$ in toluene gave tetracycle **1.29,** in excellent yield (94%). However, if DMAP was employed instead of HMPA the Meyer-Schuster product **1.30** was obtained in a high yield (87%). It was found that indoline **1.31** could be transformed into **1.29** by using the same catalyst and solvent system but discarding the HMPA. Indole **1.32** could only be obtained in low yields from all the conditions investigated [10AGE4619].



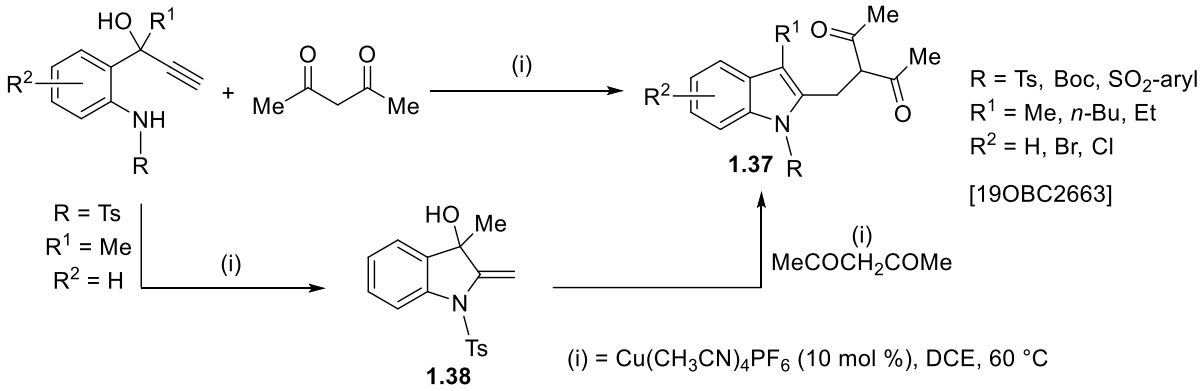
Scheme 1.18

Silver(I) was employed to cyclise the enynol **1.33**, *via* indoline **1.34**, to afford the β-carboline **1.35** in good to high yields (67 – 81%). However, with AuCl and K_2CO_3 **1.33** gave the 6-*exo*-*trig* product **1.36** exclusively (Scheme 1.19) [16AGE7737].



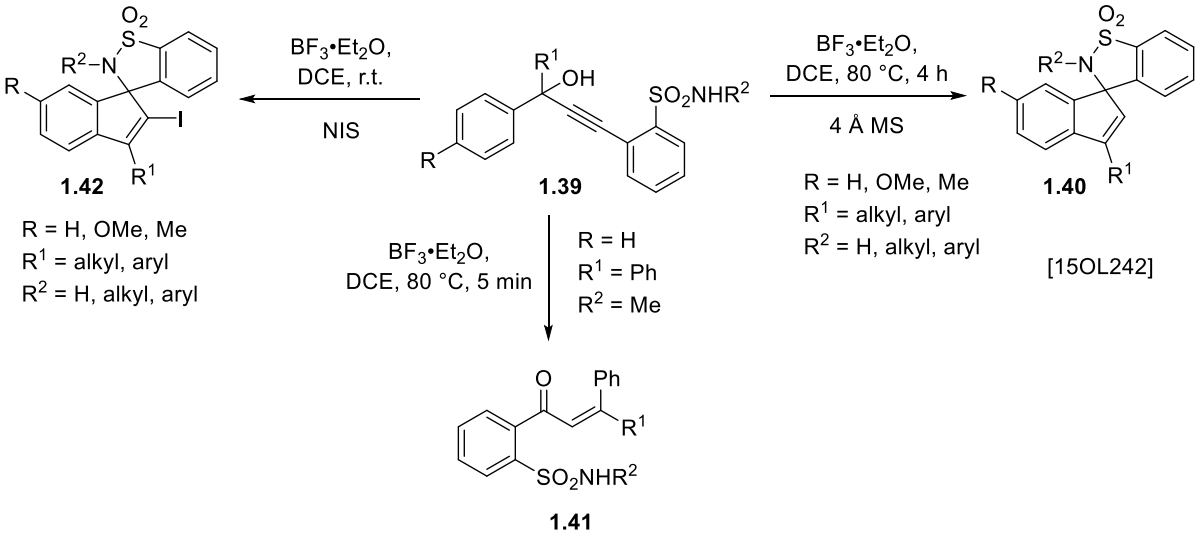
Scheme 1.19

A copper(I) species promotes the tandem cyclisation-condensation reaction of 3-(2-aminophenyl)prop-2-yn-1-ols with acetylacetone to indole **1.37.** The reaction which can also be conducted in a stepwise manner, affords indoline **1.38** in the absence of the diketone. However, access to **1.37** by the stepwise procedure is less efficient than the one-pot reaction (Scheme 1.20) [19OBC2663].



Scheme 1.20

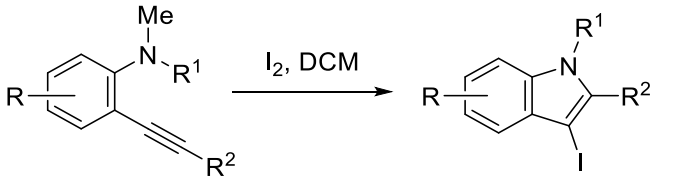
Wang and co-workers showed that alkynols **1.39** in the presence of boron trifluoride etherate, cyclised to the corresponding spiro(indenebenzosultams) **1.40** (Scheme 1.21). Interestingly, it was found that at low temperature, or after a short reaction time, the Meyer-Schuster product **1.41** could be isolated in a 94% yield. It was also found that when 1 equiv. of NIS was added to the reaction mixture, the iodospiro(indenebenzosultams) **1.42** were obtained [15OL242].



Scheme 1.21

1.4.2 From (2-Aminophenyl)acetylene Derivatives

Larock *et al.* showed that *N,N*-disubstituted-2-(*p*-tolylethynyl)anilines undergo facile iodocyclisations to indoles, in which a range of substituents on the alkyne are tolerated (Scheme 1.22) [04OL1037].

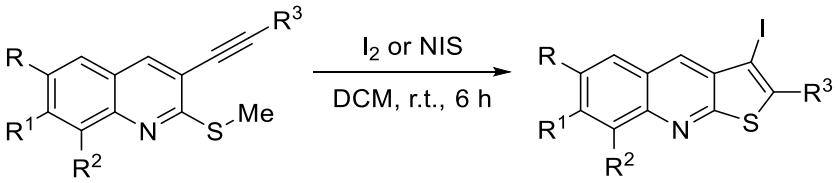


[04OL1037]

R = H, NO_2, OMe, CO_2Et
R^1 = Me, *n*-Bu
R^2 = alkyl, aryl

Scheme 1.22

Thieno[2,3-*b*]quinolines were synthesised in high yields (61 – 91%) from 3-alkynyl-2-(methylthio)quinolines *via* a 5-*endo-dig* cyclisation initiated by a positive iodine source (Scheme 1.23). It was found that the efficiency of the cyclisation was highly dependent on the nature of the iodinating reagent. However, the reaction tolerated a variety of functional groups once the optimised conditions were established [18OBC245].

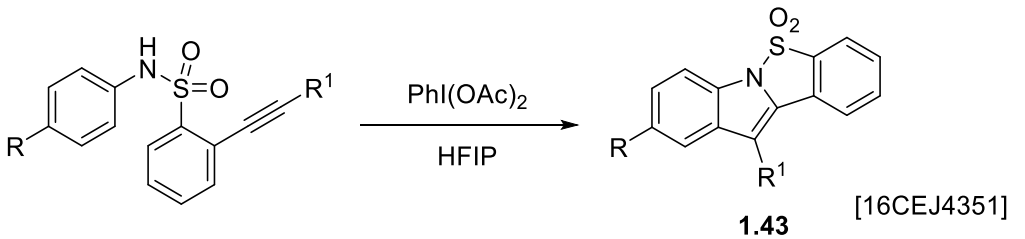


[18OBC245]

R, R^1, R^2 = H, CH_3
R^3 = H, Br, Ph, 3-$CH_3C_6H_4$, 4-$CH_3C_6H_4$, CCC_6H_5

Scheme 1.23

Muñiz and Fra used a hypervalent iodine reagent to activate the triple bond of an alkynyl sulfonamide to nucleophilic attack from the sulfonamide nitrogen. Subsequent nucleophilic attack of the aromatic ring and re-aromatisation ensued to afford the tetracycle **1.43** (Scheme 1.24) [16CEJ4351].



1.43

[16CEJ4351]

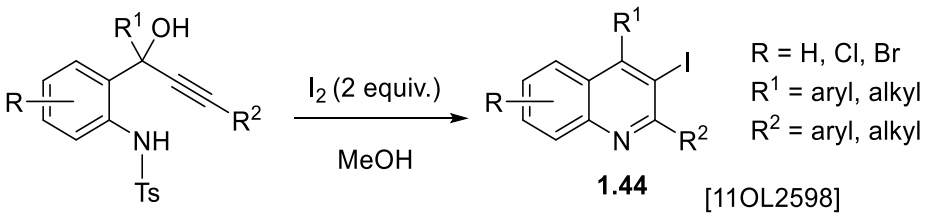
R = H, F, Cl, Me, OMe
R^1 = aryl
HFIP = hexafluoroisopropanol

Scheme 1.24

1.5 Formation of Six-Membered Rings and Benzologues

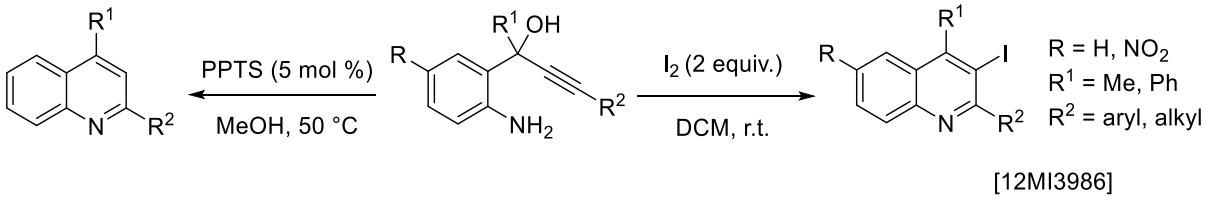
1.5.1 From 1-(2-Aminophenyl)- or 1-[2-(Alk)oxyphenyl]-prop-2-yn-1-ol Derivatives

Ali *et al*. found molecular iodine promoted the cyclisation of 1-[2-(tosylamino)phenyl]prop-2-yn-1-ols, to 3-iodoquinolines. If nitromethane was employed as the solvent, yields were poor. However, when replaced with methanol, moderate to excellent yields (40 – 99%) of the 3-iodoquinoline could be obtained **1.44** (Scheme 1.25) [11OL2598].



Scheme 1.25

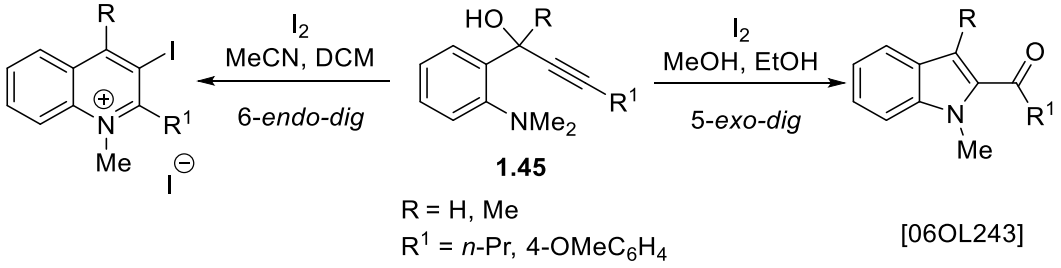
Kumer *et al.* exploited the iodocyclisation of *N*-unsubstituted 1-(2-aminophenyl)propynols to prepare quinolines. The amino function was not protected because the enhanced nucleophilicity and diminished bulk of the amino group was envisaged to increase the reaction rates. It was found that cyclisation to the 3-iodoquinoline could be achieved under mild conditions. Furthermore the 2,4-disubstituted quinolines were also easily obtained *via* a Brønsted acid catalysed cyclisation (Scheme 1.26) [12MI3986].



Scheme 1.26

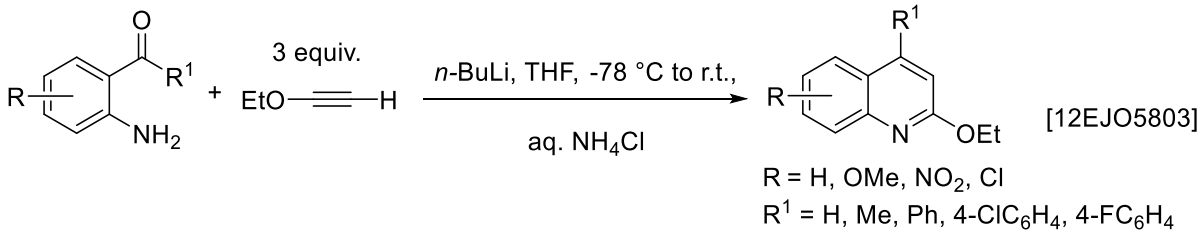
When either the secondary or tertiary 1-(2-aminophenyl)alk-2-yn-1-ols **1.45** were subjected to iodocyclisation conditions, the outcome could be manipulated by choice of solvent (Scheme 1.27). In dichloromethane or acetonitrile, the 6-*endo-dig* product was obtained. Yet when either ethanol or methanol was used a 2-acylindole derived from a 5-*exo-dig* pathway was generated [06OL243]. These results lead to the conclusion that it is the protic nature of the solvent that is the key factor in controlling the outcome of the reaction. This observation is contrary to the results of Ali – that in MeOH the 6-*endo-dig* pathway is favoured (Scheme 1.25) [11OL2598]. However, the substrates used by Hessian and Flynn

possessed a 2-dimethylamino group whereas Ali used 2-tosylamido compounds; clearly the tosyl group will greatly affect the nucleophilicity of the nitrogen.



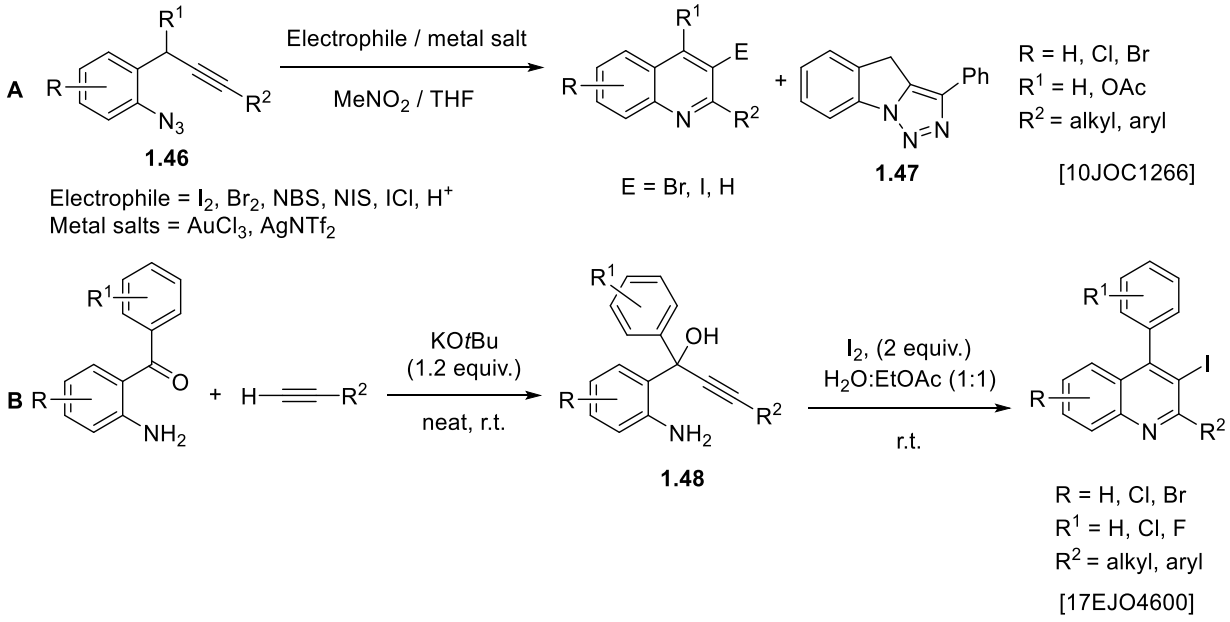
Scheme 1.27

The alkynol formed from the addition of LiC≡COEt to 2-aminobenzaldehyde or 2-aminophenyl ketones could not be isolated, as cyclisation ensued on work up with aq. NH_4Cl to afford 2-ethoxy-4-quinolines in good yields (Scheme 1.28) [12EJO5803].



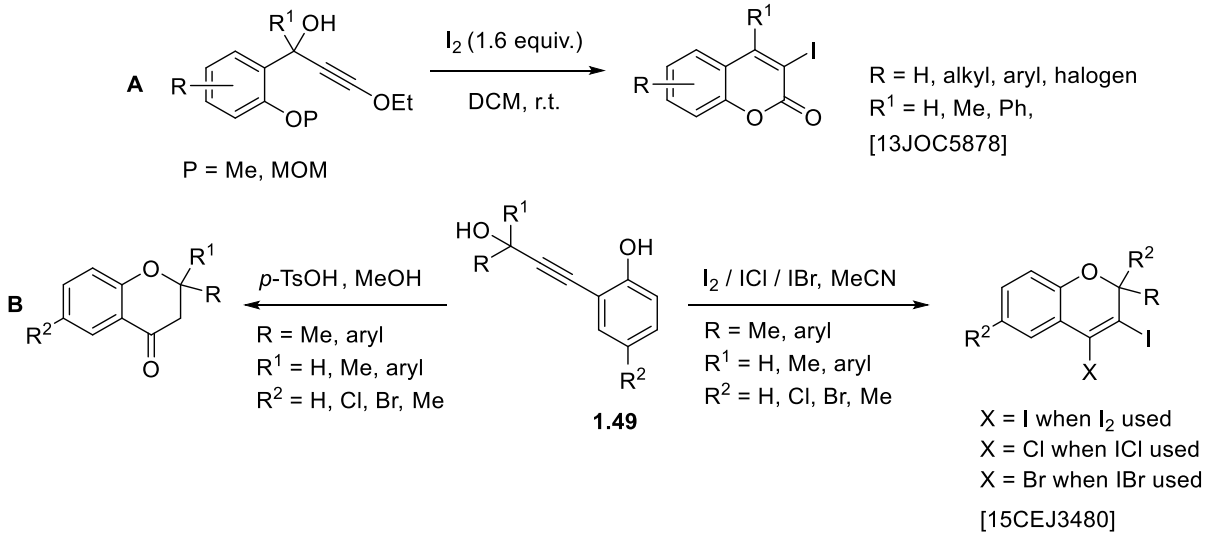
Scheme 1.28

Yamamoto and co-workers used a range of Lewis acids and Brønsted acids (e.g. I_2, Br_2, TfOH, TFA and $HNTf_2$) to cyclise 1-azido-2-(2-propynyl)benzenes (**1.46**) to afford 3-unsubstituted quinolines E = H and 3-haloquinolines E = Br, I (**A**, Scheme 1.29). It was also found that with some catalysts a small amount of 3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indole **1.47** was also obtained [10JOC1266]. 3-Iodoquinolines were synthesised from 2-aminobenzophenones and an acetylene in a single pot reaction (**B**, Scheme 1.29). The intermediary of the phenyl alkynol **1.48** was established by its isolation in quantitative yield [17EJO4600].



Scheme 1.29

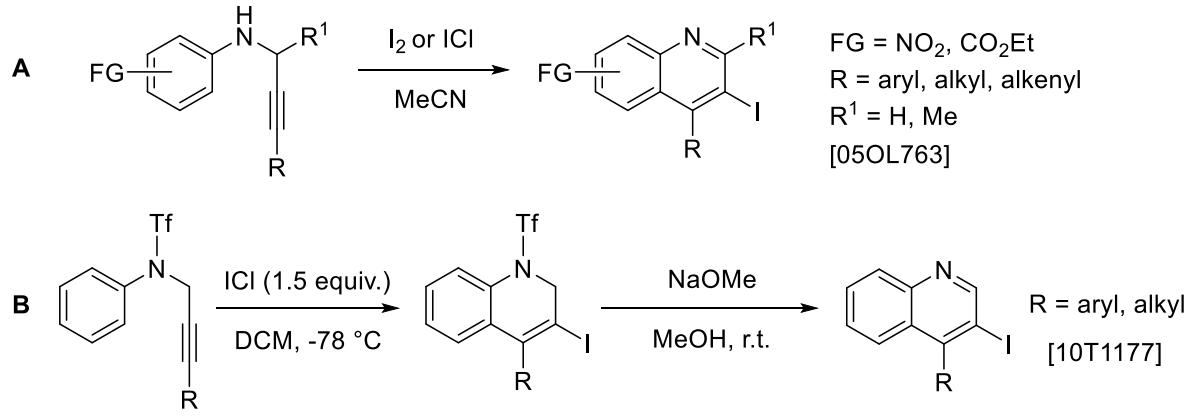
3-Iodocoumarins can be accessed easily by the cyclisation of ethoxyalkyne diols in moderate to high yields (**A**, Scheme 1.30) [13JOC5878]. Laing *et al*. found that iodination occurred twice upon cyclisation of alkynols **1.49** to afford 3,4-diiodochromenes when molecular iodine was used; with either IBr or with ICl both halogens added to the chromene. A range of chromanones could be synthesised when a Brønsted acid was used to catalyse the cyclisation of the same alkynol **1.49** (**B**, Scheme 1.30) [15CEJ3480].



Scheme 1.30

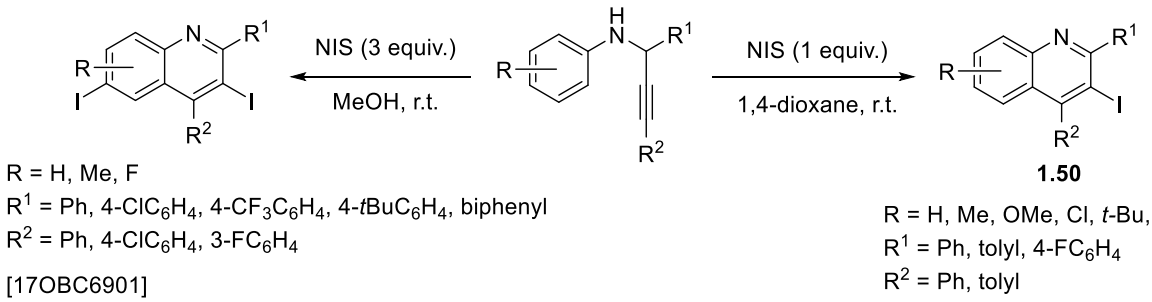
1.5.2 From *N*-Arylpropargylamines

Larock reported that iodine was an excellent electrophilic initiator for the cyclisation of *N*-(2-alkynyl)anilines [05OL763]. Iodine monochloride produced slightly lower yields but at faster reaction rates (Scheme 1.31), which is not surprising as it is a harder electrophile than molecular iodine [07CSR354]. It was found that the iodocyclisation tolerated a variety of substituents. However, the presence of electron withdrawing groups were found to also produce side products, including a 3,6-diiodoquinoline derivative when R = 4-$MeCOC_6H_4$ [05OL763]. Larock also reported that *N*-propargyltriflamides could be cyclised to 3-iodoquinolines in moderate yields (Scheme 1.31) [10T1177].



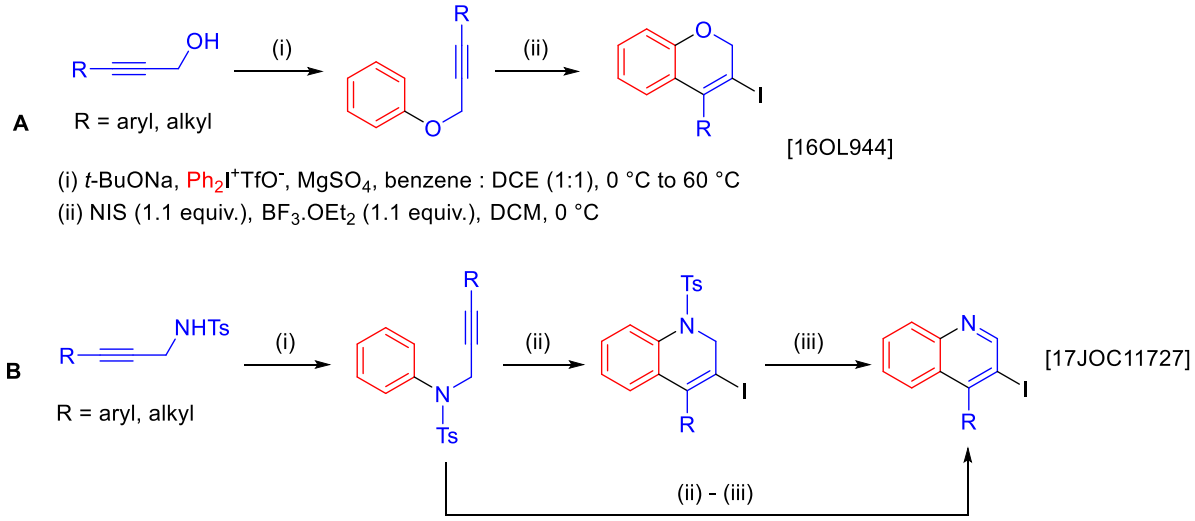
Scheme 1.31

Zhang *et al.* achieved good yields (64 – 81%) of 3-iodo-2,4-diarylquinolines (**1.50**) from *N*-phenyl propargylamines and NIS in 1,4-dioxane; together with trace amounts of the 3,6-diiodo-2,4-diphenylquinolines (Scheme 1.32). In MeOH the product distribution was reversed, suggesting that the solvent promotes *p*-iodination of the aromatic ring prior to cyclisation. Zhang *et al.* also proposed that the cyclisation proceeds *via* a radical pathway, however no evidence in support of this assertion was presented [17OBC6901].



Scheme 1.32

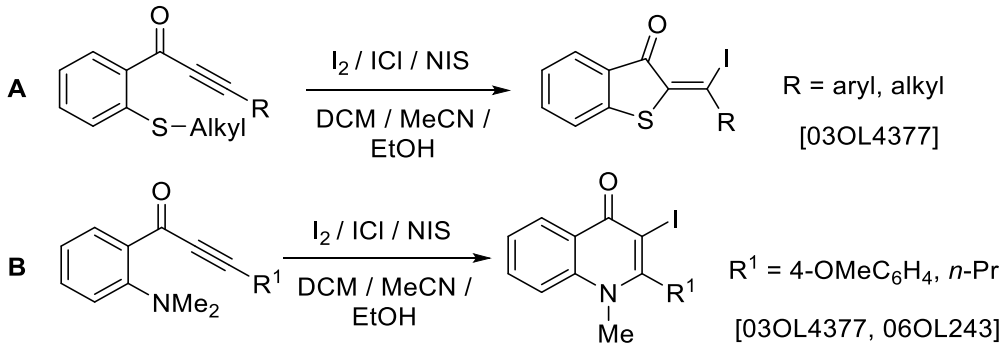
3-Iodochromenes have been synthesised in a one pot reaction, involving *in situ O*-arylation of a propargylic alcohol with diphenyliodonium triflate [13S183] and subsequent iodocyclisation under Lewis acid catalysis (**A**, Scheme 1.33). Yields could be improved by addition of DCM [16OL944]. Togo and co-workers went on to adapt the method to synthesise 3-iodoquinolines from *N*-tosylproparylamines (**B**, Scheme 1.33). The dihydroquinoline was isolated before removal of the tosyl group (**B**, step iii, Scheme 1.33). However, removal of the tosyl function (NaOH in MeOH) could also be achieved without isolation of the intermediate [17JOC11727].



Scheme 1.33

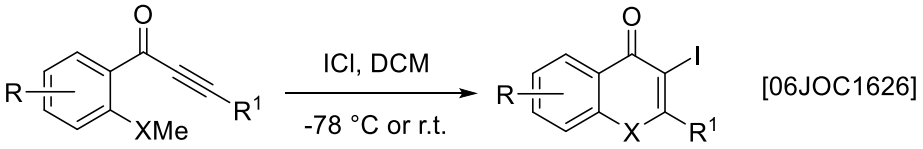
1.5.3 From 1-Arylprop-2-ynone Derivatives

Hessian and Flynn reported that regioselectivity from the iodocyclisation of 2-[2-(substituted)phenyl]alkyl-3-yn-2-ones was achievable. Thus, either the 5-*exo-dig* or 6-*endo-dig* cyclisation route could be controlled by the appropriate choice of starting material. When 1-[(2-alkylthio)phenyl]alk-2-yn-1-ones were subjected to iodocyclisation conditions they underwent exclusive 5-*exo-dig* ring closure (**A**, Scheme 1.34). However, the analogous 1-[2-(dimethylamino)phenyl]prop-2-yn-1-ones were highly selective for the 6-*endo-dig* pathway (**B**, Scheme 1.34). These pathways were unaffected by variations of the iodine source (I_2, ICl, NIS) and solvent (DCM, EtOH, MeCN) [03OL4377, 06OL243].



Scheme 1.34

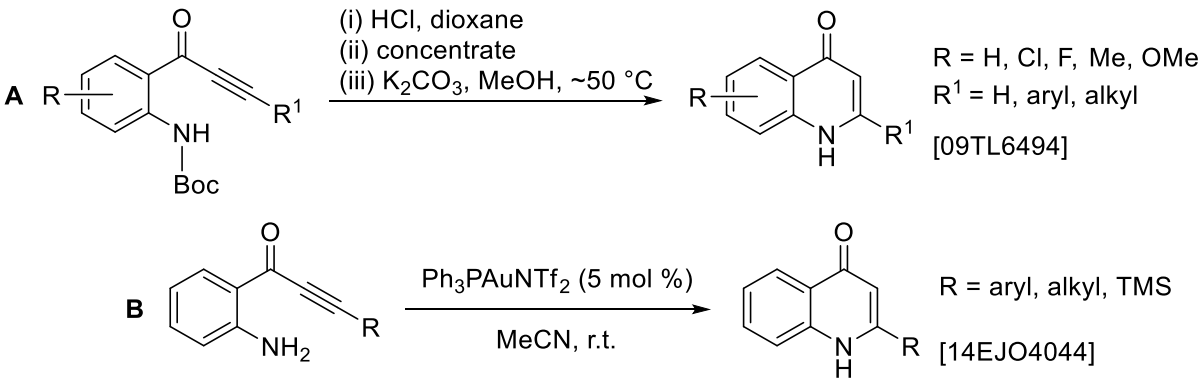
Larock and co-workers published a route to access 3-iodo(thio)chromones and 3-iodo-4-quinolones from an ICl-induced electrophilic cyclisation (6-*endo-dig*) of 1-(aryl)propyn-1-ones. The starting alkynones were synthesised from a Sonogashira coupling of a 2-substituted benzoyl chloride and a terminal acetylene, which allowed access to a variety of compounds with different substituents by utilising this approach. Cyclisations of the alkynones ensue under mild conditions affording fair to excellent yields (45 – 99%) of products (Scheme 1.35) [06JOC1626].



X = O, S, NMe
R = H, Br, F, OMe, NO_2, Ph
R^1 = alkyl, aryl, TMS

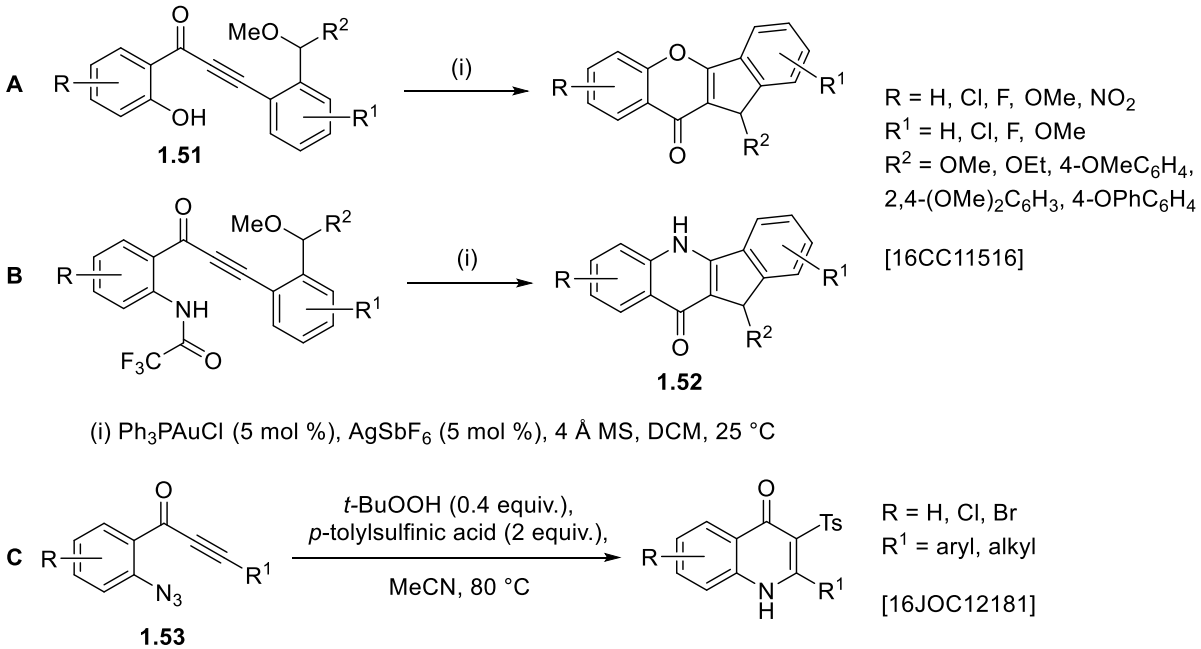
Scheme 1.35

Derivatives of 1-[2-(BocNH)phenyl]prop-2-yn-1-ones cyclise upon heating with acid, over a prolonged time (four days) to give 4-quinolones from which the Boc group has been cleaved (**A**, Scheme 1.36). When the temperature was increased, several side products were also formed [09TL6494]. Moreover, 4-quinolones have been synthesised from ynones by a gold(I)-mediated cyclisation. Helaja and co-workers obtained a range of 2-substiuted quinolones in yields ranging from 19 to 96% (**B**, Scheme 1.36) [14EJO4044].



Scheme 1.36

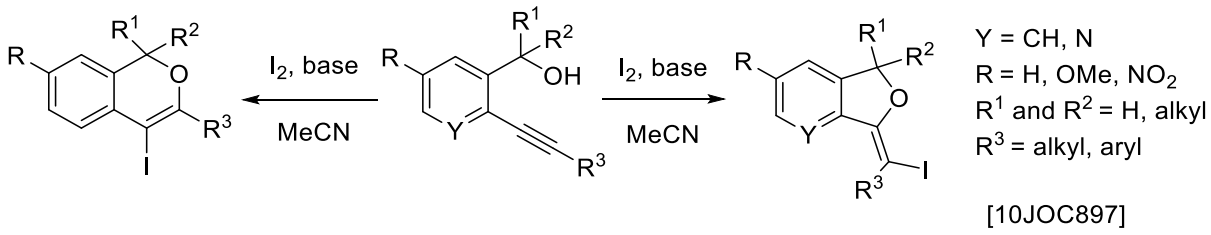
The highly alkynophilic gold(I) species $[Ph_3PAu]SbF_6$ (generated *in situ*) was used to cyclise ynones **1.51** to indenochromen-4-ones (**A**, Scheme 1.37), the substrate scope was extended to generate indenoquinoline-4-ones **1.52** (**B**, Scheme 1.37). It was proposed that activation of the triple bond by the gold(I) species is assisted by hydrogen bonding of the hydroxyl group to the carbonyl function. In the case of the amino substrate, a protecting group was needed to change the electron density of the amino group so allowing better hydrogen bonding with the ynone carbonyl function [16CC11516]. Although not involving direct electrophilic activation of the triple bond, Zhu and co-workers developed a radical process to cyclise 2-azidoaryl propynones **1.53** to obtain 2-aryl-3-tosylquinolin-4(1*H*)-one derivatives (**C**, Scheme 1.37). Attack of the ynone by the electrophilic radical $TolSO_2$• has been invoked to explain the outcome of this reaction [16JOC12181].



Scheme 1.37

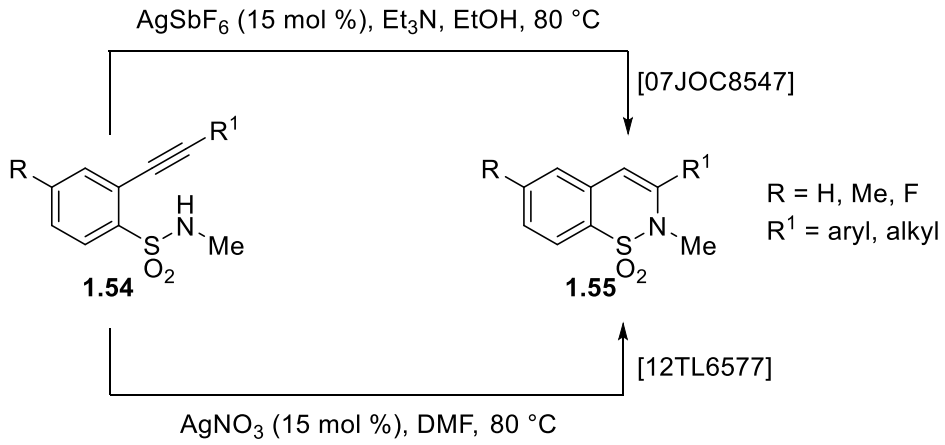
1.5.4 From *ortho*-Substituted Phenylacetylenes

Larock demonstrated that the substituents played an essential role in determining the nature of the final product when 2-(1-alkynyl)benzylic alcohols were iodocyclised with molecular iodine and an inorganic base ($NaHCO_3$, K_2CO_3, $KHCO_3$ or NaH) in acetonitrile (Scheme 1.38) [10JOC897]. When the triple bond was substituted with a 3-thienyl-, a 1-cyclohexenyl- or an *n*-butyl-group the 6-*endo*-*dig* product was generated. Furthermore, when the starting material possessed either electron withdrawing or electron donating groups *meta* to the hydroxyalkyl group, the 6-*endo*-*dig* product was formed. However, with increasing steric hindrance in the substrate, complex reaction mixtures were produced. If the substrate was configured as a tertiary alcohol function, the 5-*exo*-*dig* product was obtained.



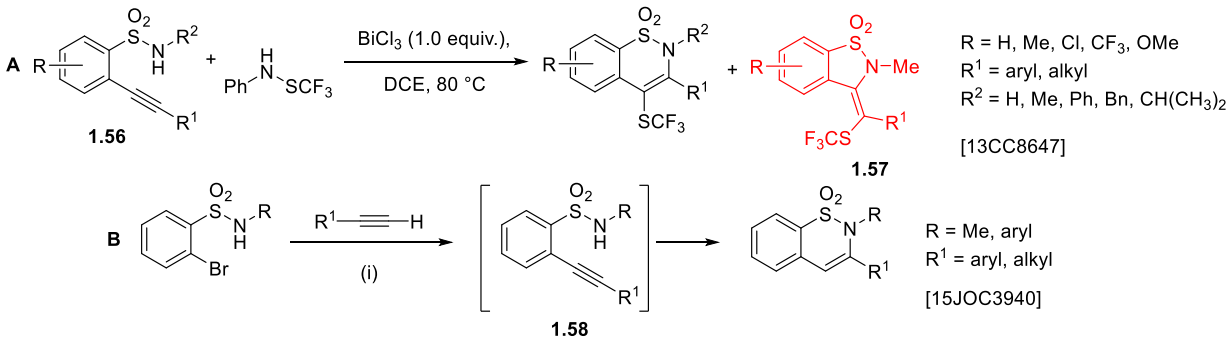
Scheme 1.38

Pal *et al.* took advantage of the alkyne moiety in 2-sulfamoylphenylacetylenes **1.54** to form 2*H*-1,2-benzothiazine 1,1-dioxides **1.55**, using a silver(I) catalyst such as $AgSbF_6$ [07JOC8547] or $AgNO_3$ [12TL6577] (Scheme 1.39). The reaction tolerated both alkyl and aryl substituents on the alkyne moiety [07JOC8547, 12TL6577]. However, the choice of solvent for each silver(I) catalyst was different, when $AgSbF_6$ was employed with DMF the yield of 2*H*-1,2-benzothiazine 1,1-dioxide was still high (82%) but EtOH increased the yield to 89% [07JOC8547].



Scheme 1.39

1,2-Benzothiazine 1,1-dioxides could be obtained from the Lewis acid-catalysed cyclisation of **1.56** with phenyltrifluoromethanesulfanylamide (**A**, Scheme 1.40). It was found that when R^1 was an alkyl group the 5-*exo-dig* product **1.57** was obtained; the cyclisation pathway could be controlled by the nature of the R group, if electron-withdrawing groups (Cl and CF_3) were used then the 6-*endo-dig* product was obtained selectively [13CC8647]. 2-Bromobenzenesulfonamides can be coupled with a range of acetylenes *via* a Sonogashira reaction to synthesise 1,2-benzothiazine 1,1-dioxides (**B**, Scheme 1.40). Intermediate **1.58** was isolated to establish how the reaction proceeds. Alkynes **1.58** could be activated by complexation with copper(I) in a separate step demonstrating that Cu(I) promotes the 6-*endo-dig* cyclisation (Scheme 1.40) [15JOC3940].

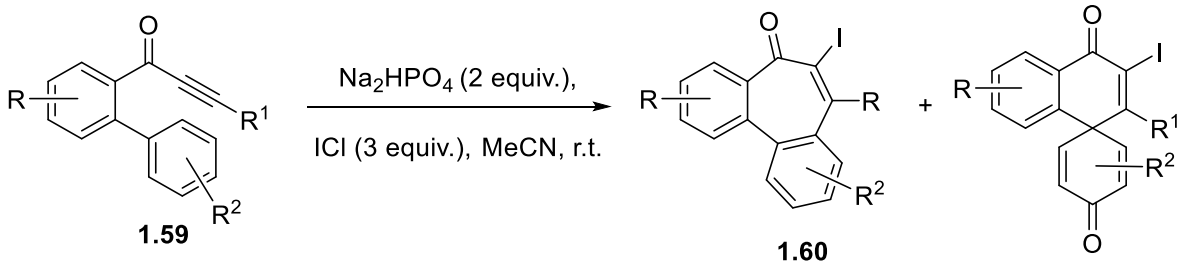


Scheme 1.40

1.6 Seven-Membered Rings *via* Electrophilic Cyclisations

Within the literature there are very few examples of electrophilic cyclisations of substrates leading to seven-membered carbocyclic or heterocyclic rings. However some examples are discussed below.

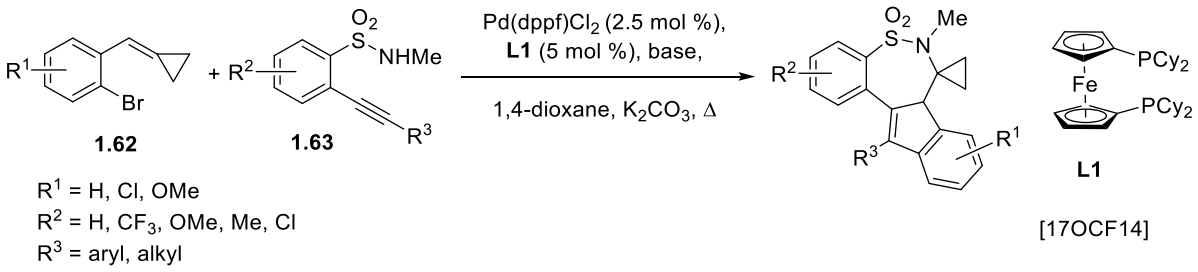
Chen and co-workers found that the iodocyclisations of alkynone **1.59** could operate *via* two pathways, to give either the 7-*endo-dig* **1.60** or the 6-*endo-dig* **1.61** product (Scheme 1.41). It was found that the substituents on the distal phenyl ring can control the cyclisation pathway. If a strong electron-donating group is present in the *para* position the 6-*endo-dig* (**1.61**) pathway is favoured, if this group is removed then the 7-*endo-dig* product (**1.60**) predominates [13CEJ9795, 14JOC3452].



R = H, OMe
R^1 = alkyl, aryl
R^2 = H, OMe, Cl, OPh, F, SMe, Me
[13CEJ9795, 14JOC3452]

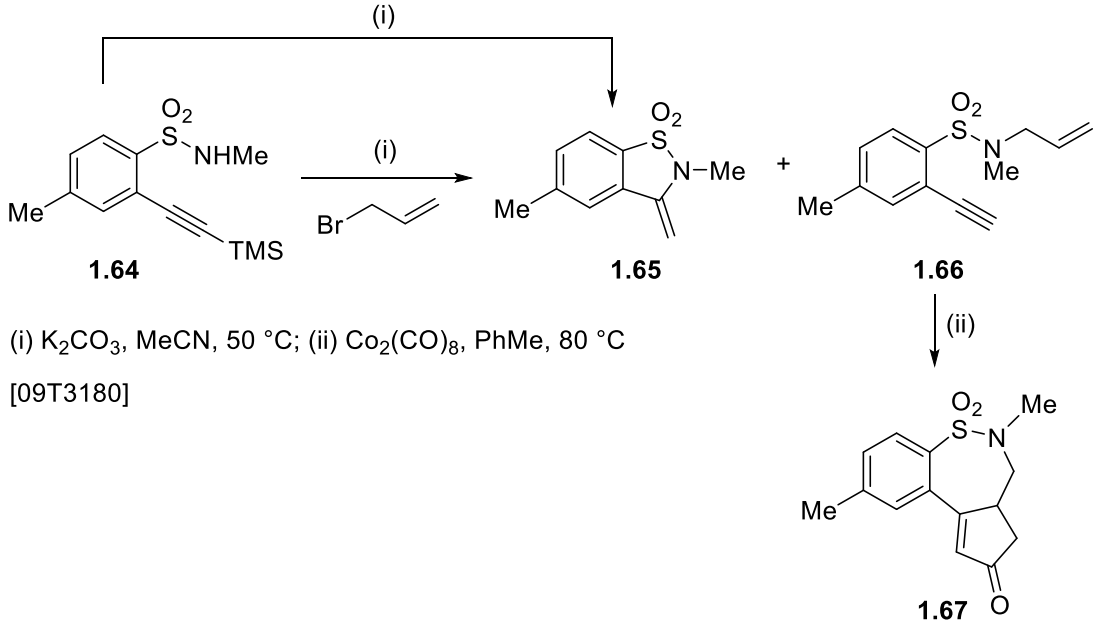
Scheme 1.41

Palladium(0) generated *in situ* has been utilised in the synthesis of polycyclic sultams by a novel tandem reaction. The ArPdBr species generated from 1-bromo-2-(cyclopropylidenemethyl)benzenes **1.62** undergoes carbopalladation with 2-alkynylbenzenesulfonamides **1.63** and rearrangement to a cyclopropyl-PdBr species (Scheme 1.42). The latter is intercepted by the sulfonamide function from which the product results with reductive elimination of Pd(0). However, it was expected that the cyclopropane ring would open under these conditions, but this pathway was not observed [17OCF14].



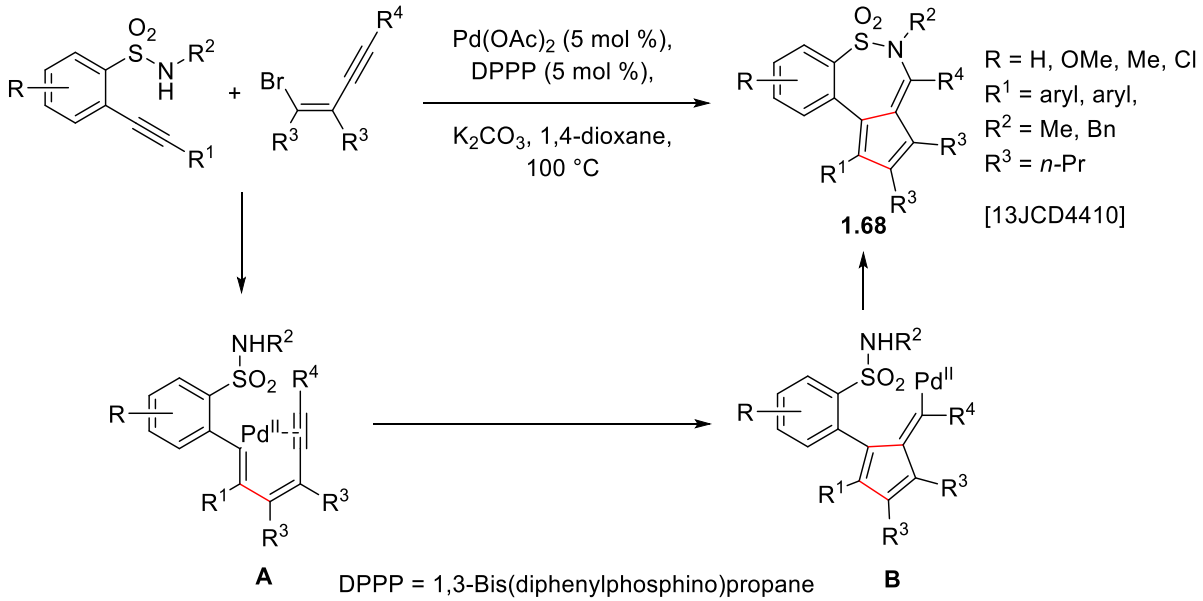
Scheme 1.42

Alkylation of the sulfonamide **1.64** in the presence of potassium carbonate in MeCN was found to facilitate the cyclisation to isothiazole **1.65** albeit in low yields (9%, Scheme 1.42). Use of the base without allyl bromide provided the isothiazole in high yields (78%) [09T3180]. Cobalt(0) was used to cyclise **1.66** in a Pauson-Khand reaction, affording the tricyclic sultam **1.67** (Scheme 1.43) [09T3180].



Scheme 1.43

1,2-Benzothiazepine 1,1-dioxide derivatives **1.68** were afforded in good to excellent yields (56 – 99%) from a Pd(II) catalysed reaction of 1-(2-alkynyl)benzenesulfonamide and 2-alkynylvinyl bromide (Scheme 1.44). Wu and co-workers suggest that the reaction proceeds *via* intermediate **A**, which after intramolecular insertion of a triple bond affords intermediate **B**. The latter then undergoes a C-N coupling to afford the 1,2-benzothiazepine 1,1-dioxide **1.68** (Scheme 1.44) [13JCD4410].



Scheme 1.44

1.7 Aims of the Project

There is a remarkable gap in the literature in that no systematic study of the electrophilic cyclisation of dialkynols, specifically derivatives of 3-arylpenta-1,4-diyn-3-ols possessing a nucleophilic *ortho* substituent have been reported.

The objective of the present study was to redress this deficiency and to:

(i) Synthesise a range of 3-phenylpenta-1,4-diyn-3-ols having an *ortho*-*N*-linked sulfonamide function *via* addition of alkynyllithiums to methyl 2-(arenesulfonamido)benzoates. The compounds so obtained will have symmetrical terminating groups on the alkyne moieties.

(ii) Synthesise a range of 3-[2-(arenesulfonamido)phenyl]penta-1,4-diyn-3-ols having electronically and sterically dissimilar alkyne terminal groups *via* addition of alkynyllithiums or alkynyl-Grignard reagents to 1-[(2-arenesulfonamido)phenyl]prop-2-yn-1-ones.

(iii) Investigate the reactivity of *N*-substituted saccharins towards alkynyllithium reagents to access novel 3-(2-sulfamoylphenyl)penta-1,4-diyn-3-ols. These *S*-linked sulfonamides, isomeric to those prepared initially in (i) have effectively a chain-extension to the nucleophilic centre.

The compounds obtained from (i) – (iii) above will then be treated with a variety of electrophilic/alkynophilic activators [e.g. TsOH, I_2, ICl, Ag(I) and In(III) salts] as the subsequent cyclisations are anticipated to generate novel alkyne-linked heterocyclic rings, which would not be accessible by other means. The scope of these cyclisations will be investigated.

Chapter 2

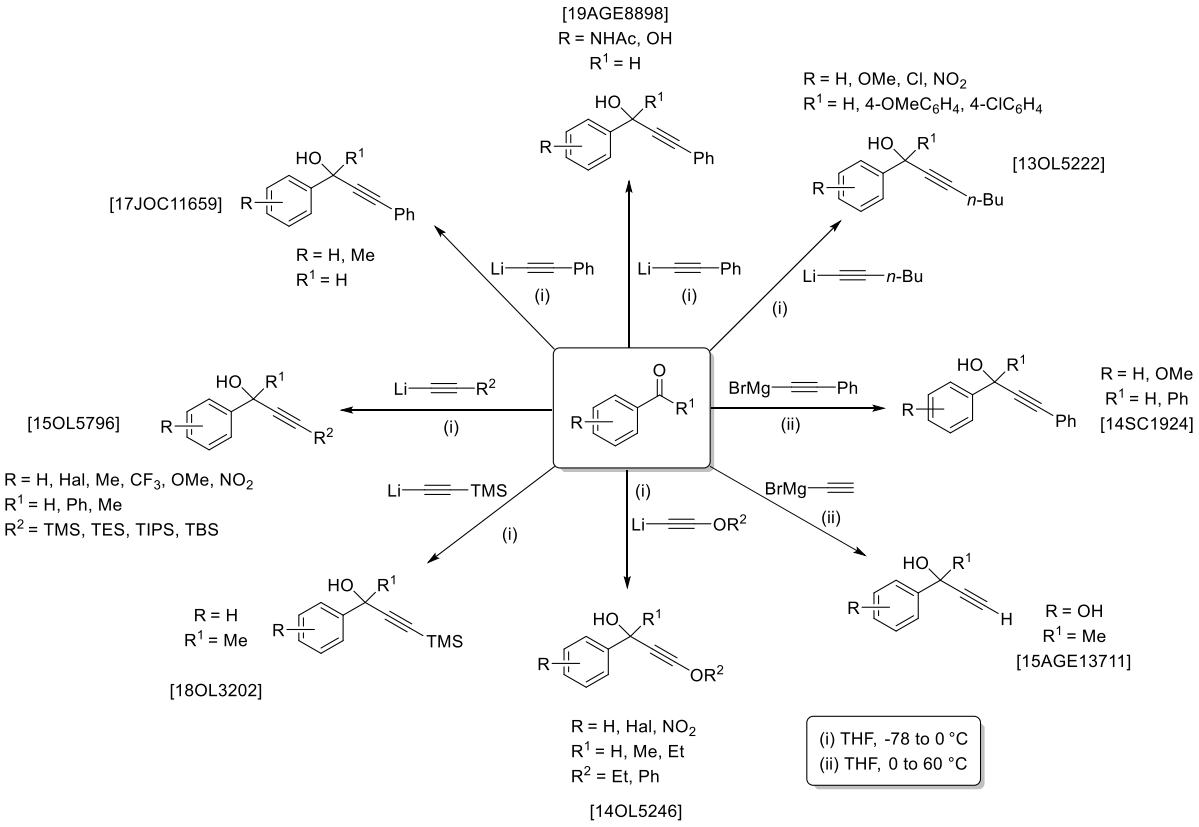
Synthesis of

3-Arylpenta-1,4-diyn-3-ols

Chapter 2 Synthesis of 3-Arylpenta-1,4-diyn-3-ols

2.1 3-[2-(Arenesulfonamido)phenyl]-penta-1,4-diyn-3-ols

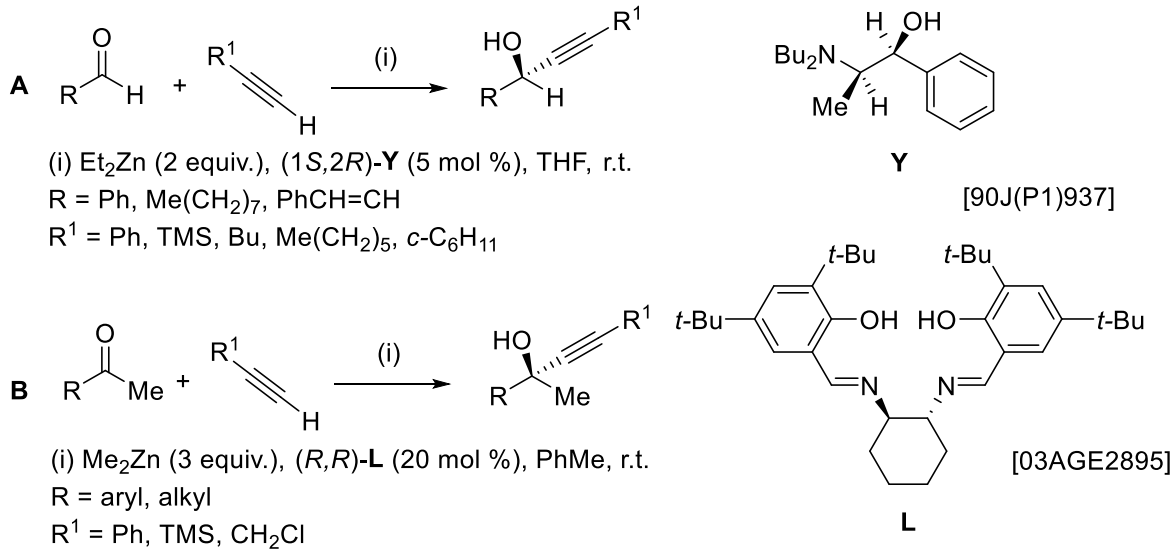
Many routes already exist to synthesise propargylic alcohols, such as 1-aryl- and 1,1-diaryl-prop-2-yn-1-ols. Generally these involve the reaction of aryl aldehydes or aryl ketones (possessing either an aryl or alkyl substituent) with an alkynyllithium or alkynylmagnesium halide. Various groups on the phenyl ring are tolerated in this reaction, including alkyl, amino, hydroxy, halogens and methoxy groups (Scheme 2.1) [13OL5222, 14OL5246, 14SC1924, 15AGE13711, 15OL5796, 17JOC11659, 18OL3202, 19AGE8898].



Scheme 2.1

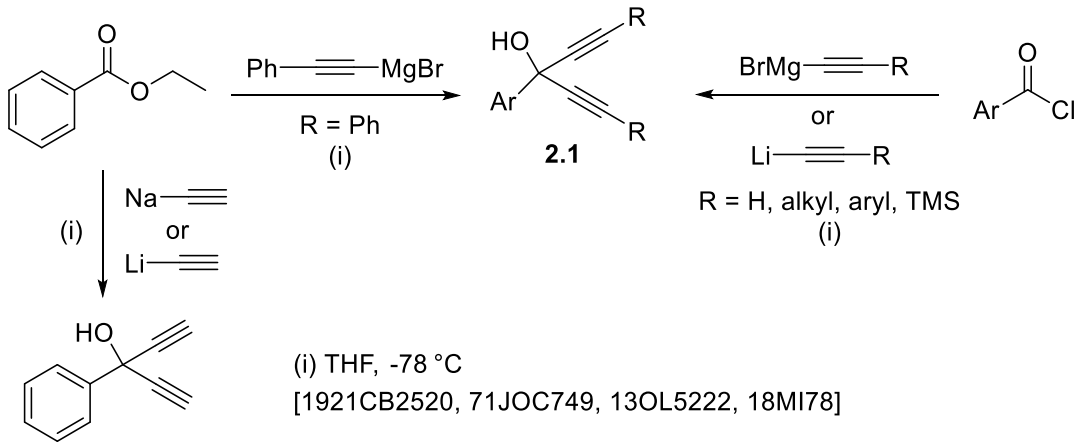
Other alkynyl organometallic reagents have been employed to generate secondary and tertiary propargylic alcohols [15MI201], for example alkynylzincs generated *in situ* from a dialkylzinc reagent (Me_2Zn or Et_2Zn). These reactions have been developed to provide enantioselective routes to alkynols, in the presence of a chiral auxiliary. Niwa and Soai varied the chiral auxiliary to optimise the *ee* and yields achieved, the β-amino alcohol ligand **Y** (**A**, Scheme 2.2) was found to be the most efficient with 99% yield and 34% *ee* (where R =

R^1 = Ph) [90J(P1)937]. Cozzi described additions of zinc alkynides to various ketones with the use of a modified salen ligand (**L**) affording enantioselectively tertiary alcohols (**B**, Scheme 2.2) [03AGE2895].



Scheme 2.2

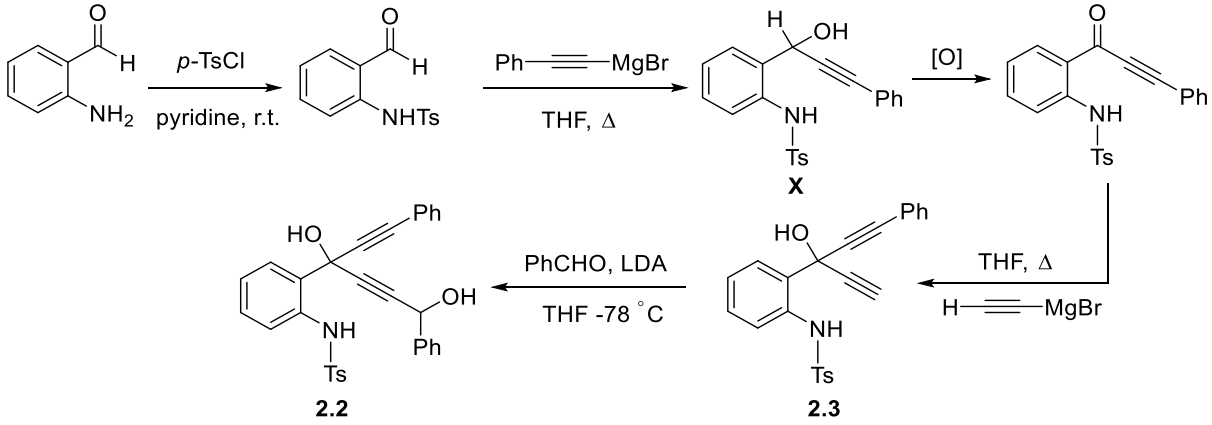
There are also numerous examples of dialkynols, some of which have been known for decades, of particular interest are 3-phenylpenta-1,4-diyn-3-ols **2.1**. Routes to these include the reaction of alkynyllithiums or alkynylmagnesium halides with aryl benzoates or aroyl chlorides (Scheme 2.3) [1921CB2520, 71JOC749, 13OL5222, 18MI78].



Scheme 2.3

However, to date there is only one example of a fully characterised 3-(2-*p*-tosylamidophenyl)penta-1,4-diyn-3-ol derivative **2.2** that was reported by Chan and co-workers (Scheme 2.4) [12CEJ6133]. No experimental details of how they obtained the 1-[(2-

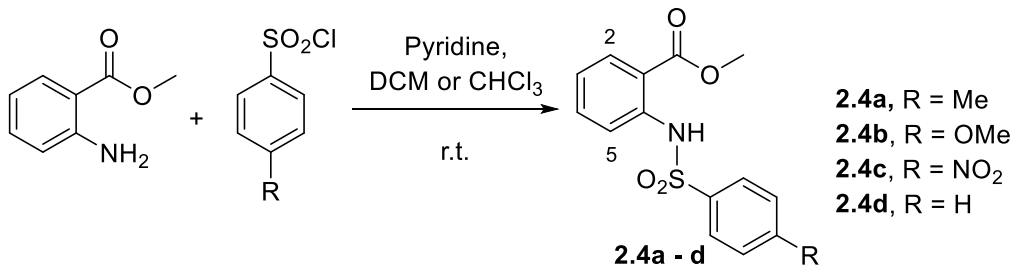
tosylamido)aryl]but-2-yne-1,4-diol **2.3** from **X** were provided. We envisage that alcohol **X** was oxidised to the ynone, followed by addition of ethynylmagnesium bromide to afford **2.3**.



Scheme 2.4

As described in Section 1.3, alkynes and to a lesser extent alkynols have been used extensively in electrophilic cyclisations to access a diverse array of heterocycles with a range of substituents. The use of alkynes and propargylamines to synthesise heterocycles has been reviewed [14COSII(4)412, 15SL1305, 16MI49730, 19AHC(127)1]. Therefore it is surprising that only one example of a 3-(2-*p*-tosylamidophenyl)penta-1,4-diyn-3-ol derivative has been described so far (**2.2**, Scheme 2.4). The latter was cyclised with a silver(I) salt to a 2,3-alkynylindole (Scheme 1.11) [12CEJ6133]. Previous work carried out by the group [16UP1] has shown that the synthesis of 3-(2-*p*-tosylamidophenyl)penta-1,4-diyn-3-ols can be carried out with ease.

Initially, the requisite 2-sulfonamido-benzoates were prepared by sulfonylation of methyl 2-aminobenzoate. Thus, a solution of the ester in DCM or $CHCl_3$ containing pyridine, was treated with the relevant sulfonyl chloride, and the mixture was stirred at room temperature overnight (Scheme 2.5). After an aqueous work up the products **2.4a** – **2.4d** (Table 2.1) were obtained in good to excellent yields, following recrystallisation from methanol. All compounds synthesised in this way were characterised by their IR, ^{1}H NMR spectra, and where appropriate, literature melting points.



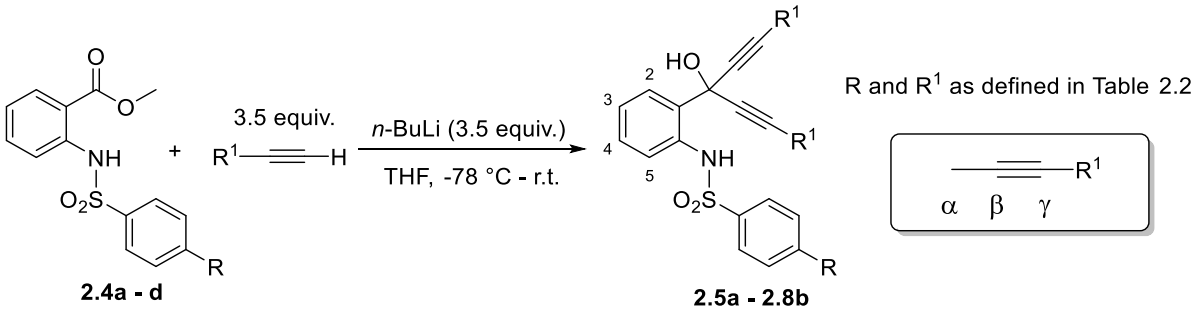
Scheme 2.5

Entry	R	Solvent	Ester	Yield (%)
1	Me	DCM	**2.4a**	81
2	OMe	$CHCl_3$	**2.4b**	62
3	NO_2	DCM	**2.4c**	71
4	H	DCM	**2.4d**	70

Table 2.1 Yields of esters **2.4a** – **2.4d**

Varying the nature of the R group on the phenylsulfonyl function will change the nucleophilicity of the sulfonamide nitrogen in **2.4**. The nitro group being electron withdrawing will render the sulfonamide less nucleophilic, and therefore cyclisations with this substrate were predicted to be slower than the others. In contrast the methoxy group, which is electron donating, should enhance the nucleophilicity of the nitrogen centre thus promoting a more efficient cyclisation when the alkyne is exposed to an electrophile.

With the sulfonamides **2.4** to hand, their reactivity towards alkynyllithiums to afford dialkynols was explored, to date only the phenyl and *n*-butyl substituted 4-methylphenyl sulfonamido compounds **2.5a** and **2.5c** (R^1 = Ph or C_4H_9) have been synthesised by the author [16UP1]. *n*-Butyllithium (3.5 equiv.) was added dropwise to a cold (-78 °C) solution of the appropriate acetylene (3.5 equiv.), to ensure complete reaction, in anhydrous THF. Excess alkynyllithium is needed to compensate for the deprotonation of the sulfonamide. A solution of the methyl 2-(arylsulfonamido)benzoate (1.0 equiv.) in anhydrous THF was added dropwise to the warm (-5 °C to 5 °C) solution of the alkynyllithium compound. After stirring for 1 h or until complete by TLC, the mixture was quenched with aqueous NH_4Cl and diluted with ethyl acetate (Scheme 2.6). Purification of crude products either by recrystallisation or by flash column chromatography afforded the corresponding dialkynols **2.5 – 2.8** in varying, generally high yields (Table 2.2).

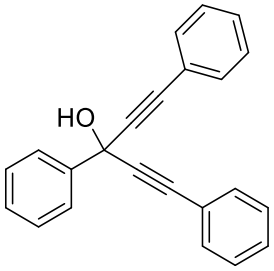


Scheme 2.6

Entry	Ester	R	R^1	Dialkynol	Yield (%)	Quaternary carbons δ_C (ppm)		
						α	β	γ
1	**2.4a**	Me	Ph	**2.5a**	80	66.27	87.01	86.87
2	**2.4a**	Me	C_3H_7	**2.5b**	78	65.36	87.79	79.40
3	**2.4a**	Me	4-$MeOC_6H_4$	**2.5c**	90	66.27	86.85	86.00
4	**2.4a**	Me	C_4H_9	**2.5d**	89	65.36	87.79	79.40
5	**2.4a**	Me	TMS	**2.5e**	39	65.33	102.21	92.62
6	**2.4a**	Me	CH_2OMe	**2.5f**	0	–	–	–
7[a]	**2.4a**	Me	Me	**2.5g**	16	65.40	83.56	78.31
8	**2.4a**	Me	OEt	**2.5h**	0	–	–	–
9	**2.4a**	Me	CH_2OH	**2.5i**	0	–	–	–
10	**2.4a**	Me	*t*-Bu	**2.5j**	79	64.98	95.54	78.00
11	**2.4a**	Me	$(CH_3)C=CH_2$	**2.5k**	65	65.89	87.88	85.92
12[b]	**2.4a**	Me	H	**2.5l**	0	–	–	–
13	**2.4b**	OMe	Ph	**2.6a**	70	66.27	87.09	86.82
14	**2.4b**	OMe	C_3H_7	**2.6b**	73	65.35	87.77	79.44
15	**2.4c**	NO_2	Ph	**2.7a**	10	67.53	92.19	82.23
16	**2.4c**	NO_2	C_3H_7	**2.7b**	11	64.96	86.19	80.18
17	**2.4d**	H	Ph	**2.8a**	65	66.28	86.96	86.94
18	**2.4d**	H	C_3H_7	**2.8b**	0	–	–	–

Table 2.2 Yields of dialkynols **2.5** – **2.8.** a = From 1-bromopropene and excess LDA, b = reaction with ethynylmagnesium bromide in warm (40 °C) THF

All of the dialkynol compounds **2.5 – 2.8** showed two characteristic signals in their ^{13}C NMR spectra (β, γ, Table 2.2) corresponding to the acetylenic carbons. These are similar to the shifts reported by Komatsu *et al.* for the dialkynol 1,3,5-triphenylpenta-1,4-diyn-3-ol **2.9**, in which the acetylenic carbons resonate at δ_C 89.1 (β) and 84.9 (γ) ppm and the quaternary benzylic **C**-OH carbon (α) resonated at δ_C 65.7 ppm [88TL5157]. The disappearance of the ester methyl protons in the ^1H NMR spectra further confirmed the formation of the dialkynols, as did the appearance of a singlet for the OH proton between δ_H 2.90 and 4.11 ppm.



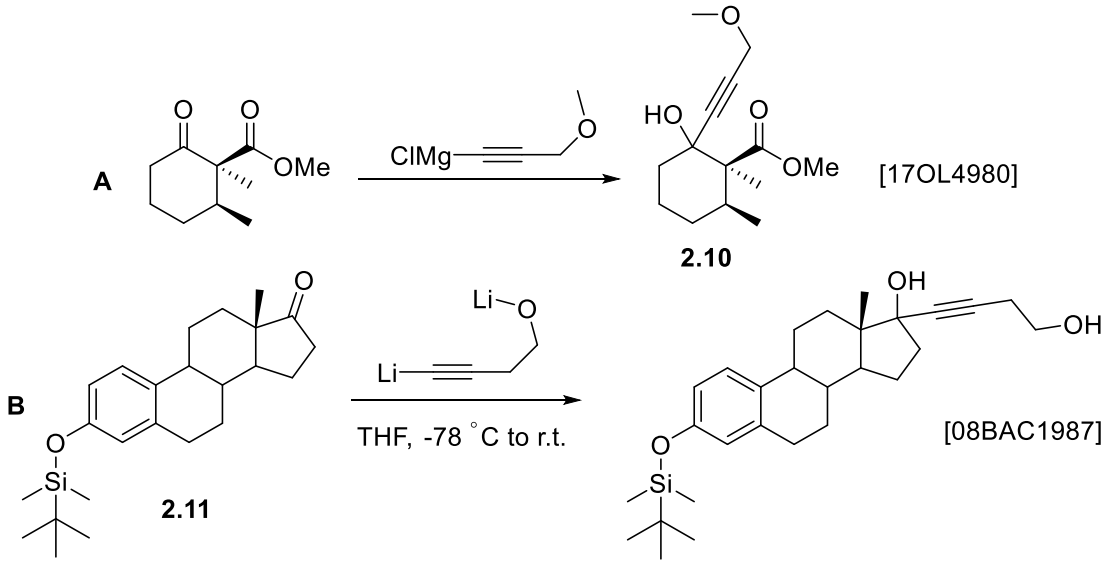
2.9

The nitrophenylsulfonamides (entries 15 and 16, Table 2.2) provided the poorest yields of products presumably due to side reactions of the nitro group with the organolithium reagent. Nitro arenes are known to undergo *ortho* lithiation, [82ACR300] other side reactions can occur also with Grignard reagents and nitro groups [12OL5618].

Attempts to synthesise the terminal alkyne analogue **2.5l** R^1 = H (entry 12, Table 2.2) involved addition of ethynylmagnesium bromide to **2.4a** in warm (40 °C) anhydrous THF followed by heating under reflux. Unfortunately, the crude material obtained following aqueous work-up was a complex mixture which afforded no identifiable products.

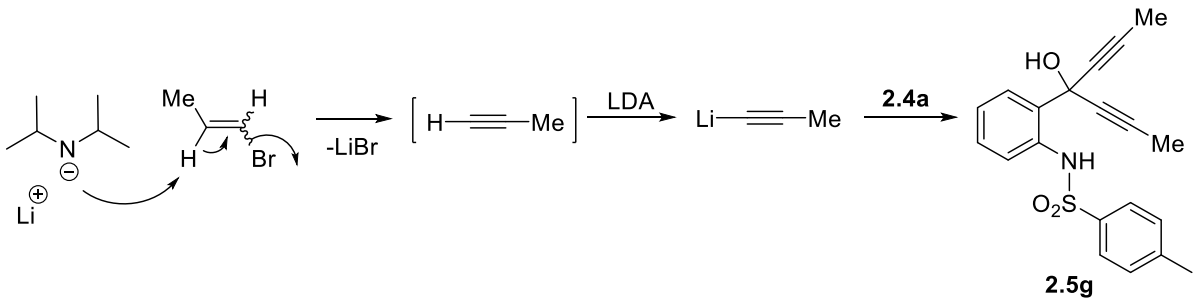
Compound **2.8b** (entry 18, Table 2.2) was shown by ^1H NMR to be approximately 50% pure, unfortunately attempts at purification were thwarted, as it co-eluted with unreacted starting material. Methyl 2-(*p*-tosylamido)benzoate **2.4a** was reacted with $LiC{\equiv}CCH_2OMe$, derived from methyl propargyl ether or with the dianion $LiC{\equiv}CCH_2OLi$ derived from propargyl alcohol (entries 6 and 9 respectively, Table 2.2). Unfortunately, both acetylides failed to react and in each case only starting material was recovered. Evidently double addition of these acetylides to the ester function was not favoured. Formation of the 2-hydroxy-2-(3-methoxyprop-1-yn-1-yl)-cyclohexane-1-carboxylate **2.10** (**A**, Scheme 2.7) by preferential addition of the (3-methoxyprop-1-yn-1-yl)magnesium chloride to the ketone

moiety has been reported [17OL4980]. In a similar manner the dianion LiC≡CCH$_2$OLi reacted smoothly with the steroidal ketone **2.11** (**B**, Scheme 2.7) [08BAC1987].



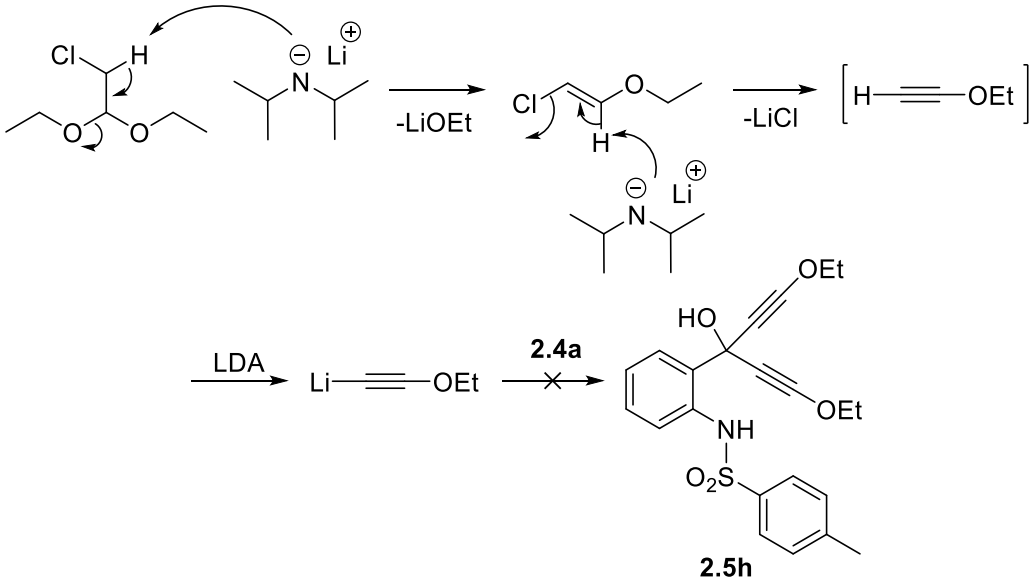
Scheme 2.7

Prop-1-yn-1-yllithium was generated *in situ* from treatment of 1-bromopropene with excess LDA in THF [92SC2997], as shown in Scheme 2.8. Addition of the ester **2.4a** to the propynyllitium solution afforded dialkynol **2.5g** in only 16% yield (entry 7, Table 2.2), this is the lowest yield achieved from acetylide addition to ester **2.4a** (Table 2.2).



Scheme 2.8

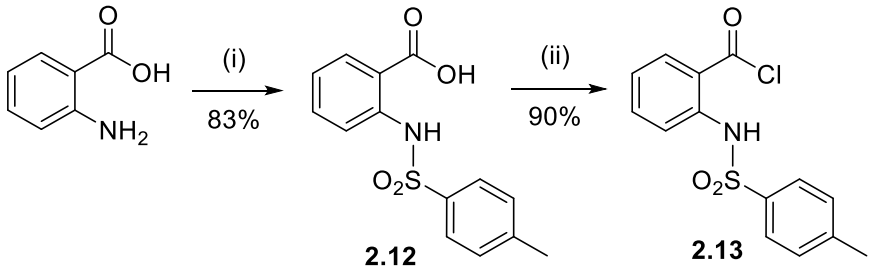
Ethoxyethynyllithium generated *in situ* from chloroacetaldehyde diethyl acetal and LDA (Scheme 2.9) [87JOC2332, 05MI254], also failed to provide the corresponding ethoxyalkynol **2.5h** (entry 8, Table 2.2). Only a complex black mixture was obtained from the reaction, this could have been due to the unfavourable double addition to an ester moiety or the degradation of the acetylene.



Scheme 2.9

Regrettably, lithiation of commercially available ethoxyacetylene (solution in hexanes) was also unsuccessful in affording the desired alkynol **2.5h**. Many reactions have been reported with effective addition of ethoxyacetylene to ketones and aldehydes [06JA15106, 07JOC9736, 08JA13528, 12EJO5803, 12SL1675, 14AGE10747, 14OL1176].

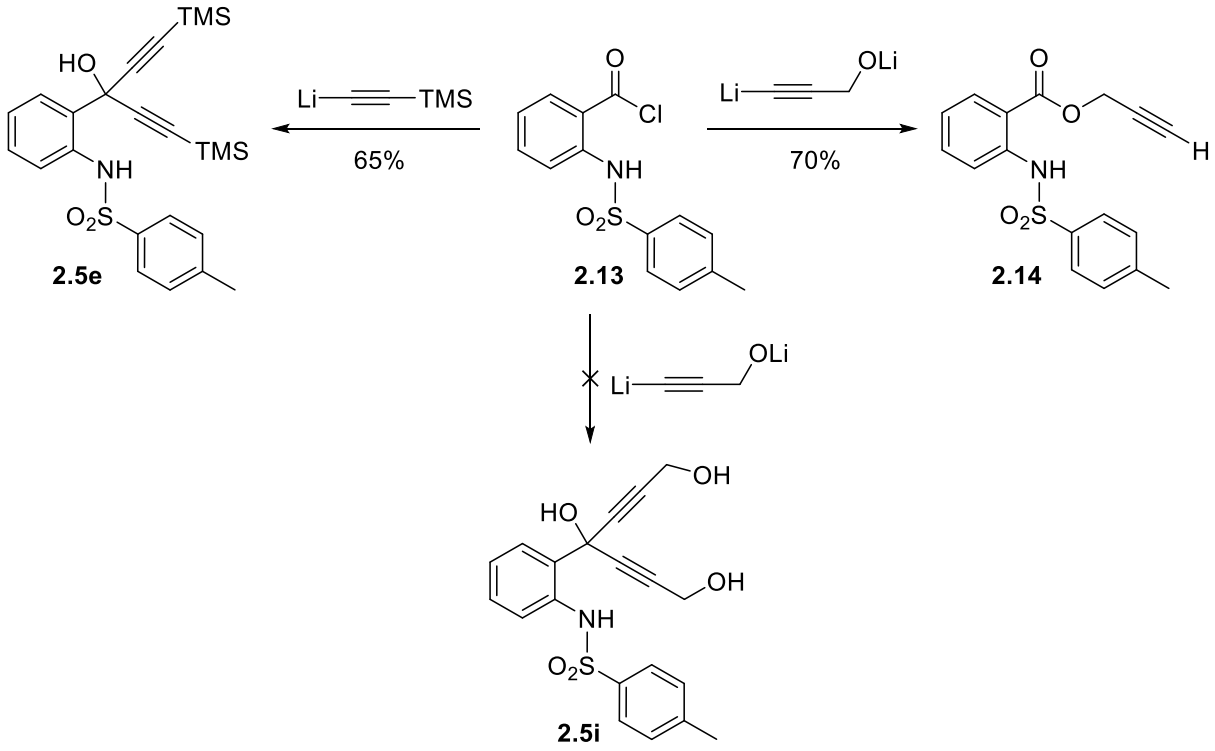
Acyl chlorides are more reactive than esters towards nucleophiles due to the electron withdrawing chlorine, which in-turn makes the sp^2 carbon of the carbonyl group more electrophilic. Therefore a suitable acyl chloride may provide an alternative starting material for the dialkynols which could not be accessed from **2.4a**. 2-(Tosylamido)benzoyl chloride **2.13** was synthesised from *N*-tosylanthranilic acid as shown in Scheme 2.10 [11T5564].



(i) TsCl, H_2O, NaOH (1 equiv.), r.t., 24 h
(ii) anhydrous DCM, $(COCl)_2$ (1.5 equiv.), cat. DMF, 2 h

Scheme 2.10

2-(Tosylamido)benzoyl chloride was used in the reactions that had either failed or had provided some of the lower yielding products from ester **2.4a**. Thus, reaction of the benzoyl chloride **2.13** with excess lithium (trimethylsilyl)acetylide provided dialkynol **2.5e** in a substantially better yield (65%, Scheme 2.11) than from methyl *N*-tosylanthranilate **2.4a** (39%, entry 5, Table 2.2). It was thought that the acid chloride would react smoothly with the dianion LiC≡CCH$_2$OLi, derived from propargyl alcohol at the terminal carbon anion to afford the desired dialkynol **2.5i**. However, the only product obtained from the reaction was readily identified as propynyl *N*-tosylanthranilate **2.14** (Scheme 2.11), which is a novel compound.



Scheme 2.11

The ^{13}C NMR signals of **2.14** showed the presence of an ester carbonyl rather than the quaternary sp^3 centre from a tertiary alcohol. Hradil previously reported the propargyl ester **2.15** (Figure 2.1), prepared from isatoic anhydride and HC≡CHCH$_2$ONa, for which the NMR (^{1}H and ^{13}C) resonances are similar to these observed for **2.14** [13JHC528].

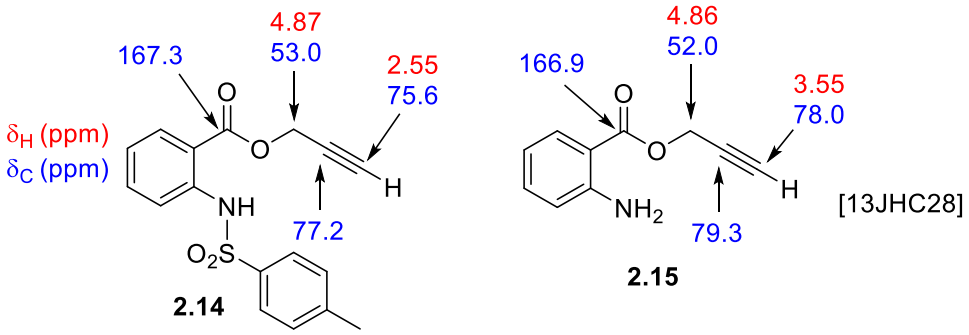
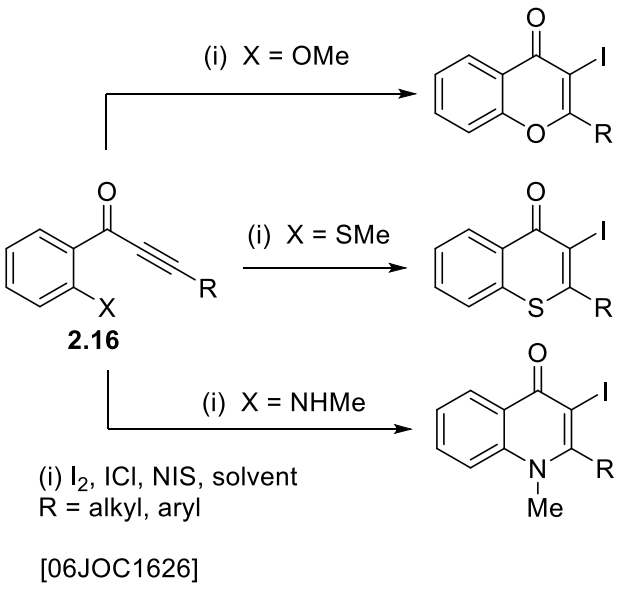


Figure 2.1 NMR (^{1}H and ^{13}C) comparison of **2.14** ($CDCl_3$) and **2.15** (DMSO-d_6)

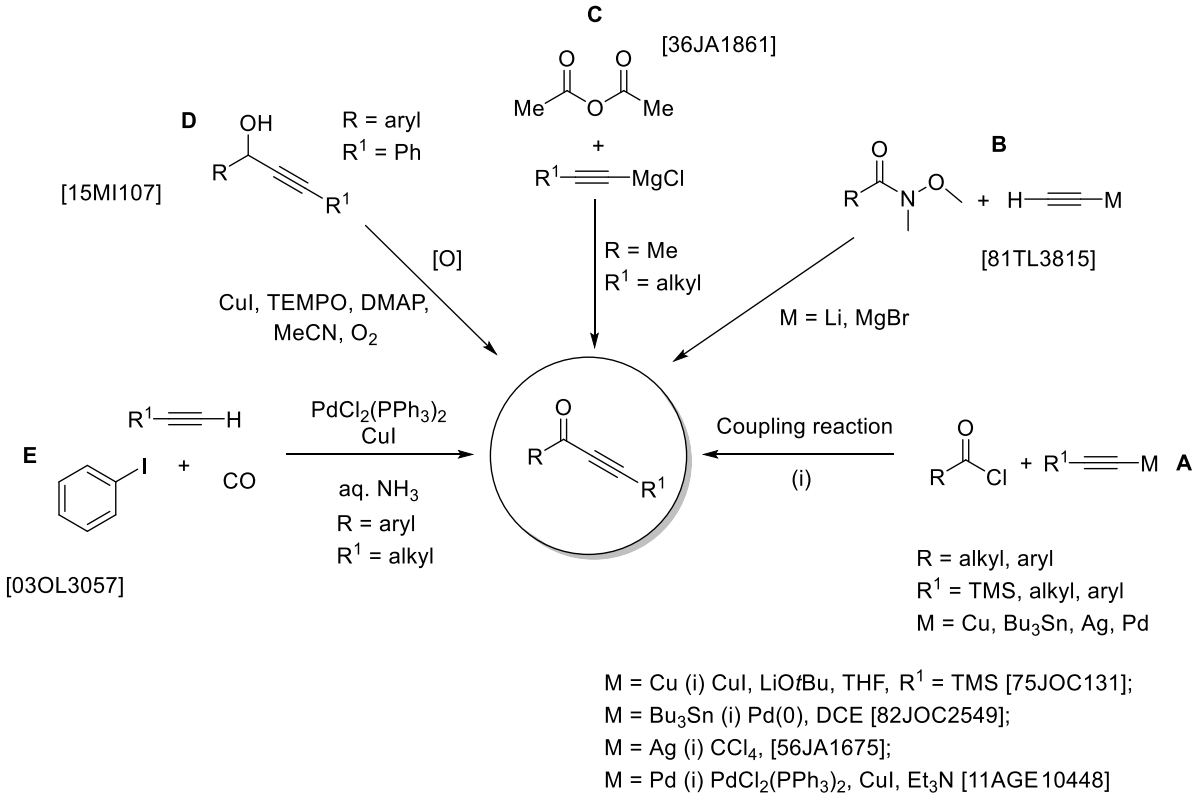
Ynones exemplified by structure **2.16** provide an interesting set of compounds, as they have been shown to cyclise in the presence of an iodine electrophile. Larock demonstrated that 1-(2-methoxyphenyl)prop-2-yn-1-ones having either a 3-alkyl- or a 3-aryl- substituent cyclised easily to 3-iodochromones with ICl to give mostly high yields (44 – 99%) (Scheme 2.12). They also reported the synthesis of 3-iodothiochromones and 3-iodoquinolin-4-ones *via* this procedure, again in high yields (Scheme 2.12) [06JOC1626].



Scheme 2.12

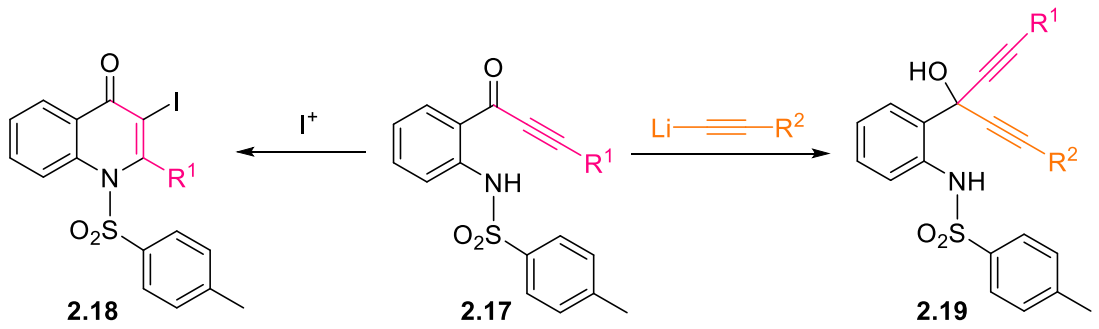
There are a plethora of routes to synthesise ynones and some of the more useful pathways are shown in Scheme 2.13 [19CRV11110]. A large number of examples provided are by the C-H bond insertion of a metal to a terminal alkyne and the subsequent coupling reaction with an acyl chloride (**A**, Scheme 2.13) [56JA1675, 82JOC2549, 75JOC131, 11AGE10448]. Other examples include; organometallic (alkynylmetal) addition to a Weinreb amide (**B**,

Scheme 2.13) [81TL3815], alkynyl Grignard reagent addition to an acid anhydride (**C**, Scheme 2.13) [36JA1861], oxidation of a secondary propargyl alcohol (**D**, Scheme 2.13) [15MI107] or the Pd-mediated carbonylative coupling of a terminal acetylene and an aryl halide (**E**, Scheme 2.13) [03OL3057].



Scheme 2.13

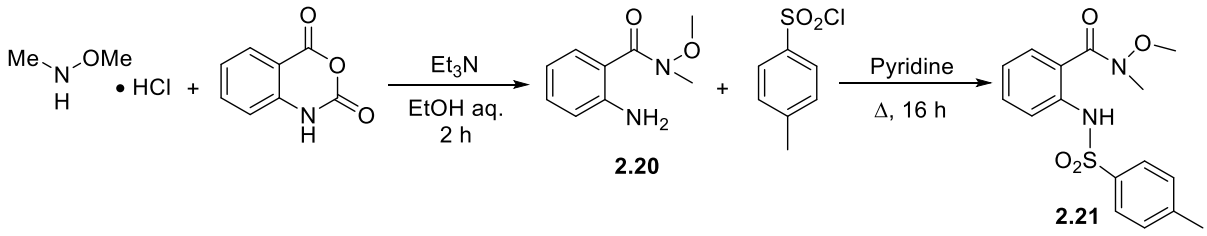
Cyclisations of 1-[2-tosylamidophenyl]propynones **2.17** could offer a simple route to synthesise 3-iodo-1-tosyl-4-quinolones **2.18** of which there are currently no examples. Furthermore, it was envisaged that addition of a lithium acetylide would provide an entry to access unsymmetrical dialkynols **2.19**, Scheme 2.14.



Scheme 2.14

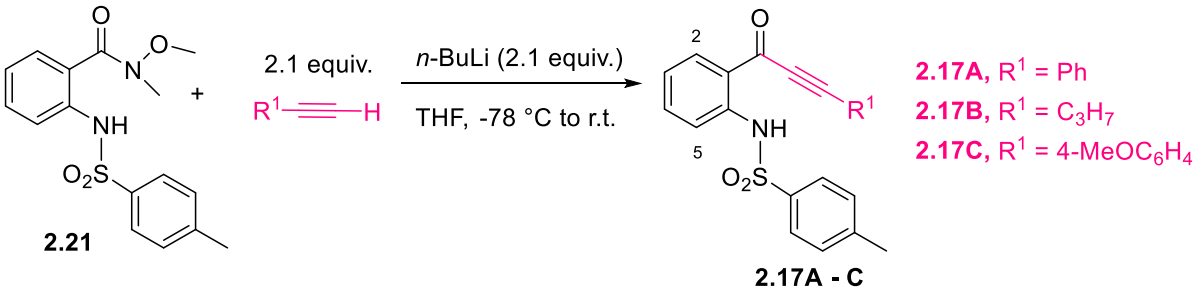
Initially access to the ynones **2.17** utilised the Weinreb amide **2.20** (2-amino-*N*-methoxy-*N*-methylbenzamide) that was synthesised by acylation of *N,O*-dimethylhydroxylamine with isatoic anhydride in aqueous EtOH under basic conditions. Following work-up, flash column chromatography provided the Weinreb amide **2.20** in 50% yield (Scheme 2.15) [14CC12293].

The ^{1}H NMR spectrum of **2.20** showed the appearance of two singlets corresponding to the methyl protons, indicating that isatoic anhydride unit was no longer intact. Subsequent *N*-sulfonylation of the Weinreb amide (**2.20**) was accomplished by treatment with TsCl in refluxing pyridine (Scheme 2.15). Following an acidic aqueous workup, the crude material was purified by flash column chromatography and trituration of the resulting oil with ether to afford the tosylated amide **2.21** in 81% yield [16JOC2930].



Scheme 2.15

The 1-arylpropynones **2.17** were synthesised simply by treatment of Weinreb amide **2.21** with an excess of alkynyllithium in THF at -78 °C to 0 °C for 1 h (Scheme 2.16). After this time the mixture was quenched with aqueous NH_4Cl. Isolation *via* EtOAc gave an orange oil which crystallised on trituration with ether. This crude product was washed with cold ether to afford the compounds in Table 2.3.



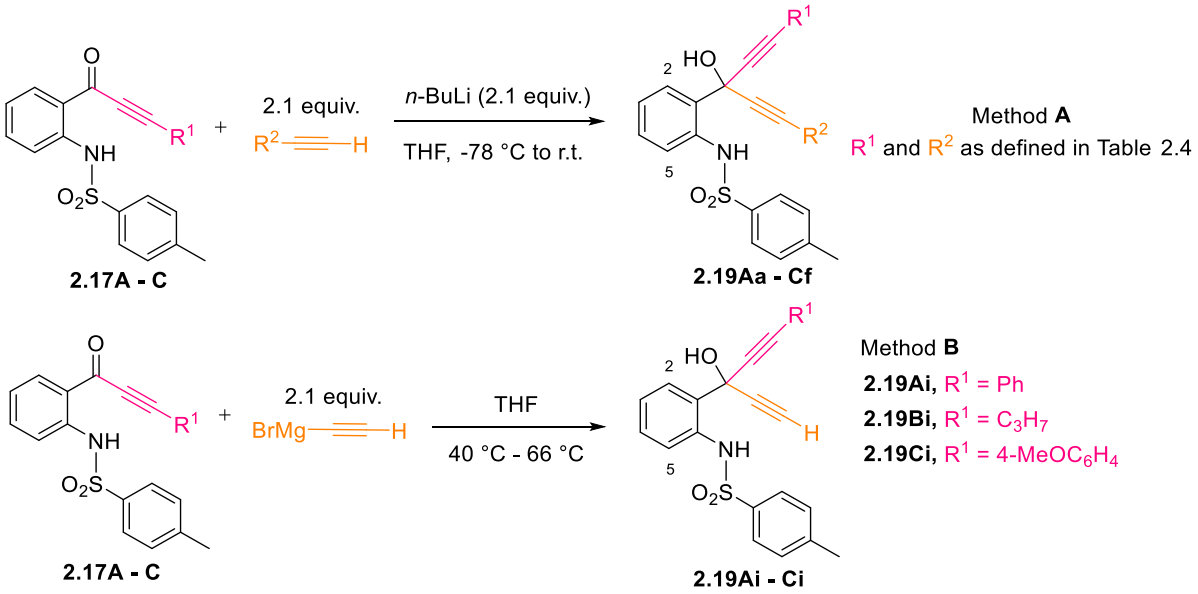
Scheme 2.16

Entry	R^1	Ynone	Yield (%)
1	Ph	**2.17A**	55
2	C_3H_7	**2.17B**	66
3	4-$MeOC_6H_4$	**2.17C**	66

Table 2.3 Yields of ynones **2.17**

The ^{1}H NMR spectra of ynones **2.17** matched those reported by Ramasastry *et al.* [16AGE7737]. The ynone R^1 = C_3H_7 (**2.17B**) is a novel compound and so was further confirmed by HRMS, that exhibited a molecular ion $[M+H]^+$ at *m/z* 342.1148 corresponding to $C_{19}H_{19}NO_3S$.

1-(2-Tosylamidophenyl)propynones **2.17** were the primary starting materials for the unsymmetrical dialkynols (**2.19**). The latter were obtained by two methods with the majority being synthesised by simple treatment with an excess of an alkynyllithium in THF for 1 h (Method **A**, Scheme 2.17). After this time the mixture was quenched with aqueous NH_4Cl. Isolation *via* EtOAc gave the crude product which was purified either by recrystallisation or by flash column chromatography, to afford the novel compounds in Table 2.4 in generally high yields. Excess ethynylmagnesium bromide (0.5 M in THF) was added to a warm solution of **2.19** in anhydrous THF and refluxed until complete by TLC (Method **B**, Scheme 2.17). After this time the mixture was allowed to cool and quenched with aqueous NH_4Cl, isolation *via* EtOAc gave the crude product, which was purified by flash column chromatography, to afford the novel compounds in Table 2.4



Scheme 2.17

Entry	Ynone	R^1	R^2	Method	Unsymmetrical dialkynol	Yield (%)
1	**2.17A**	Ph	C_3H_7	**A**	**2.19Ab**	86
2	**2.17A**	Ph	4-$MeOC_6H_4$	**A**	**2.19Ac**	86
3	**2.17A**	Ph	CH_2OMe	**A**	**2.19Af**	73
4[a]	**2.17A**	Ph	Me	**A**	**2.19Ag**	28
5	**2.17A**	Ph	*t*-Bu	**A**	**2.19Aj**	88
6	**2.17A**	Ph	$(CH_3)C=CH_2$	**A**	**2.19Ak**	76
7	**2.17A**	Ph	H	**B**	**2.19Ai**	65
8	**2.17B**	C_3H_7	H	**B**	**2.19Bi**	64
9	**2.17C**	4-$MeOC_6H_4$	C_3H_7	**A**	**2.19Cb**	74
10	**2.17C**	4-$MeOC_6H_4$	CH_2OMe	**A**	**2.19Cf**	73
11	**2.17C**	4-$MeOC_6H_4$	H	**B**	**2.19Ci**	64

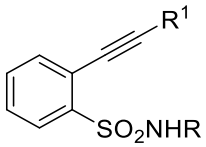
Table 2.4 Yields of unsymmetrical dialkynols **2.19.** a = From 2-bromopropene and excess LDA

All the compounds **2.19** (Table 2.4) exhibited four carbon signals in the range δ_C 60 – 89 ppm corresponding to the acetylenic carbons and the quaternary **C**-OH signal between δ_C 65 – 66 ppm. Of particular note was that some of the acetylides which did not react with the ester **2.4a** added smoothly to the ynones **2.17** (entry 3, 7, 8, 10 and 11, Table 2.4); (3-

methoxyprop-1-yn-1-yl)lithium (entry 3 and 10 Table 2.4) and ethynylmagnsium bromide (entry 7, 8, and 11 Table 2.4) provided good yields of products. No doubt smooth addition of the acetylide and Grignard reagent was facilitated by the less conjugated, less hindered carbonyl group in the ynone **2.17** compared to that in the ester **2.4a**. The ready formation of **2.19** indicated that double addition and/or addition to an ester, of these acetylides, was unfavourable.

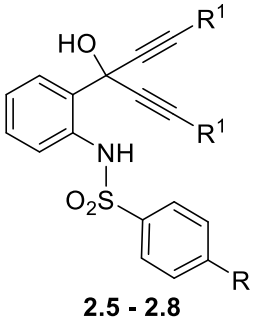
2.2 3-[2-(Sulfamoyl)phenyl]penta-1,4-diyn-3-ols

To date there are few aryl (di)alkynols in which the aryl ring is substituted with a primary, secondary or tertiary sulfamoyl group i.e. $-SO_2NH_2$, $-SO_2NHR$ or $-SO_2NR_2$ respectively. The majority of known compounds have the alkyne moiety bonded to the same aromatic ring as the sulfonamide function e.g. **2.22** (*via* $C_{sp} - C_{sp^2}$ bond), rather than as a tertiary propargylic alcohol function (*via* $C_{sp} - C_{sp^3} - C_{sp^2}$ linkages) e.g. **2.23**.



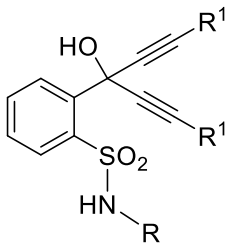
2.22

Compounds of the general structure **2.5** – **2.8** represent *N*-linked sulfonamides as described previously (Section 2.1). Isomeric to these are the *S*-linked sulfonamides **2.23** (2-sulfamoylphenyl dialkynols) which will be referred to as reversed sulfonamides (in some cases) throughout.



2.5 - 2.8

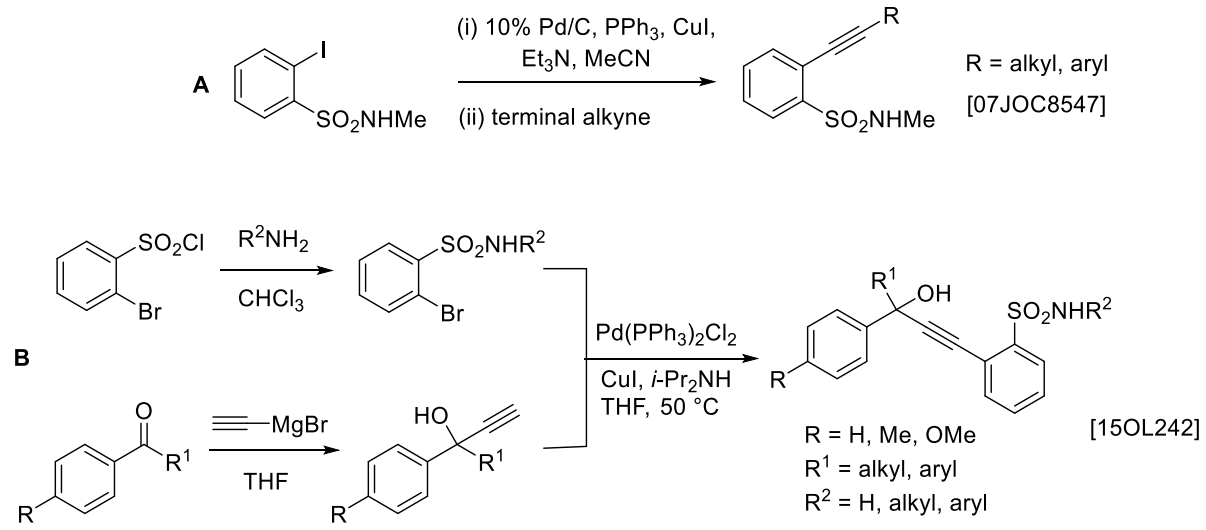
N-linked sulfonamides
referred to as **sulfonamides**



2.23

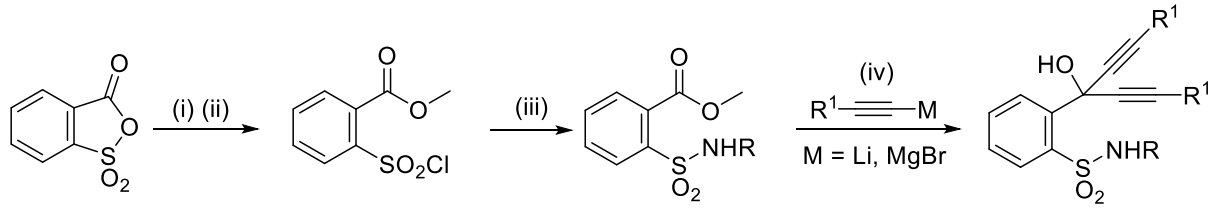
S-linked sulfonamides
referred to herein as **reversed sulfonamides**

Pal *et al.* employed a Sonogashira cross-coupling to 2-iodo-*N*-methylbenzenesulfonamides, to give a range of 2-alkynyl benzenesulfonamides in high yields **A**, Scheme 2.18 [07JOC8547]. Wang and co-workers also utilised a Sonogashira coupling to synthesise a range of propargylic alcohols **B**, Scheme 2.18 [15OL242].



Scheme 2.18

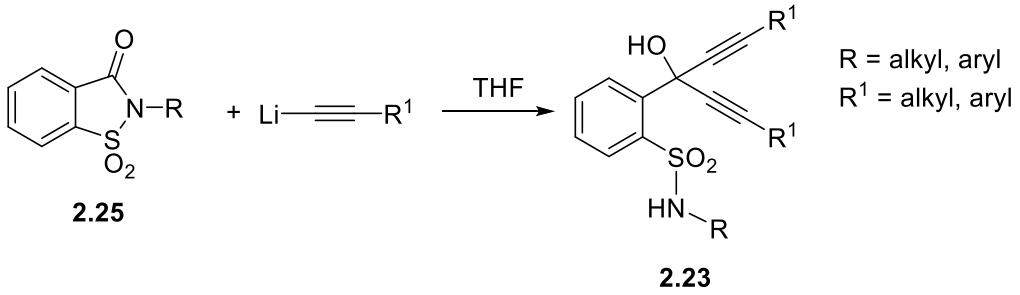
2-Sulfamoylphenyl dialkynols could be potentially synthesised by the ring opening of *o*-sulfobenzoic anhydride with MeOH and subsequent halogenation with PCl_5 [06JA11693] to obtain methyl 2-(chlorosulfonyl) benzoate. Subsequent reaction with an aromatic amine and DMAP would afford ester **2.24** [WO9912916]. Nucleophilic addition to the ester moiety would afford the target dialkynol **2.23** (Scheme 2.19).



(i) MeOH, Δ; (ii) PCl_5, 95 °C; [06JA11693] (iii) RNH_2, Pyridine, DMAP, r.t. [WO9912916];
(iv) H—≡—R^1, *n*-BuLi (3.5 equiv.), THF, -78 °C or EtMgBr in THF

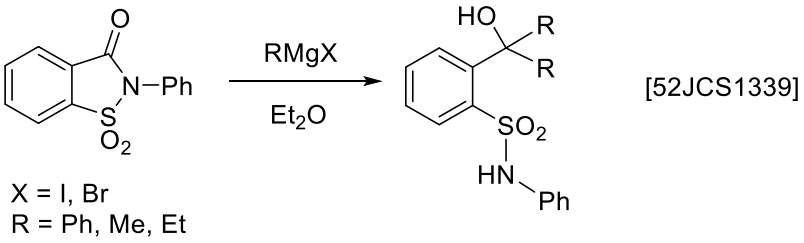
Scheme 2.19

A drawback to this approach is the number of steps to provide dialkynol **2.23**, as well as the cost of *o*-sulfobenzoic anhydride (£10.00 per g, Fluorochem). The anhydride can also be synthesised from saccharin, *via* hydrolysis-dehydration with H_2SO_4 [11SC1101]. However this process will add an extra step in the sequence. A more direct route to the corresponding 1,5-disubstituted-3-[2-(*N*-arlysulfamoyl)phenyl]penta-1,4-diyn-3-ols **2.23** would involve addition of an alkynyllithium to an *N*-substituted saccharin derivative **2.25** (Scheme 2.20).



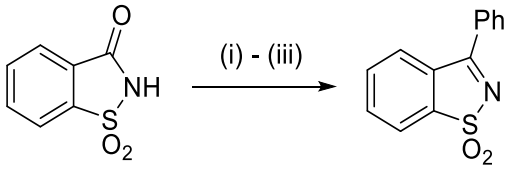
Scheme 2.20

Surprisingly the reaction of organometallic reagents to saccharin derivatives has received almost no attention [03T7445, 10CME65]. The only report for many decades related to the reaction of *N*-phenylsaccharin with Grignard reagents (MeMgI, EtMgBr and PhMgBr) to afford the tertiary alcohol, from an addition, ring cleavage addition sequence as shown in Scheme 2.21 [52JCS1339].



Scheme 2.21

However, more recently, the reaction of saccharin with excess PhMgBr has been reported. The crude reaction mixture was subjected to treatment with acid (TsOH) to afford the cyclodehydration product, 3-phenyl-1,2-benzoisothiazole 1,1-dioxide (Scheme 2.22) [19ASC4495].



[19ASC4495]

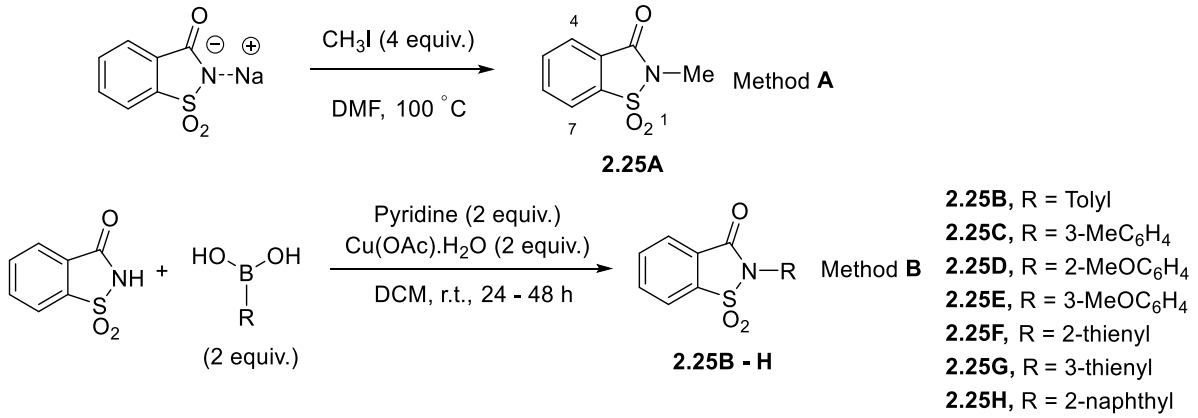
(i) PhMgBr (2.0 equiv.), THF, 0 °C to r.t.
(ii) aq. NH_4Cl
(iii) TsOH, PhMe, Δ

Scheme 2.22

Earlier work by Oppolzer described the preparation of 3-alkyl-1,2-benzisothiazole 1,1-dioxides from reaction of saccharin with either methyllithium [90TL4117] or with *t*-BuLi [91TL4893] in THF at low temperature. No tertiary alcohols were observed from these reactions.

Initially a series of substituted saccharins were synthesised by either *N*-alkylation or *N*-arylation. For example, iodomethane was added dropwise to a solution of sodium saccharin in DMF, the mixture was stirred at 100 °C overnight (Method **A**, Scheme 2.23). After this time the reaction mixture was allowed to cool, quenched with water and the resultant precipitate was collected to afford **2.25A** in a 63% yield [15CEJ5532].

For *N*-aryl saccharins a Chan-Lam-(Evans) coupling of saccharin with arylboronic acids in the presence of $Cu(OAc)_2$ and pyridine (Method **B**, Scheme 2.23) was employed to afford **2.25B – 2.25H** (Table 2.5) in variable yields.



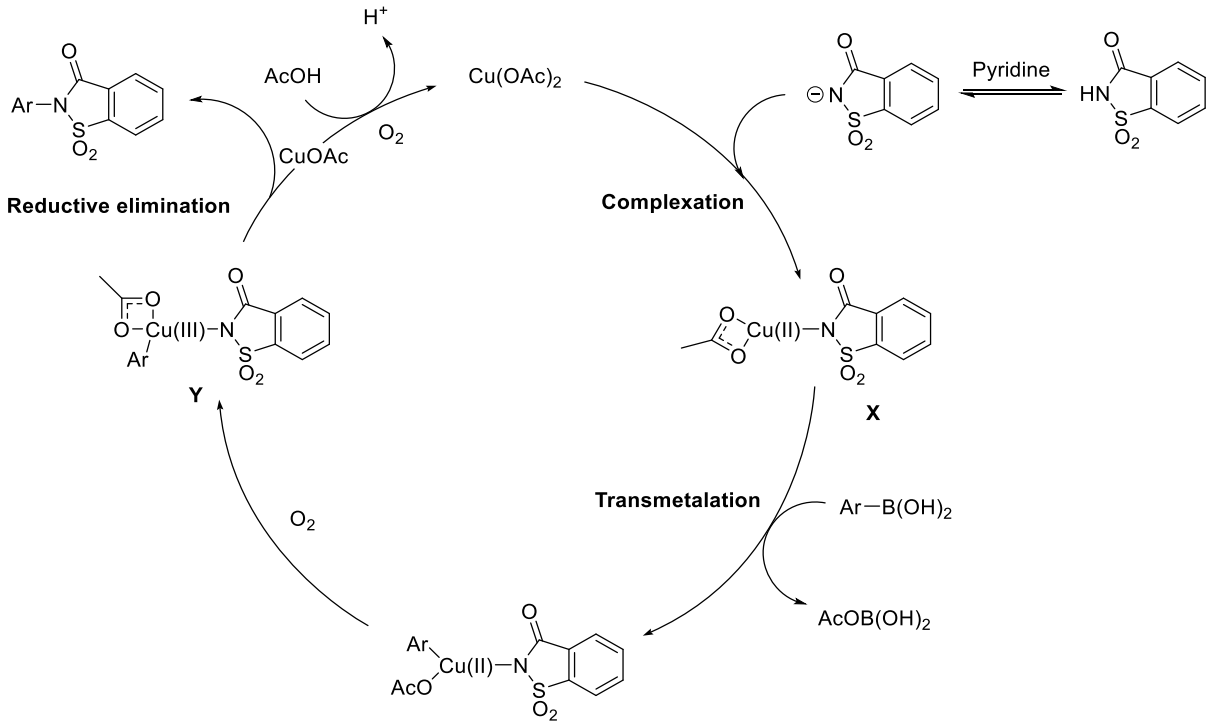
Scheme 2.23

Entry	Method	R	Product	Yield (%)
1	A	Me	**2.25A**	63
2	B	Tolyl	**2.25B**	95
3	B	3-MeC_6H_4	**2.25C**	59
4	B	2-$MeOC_6H_4$	**2.25D**	48
5	B	3-$MeOC_6H_4$	**2.25E**	82
6	B	2-thienyl	**2.25F**	0
7	B	3-thienyl	**2.25G**	65
8	B	2-naphthyl	**2.25H**	87

Table 2.5 Yields of *N*-substituted saccharins **2.25A – H**

A proposed catalytic pathway for the Chan-Lam-(Evans) coupling reaction of saccharin and arylboronic acids is shown in Scheme 2.24 [17JA4769, 17OBC801]. First saccharin is deprotonated by pyridine, followed by complexation with the Cu(II) to give species **X**. Subsequent transmetallation with the arylboronic acid leads to the transfer of the aryl group from the boronic acid to the Cu(II) species and concomitant oxidation generated the copper(III) intermediate (**Y**). Reductive elimination of the *N*-substituted saccharin and sequential oxidation and ligand exchange regenerates the $Cu(OAc)_2$.

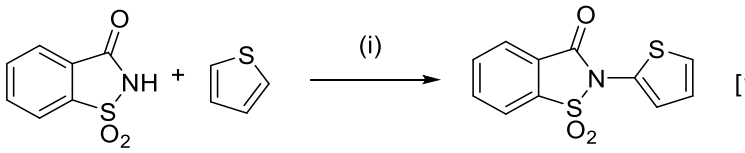
The pathway depicted in Scheme 2.24 is based upon the stabilities of intermediates in related Chan-Lam reactions as predicted by DFT calculations [17OBC801].



Scheme 2.24

The constitution of all of the *N*-substituted saccharins **2.25** were confirmed by comparison of their m.p., ^{1}H and ^{13}C NMR spectra to those in the literature [15CEJ5532, 17SL2000]. The *N*-substituted saccharins **2.25** are all known compounds, with **2.25A**, **B** and **E – H** (entries 1, 2, 5, 7 and 8, Table 2.5) being synthesised *via* a Chan-Lam coupling of the relevant aryl boronic acid and saccharin [15CEJ5532]. However, compounds **2.25C – D** (entries 3 and 4, Table 2.5) were prepared previously by a Pd-catalysed carbonylative cyclisation of *N*-aryl-2-iodobenzenesulfonamides [17SL2000]. Use of the Chan-Lam coupling therefore represents a new route to these *N*-aryl saccharins.

Attempted *N*-arylation of saccharin with thiophene-2-boronic acid gave none of the desired product **2.25F** (entry 6, Table 2.5). No doubt this failure stems from the propensity of thiophene-2-boronic acid to undergo protodeboronation under a variety of conditions [10JA14073]. On the other hand, coupling of thiophene-3-boronic acid to saccharin afforded **2.25G** in 65% yield with a m.p. 170 – 172 °C (literature m.p. 173 – 175 °C) [15CEJ5332]. 2-(2-Thienyl)saccharin **2.25F** is a known compound but was prepared *via* an oxidative (Selectfluor) copper-catalysed (CuCl) amination reaction of thiophene with saccharin Scheme 2.25 [15MI1354].

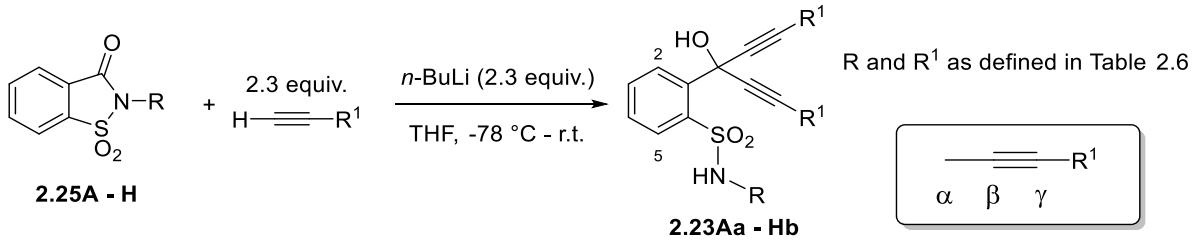


[15MI1354]

(i) CuCl (10 mol %), 1,10-phenanthroline, Selectfluor (2.0 equiv.), K_2CO_3, $MeNO_3$, 90 °C

Scheme 2.25

With a series of *N*-substituted saccharins (**2.25**) now available their reactivity towards a variety of alkynyllithiums was investigated. Thus, *n*-butyllithium (2.3 equiv.) was added slowly to a cold (-78 °C) solution of the appropriate acetylene (2.3 equiv.) in anhydrous THF. A solution of the saccharin derivative **2.25** (1.0 equiv.) in anhydrous THF was added slowly to the cold (-5 °C to 5 °C) lithium acetylide solution. After stirring for 1 h the mixture was then quenched with aqueous NH_4Cl and diluted with EtOAc (Scheme 2.26). Purification of crude products either by recrystallisation or by flash column chromatography afforded the novel compounds **2.23Aa – Hb** (Table 2.6) in varying yields.

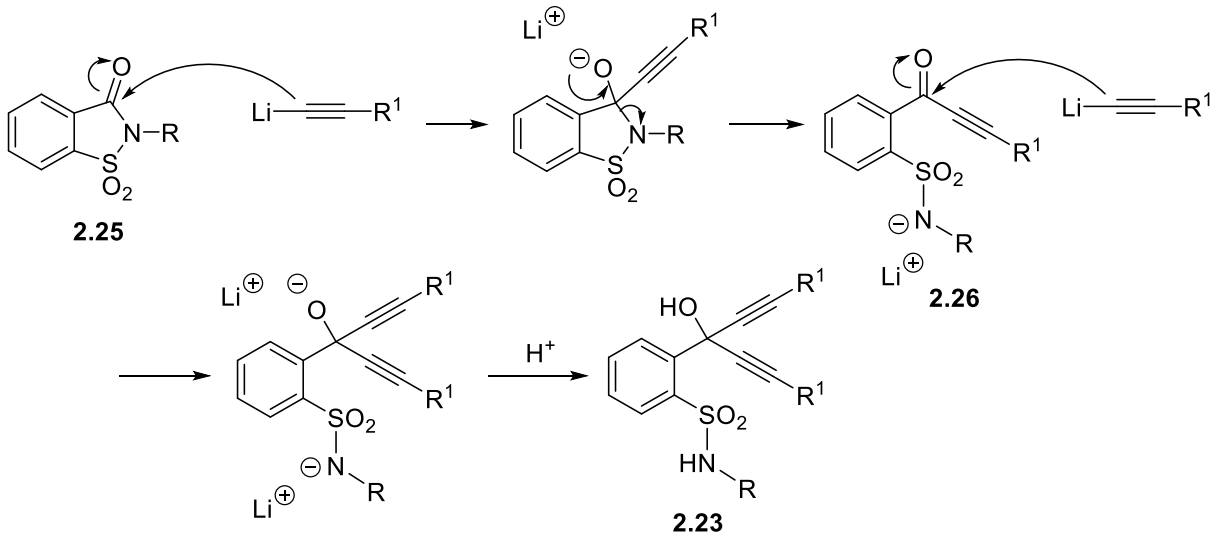


Scheme 2.26

Entry	Saccharin Derivative	R	R^1	Dialkynol	Yield (%)	Quaternary carbons δ_c (ppm)		
						α	β	γ
1	**2.25A**	Me	Ph	**2.23Aa**	98	67.02	88.54	86.61
2	**2.25A**	Me	C_3H_7	**2.23Ab**	97	66.29	87.23	81.04
3	**2.25A**	Me	TMS	**2.23Ae**	68	66.30	92.14	87.10
4	**2.25B**	Tolyl	Ph	**2.23Ba**	80	67.05	88.80	86.92
5	**2.25B**	Tolyl	C_3H_7	**2.23Bb**	76	66.28	87.62	81.44
6	**2.25B**	Tolyl	4-$MeOC_6H_4$	**2.23Bc**	93	67.06	87.78	86.92
7	**2.25B**	Tolyl	TMS	**2.23Be**	63	66.83	105.25	93.09
8	**2.25B**	Tolyl	CH_2OMe	**2.23Bf**	66	65.72	85.84	82.84
9	**2.25B**	Tolyl	OEt	**2.23Bh**	0	–	–	–
10	**2.25B**	Tolyl	CH_2OH	**2.23Bi**	0	–	–	–
11	**2.25C**	3-MeC_6H_4	Ph	**2.23Ca**	94	67.08	88.82	86.90
12	**2.25C**	3-MeC_6H_4	C_3H_7	**2.23Cb**	84	66.31	87.59	81.46
13	**2.25D**	2-$MeOC_6H_4$	Ph	**2.23Da**	59	66.41	89.63	85.31
14	**2.25D**	2-$MeOC_6H_4$	C_3H_7	**2.23Db**	74	66.15	87.17	80.88
15	**2.25D**	2-$MeOC_6H_4$	TMS	**2.23De**	62	66.32	104.00	91.87
16	**2.25E**	3-$MeOC_6H_4$	Ph	**2.23Ea**	84	67.08	88.78	86.90
17	**2.25E**	3-$MeOC_6H_4$	C_3H_7	**2.23Eb**	74	66.33	87.62	81.43
18	**2.25G**	3-thienyl	Ph	**2.23Ga**	42	67.05	88.66	86.87
19	**2.25G**	3-thienyl	C_3H_7	**2.23Gb**	69	66.31	87.57	81.30
20	**2.25H**	2-naphthyl	Ph	**2.23Ha**	98	67.16	88.85	86.96
21	**2.25H**	2-naphthyl	C_3H_7	**2.23Hb**	89	66.40	87.68	81.40

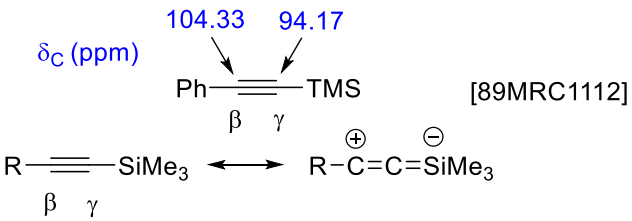
Table 2.6 Yields of reversed sulfonamide dialkynols **2.23**

The formation of the reversed sulfonamides **2.23Aa – Hb** can be rationalised as shown in Scheme 2.27. Initial nucleophilic addition of a lithium acetylide unit to the amide carbonyl group results in ring opening to afford ynone **2.26**, which possess a sulfonamide-stabilised anion. Facile addition of the second lithium acetylide species will then take place. Finally, an aqueous acidic work up will lead to the formation of the corresponding dialkynol (**2.23Aa – Hb**).



Scheme 2.27

All reversed sulfonamides **2.23Aa – Hb** showed two characteristic signals in their ^{13}C NMR spectra (β, γ, Table 2.6) corresponding to the acetylenic carbons, which are similar to that seen for the dialkynols **2.5 – 2.8** (Table 2.2). Of note is the downfield shift of the β carbon in the TMS substituted compounds **2.23Ae, 2.23Be** and **2.23De** (entries 3, 7 and 15, Table 2.6). Trimethyl(phenylethynyl)silane has been reported to have similar ^{13}C shifts (Scheme 2.28) to those seen in the TMS substituted reversed sulfonamides **2.23Ae, 2.23Be** and **2.23De**, this deshielding of the β-carbon has been attributed to the resonance form shown in Scheme 2.28 [89MRC1112].



Scheme 2.28

Interestingly these sulfamoyl-substituted dialkynols or reversed sulfonamides (**2.23Aa – Hb**) have very different ^{1}H NMR spectra to those of the 2-tosylamido dialkynols **2.5 – 2.8** derived from the *N*-tosyl anthranilate. The ^{1}H NMR spectra in Figure 2.2 (**2.5a** and **2.23Ba**) are illustrative of the striking difference between the two species. The most deshielded proton in **2.5a** gives rise to the apparent doublet at δ_H 7.91 ppm (black star, red spectrum, Figure 2.2) whereas in the reversed sulfonamide **2.23Ba** the same signal is substantially deshielded and absorbs at δ_H 8.44 ppm (black star, blue spectrum, Figure 2.2). In both cases the low field signal originates from the 2-*H* proton i.e. *ortho* to the dialkynylmethanol moiety. The assignments of both these (black stars) signals was established from consideration of the 2D NMR spectra (^{1}H – ^{1}H COSY, HSQC and HMBC) of both compounds.

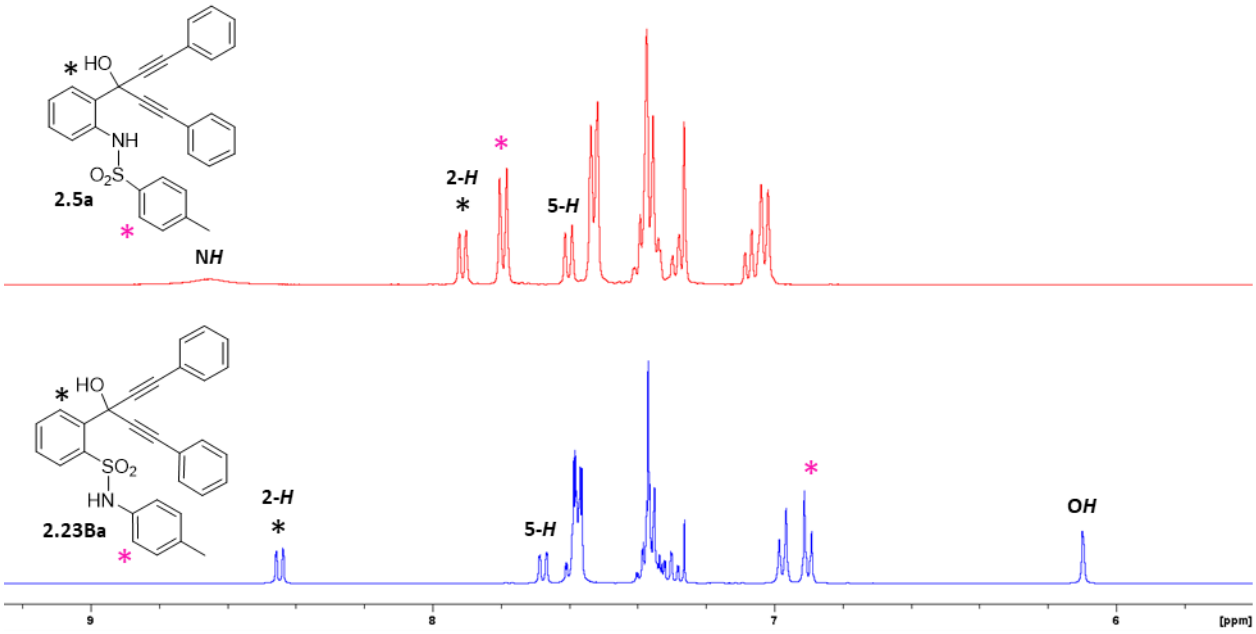


Figure 2.2 400 MHz ^{1}H NMR spectral comparison of **2.5a** and **2.23Ba** in $CDCl_3$

The HMBC spectrum of **2.5a** provided definitive confirmation that the apparent doublet at δ_H 7.91 ppm (black star, red spectrum, Figure 2.2) corresponds to 2-*H* because of a correlation (^3J coupling) with the quaternary sp^3 **C**-OH at δ_C 66.27 ppm (Figure 2.3). The ^{1}H – ^{1}H COSY spectrum (Figure 2.3) of **2.5a** enabled identification of the tosyl group protons. Thus, the two-proton doublet at δ_H 7.79 ppm (red spectrum, pink star, Figure 2.2) can be assigned to the protons *ortho* to the sulfone function. The COSY exhibits a cross peak between the doublet (δ_H 7.79 ppm) and the partially overlapped doublet at δ_H 7.01 ppm. The latter signal is coupled to the methyl protons (δ_H 2.28 ppm) and consequently corresponds to the *meta* Ar-*H* protons (Figure 2.3).

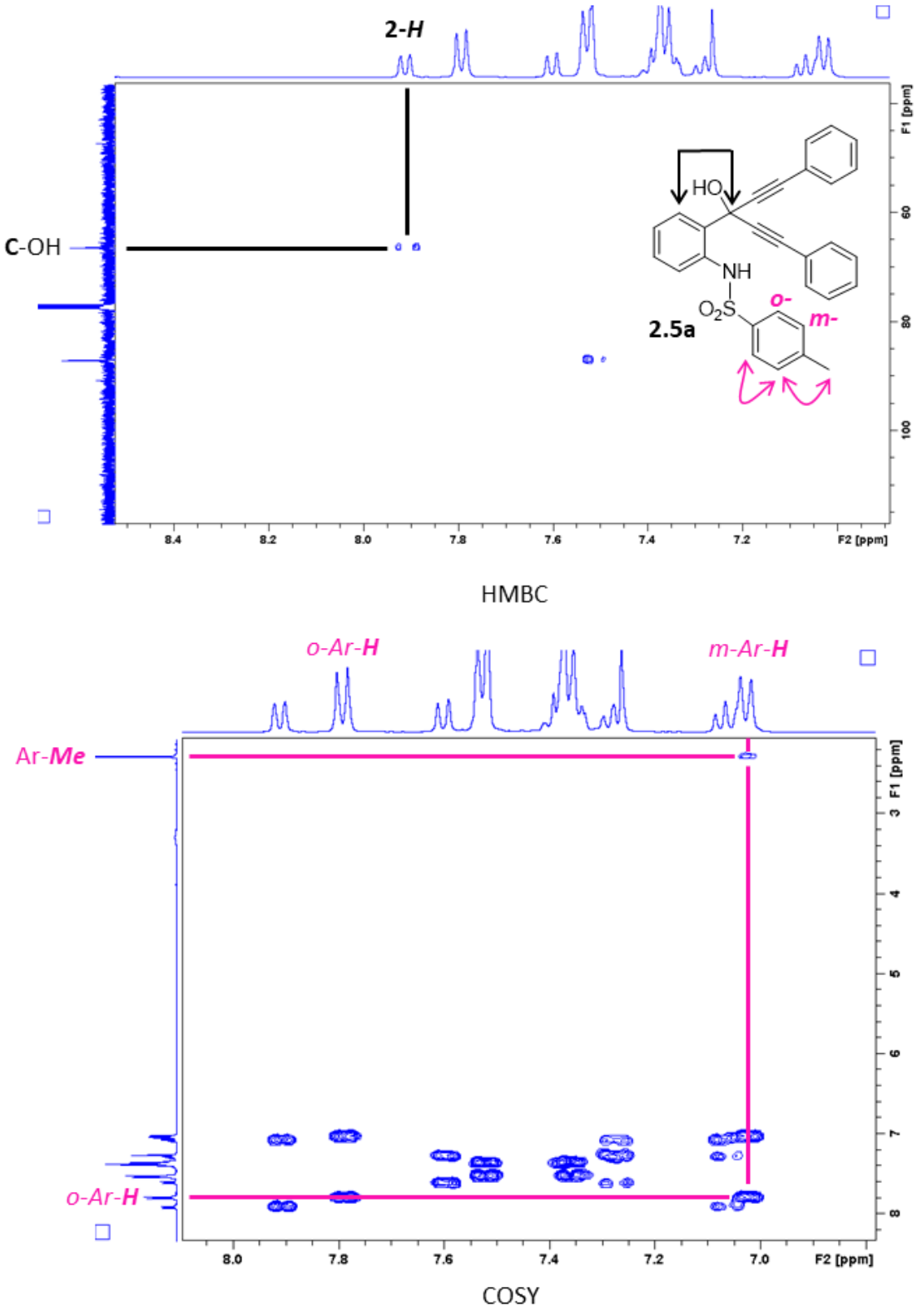


Figure 2.3 2D NMR spectra (HMBC and COSY) of **2.5a**

In the ^{1}H NMR spectrum of the reversed sulfonamide 2-(*N*-tolylsulfamoyl)dialkynol **2.23Ba**, the doublet at δ_H 6.90 ppm (blue spectrum, pink star, Figure 2.2) corresponds to the two tolyl ring protons *ortho* to the NH function. The ^{1}H – ^{1}H COSY spectrum (Figure 2.4) revealed the Ar-*H* protons *ortho* to the Ar-*Me* group absorb at δ_H 6.97 ppm, confirming the assignment of the pink starred signal (blue spectrum, Figure 2.2).

Most striking in the ^{1}H NMR spectrum of **2.23Ba** (blue spectrum, Figure 2.2) is the low field doublet of doublets at δ_H 8.45 ppm (black star, blue spectrum, Figure 2.2). At first it was thought the signal corresponded to the 5-*H* proton (*ortho* to the electron withdrawing sulfamoyl group, -SO_2NHTolyl). However this was dismissed by examination of the HMBC spectrum (Figure 2.4) which revealed an interaction (^{3}J) between the 2-*H* proton and the quaternary sp^3 carbon **C**-OH (δ_C 67.05 ppm). The pronounced downfield shift of the 2-*H* in **2.23Ba** (black star, blue spectrum, Figure 2.2) is most unusual and is observed throughout the reversed sulfonamide series **2.23Aa – Hb.** Presumably this deshielding originated from the proximity of the 2-*H* to one of the anisotropic alkyne units. Protons situated above alkene or alkyne moieties are known to experience deshielding and the origins of this have been reviewed [14MI308].

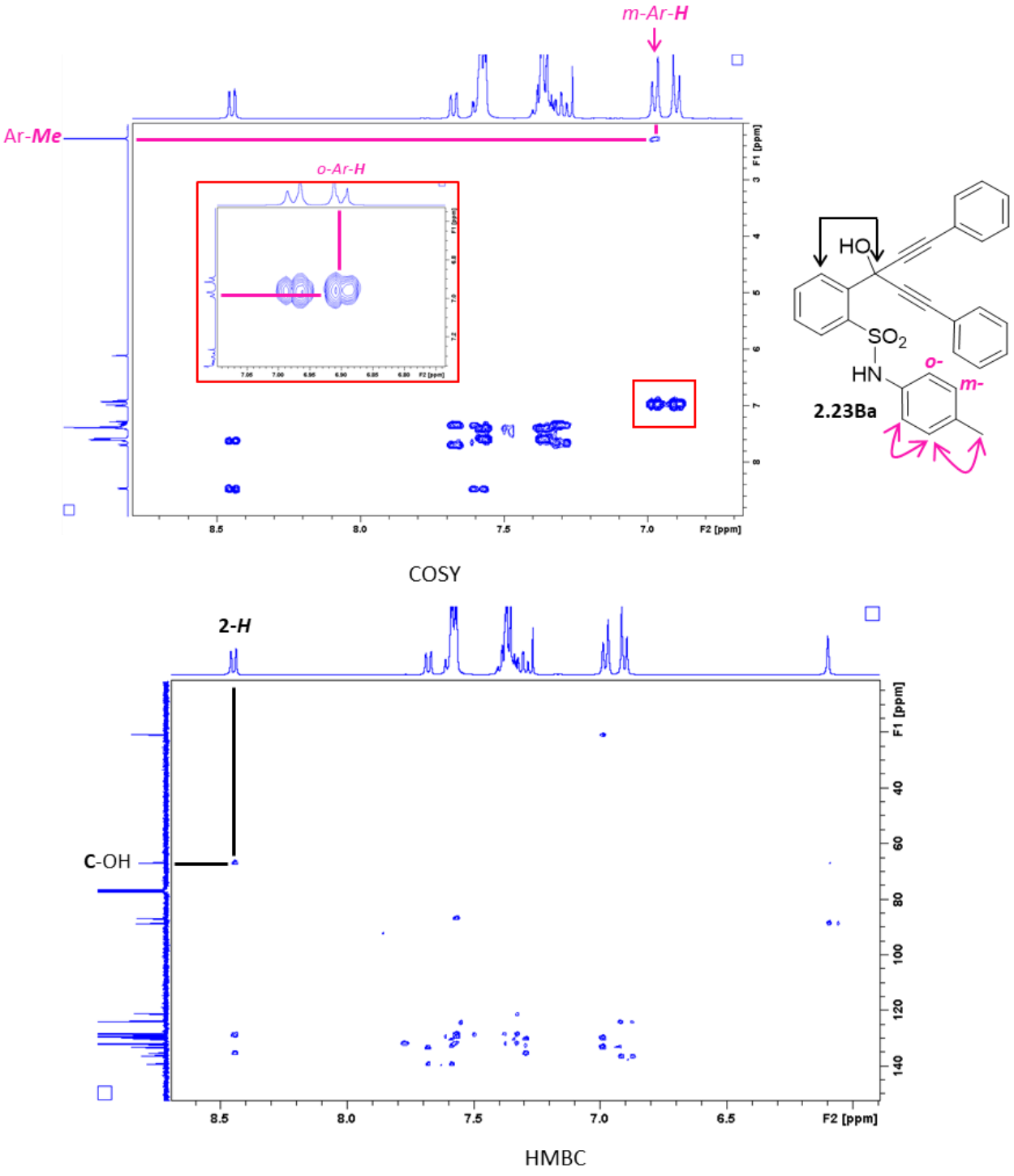


Figure 2.4 2D NMR spectra (COSY and HMBC) of **2.23Ba**

Interestingly the X-ray crystal structure of **2.23Bb** (Figure 2.5) revealed that the 2-*H* proton is located (in the crystal) near one of the alkyne functions. Of course, it must be recognised that the conformation may differ in solution.

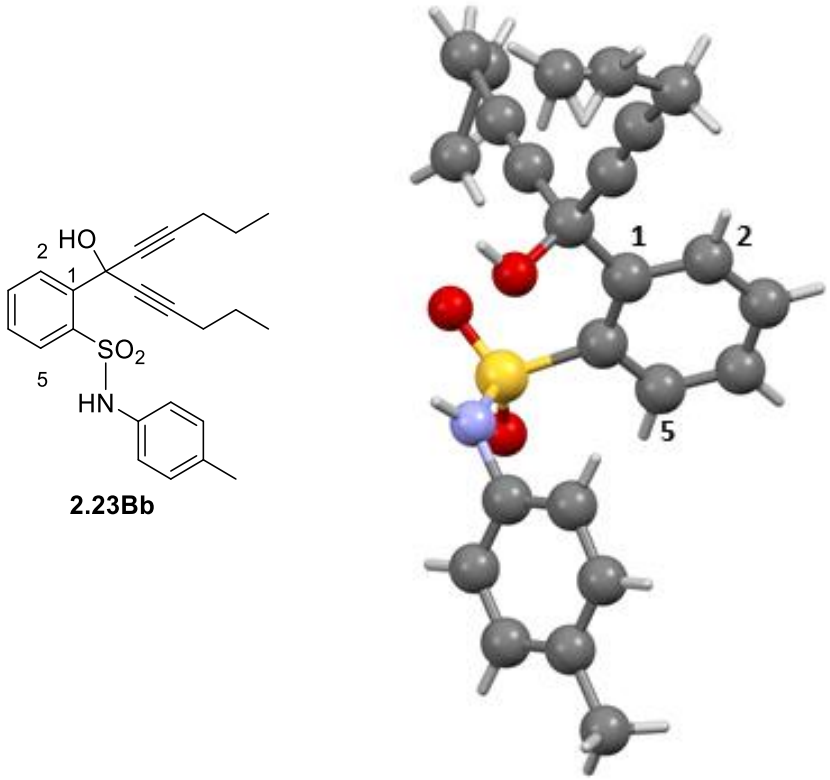
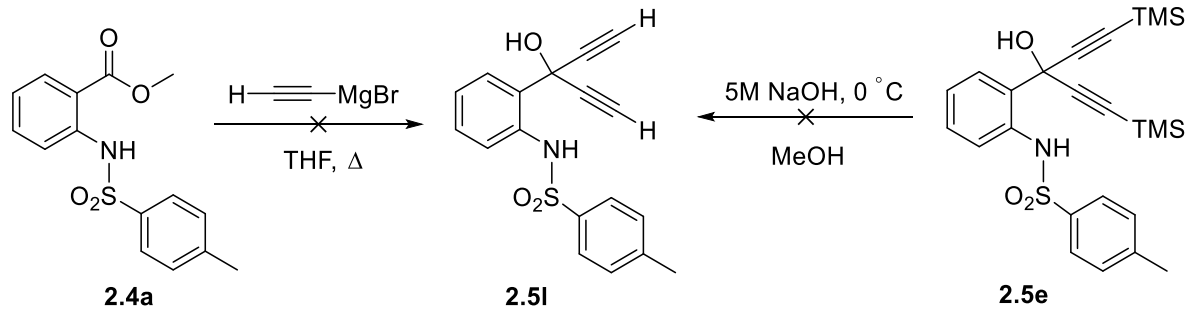


Figure 2.5 X-Ray crystal structure of 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide **2.23Bb**

Lithium ethoxyacetylide and the dianion $LiC{\equiv}CCH_2OLi$, from propargyl alcohol both failed to react with *N*-(*p*-tolyl)saccharin (entry 9 and 10, Table 2.6). In the case of the ethoxyacetylide entry 10 (Table 2.6) a very complex mixture was obtained, whereas with the dianion (entry 10, Table 2.6) only starting material was recovered. These observations support the previous findings that the double addition of these lithium acetylides ($LiC{\equiv}CCH_2OLi$ and $LiC{\equiv}COEt$) is not favourable (cf. Section 2.1, page 51).

2.3 Base-Mediated 5-*Exo-Dig* Cyclisation of 3-[2-(Tosylamido)phenyl]penta-1,4-diyn-3-ols

As the addition of ethynylmagnesium bromide to ester **2.4a**, did not yield any tractable products (entry 12, Table 2.2), attempts to access the parent dialkynol **2.5l** (R^1 = H) then focused on removal of the TMS groups from dialkynol **2.5e**, which was envisaged to proceed straightforwardly (Scheme 2.29).

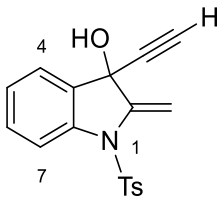


2.4a **2.5l** **2.5e**

Scheme 2.29

Thus, 1,5-bis(trimethylsilyl)-3-[2-(tosylamido)phenyl]penta-1,4-diyn-3-ol was stirred in cold MeOH with the slow addition of aqueous 5M NaOH (2 equiv.). After dilution with water and isolation *via* EtOAc, attempts to purify the mixture by column chromatography produced numerous decomposition products and only one identifiable fraction was isolated in a very low yield (2%). The ^{1}H NMR spectrum (Figure 2.6) of this material showed the presence of an alkene moiety, due to the appearance of two doublets (^2J = 2.0 Hz) each integrating for one proton at δ_H 5.90 and 5.47 ppm (Figure 2.6).

After careful examination of both 1D and 2D NMR spectra (^{1}H – ^{1}H COSY, HSQC and HMBC) the unknown product was characterised as 3-ethynyl-2-methylene-1-tosyl-2,3-dihydroindol-3-ol **2.27** a hitherto unknown compound.



2.27

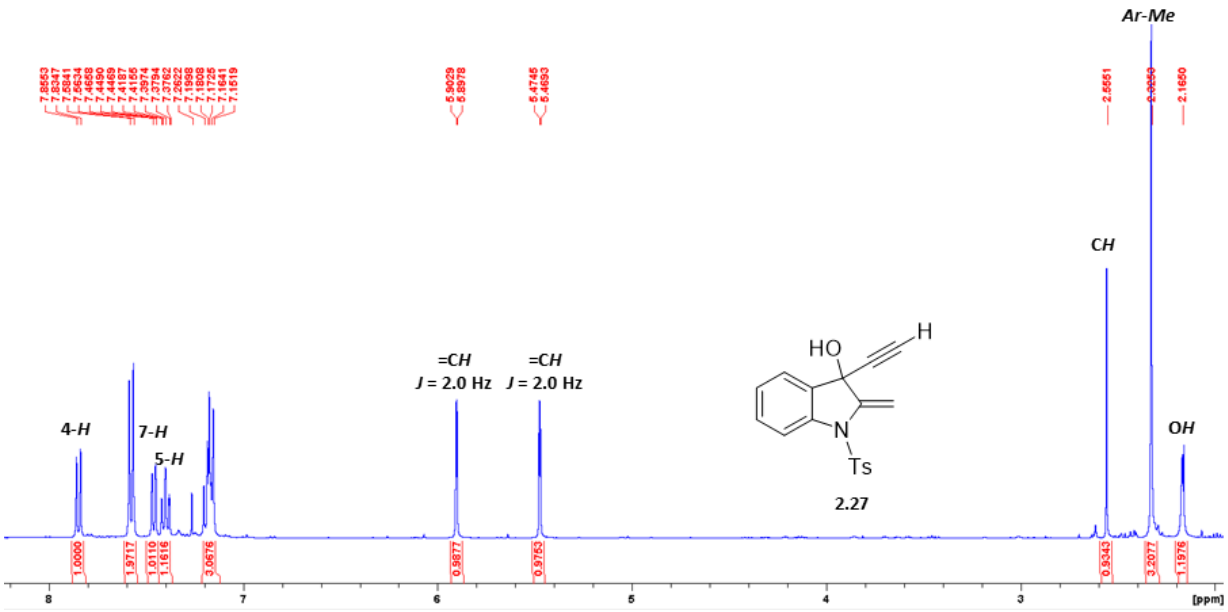
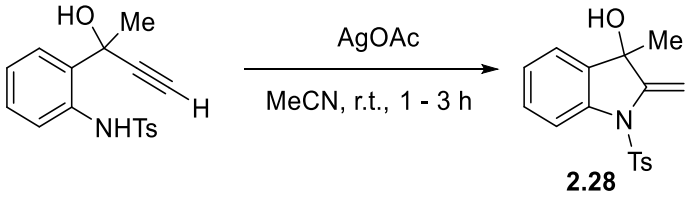


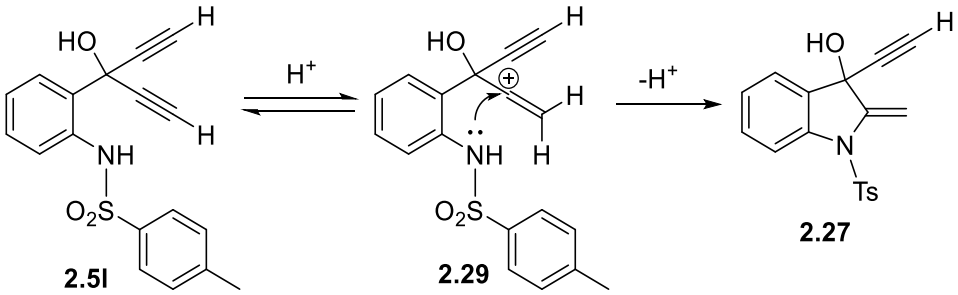
Figure 2.6 400 MHz ^{1}H NMR spectrum of **2.27** in $CDCl_3$

The doublets at δ_H 5.92 and 5.48 ppm have similar shifts to those reported by Chan and co-workers, for a related indoline (**2.28**, Scheme 2.30), prepared by Ag(I)-mediated cyclisation of an *o*-(tosylamido)phenylpropynol, with singlets at δ_H 5.78 and 5.14 ppm [12JOC7166].



Scheme 2.30

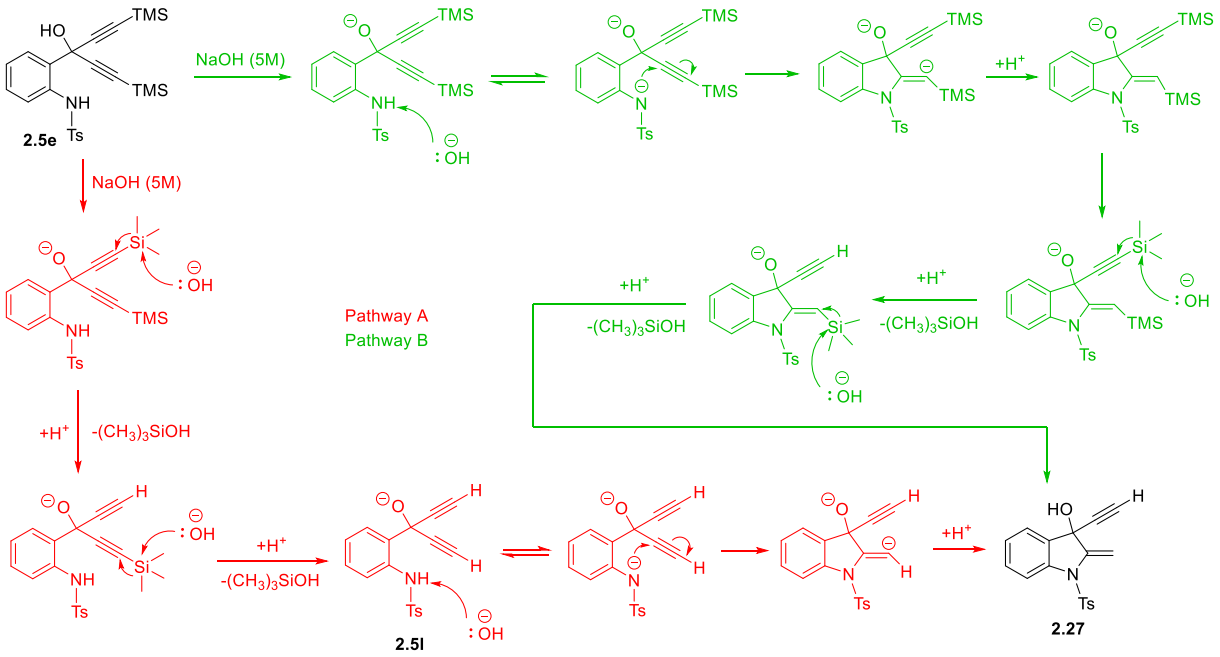
Initially it was thought that the formation of **2.27** could be due to the acidity of the silica used in flash column chromatography, and can be rationalised by protonation of one of the alkyne units to give the vinylic carbocation **2.29**, which is susceptible to attack from the sulfonamido group, with cyclisation to afford 3-ethynyl-2-methylene-1-tosyl-2,3-dihydroindol-3-ol **2.27** (Scheme 2.31). No improvement in yield was observed if the reaction mixture (crude desilylation) was acidified (AcOH) or heated with AcOH. Unfortunately attempts to further purify the material from acidic reactions was unsuccessful, producing a complex mixture of products. Due to the difficulty in purification, no other acid catalysts were explored.



Scheme 2.31

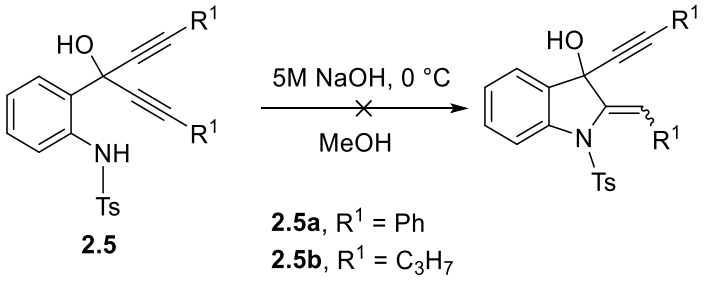
As acid did not promote cyclisation of the expected terminal dialkynol **2.5l** to **2.27** as anticipated, it was thought that the cyclisation must occur during removal of the TMS groups. Removal of the TMS groups from **2.5e** was again attempted, but a large excess of aqueous 5M NaOH (28.3 equiv.) was used. After an aqueous workup the ^{1}H NMR spectrum showed that crude material was indeed the desired 1-tosylindoline **2.27**, moreover the conversion was quantitative. Consequently, the cyclisation is base catalysed.

It is not known whether the cyclisation proceeds with initial desilylation (pathway A, Scheme 2.32) or if this step follows formation of the indoline ring (pathway B, Scheme 2.32). Therefore, the proposed mechanisms for both the TMS protected dialkynol and the deprotected dialkynol are shown in Scheme 2.32. In both cases the sulfonamide nitrogen will be deprotonated under basic conditions and can then undergo nucleophilic attack on the triple bond to cyclise *via* a 5-*exo*-*dig* pathway affording **2.27**.



Scheme 2.32

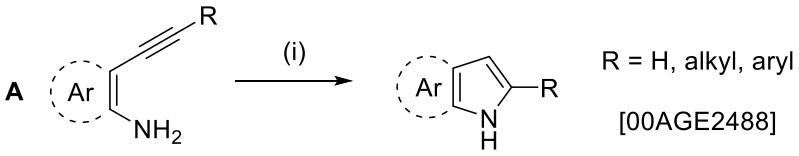
This novel base-mediated indoline ring synthesis was investigated further. Replacement of the alkyne terminal groups was explored (Scheme 2.33). Thus, **2.5a** and **2.5b** were subjected to basic conditions to investigate whether internal alkynes would also cyclise. Unfortunately only starting material was recovered from these reactions, suggesting that either the presence of a silyl moiety or a terminal alkyne group is a necessary prerequisite.



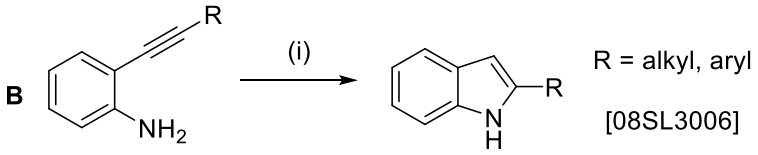
Scheme 2.33

Literature examples of purely base-mediated cyclisations onto pendant alkynes are scarce, and of relevance is the 5-*exo*-*dig* cyclisation of 2-alkynylanilines to afford mostly indoles (Scheme 2.34). Knochel and co-workers synthesised a variety of indoles and related ring-fused derivatives, it was found the reaction worked with a range of bases but KH or KO*t*Bu were used in varying ratios (**A**, Scheme 2.34) [00AGE2488]. Sodium hydroxide was used to promote the base-mediated cyclisation of 2-alkynylanilines affording a range of indoles in

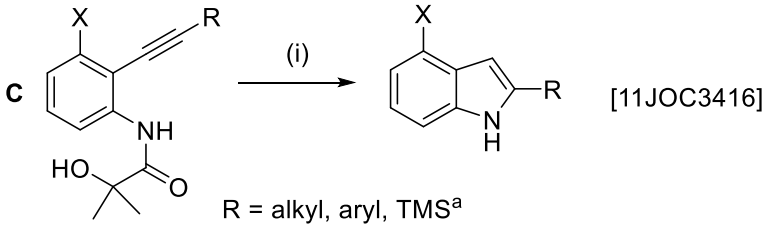
high yields (74 – 91%) (**B**, Scheme 2.34). However the conditions used were rather harsh [08SL3006, 11JOC3416]. Sanz *et al.* also observed the deprotection of the silyl groups when *o*-trimethylsilylethynylanilides were used (**C**, Scheme 2.34), affording 2-unsubstituted 4-halo-1*H*-indoles (R = H). They did not allude to the point of the desilylation step in the cyclisation [11JOC3416].



(i) KH (1.3 - 1.7 equiv.), NMP, r.t. or KO*t*Bu (1.3 - 2.1 equiv.), NMP, r.t.
NMP = *N*-Methyl-2-pyrrolidone



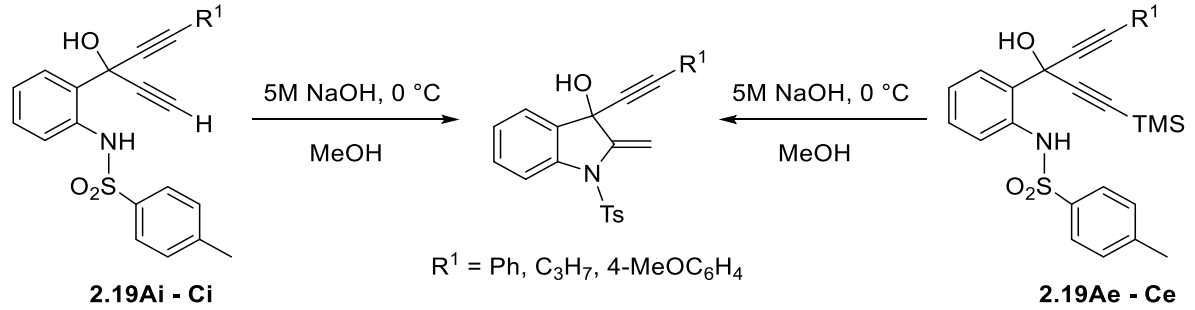
(i) NaOH (3 equiv.), DMF, 140 °C or NaOH (1.5 equiv), MW (170 °C)



(i) NaOH (3 equiv.), DMF, 140 °C; a = product R = H

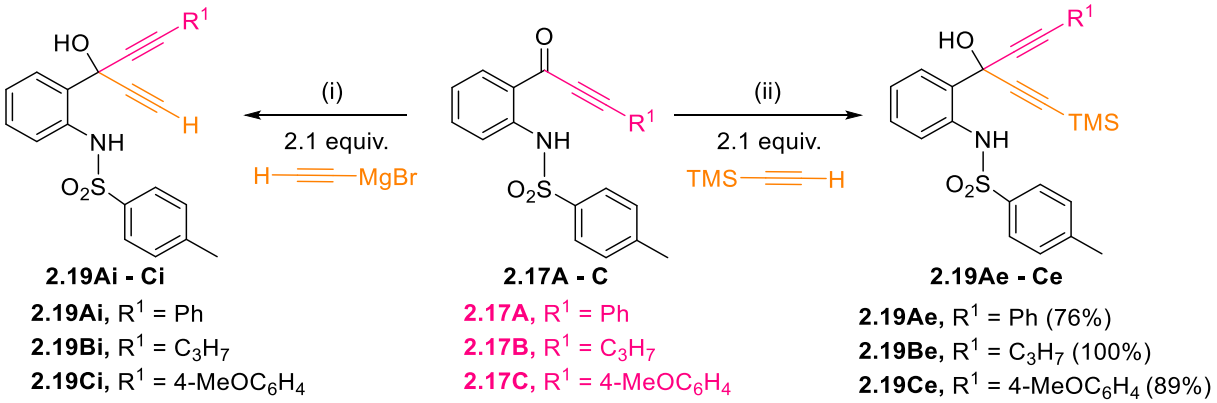
Scheme 2.34

With this novel pathway to indoline **2.27** it was envisioned that previously synthesised unsymmetrical dialkynols **2.19Ai, 2.19Bi** and **2.19Ci** may also undergo this base mediated 5-*exo-dig* cyclisation, Scheme 2.35.



Scheme 2.35

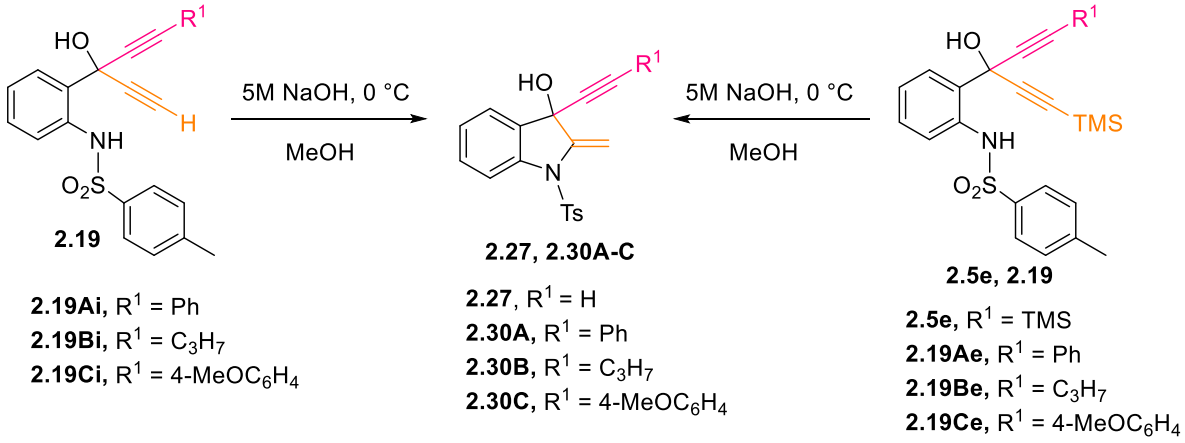
In order to verify this proposal, a range of other TMS-substituted unsymmetrical dialkynols **2.19Ae, 2.19Be** and **2.19Ce** (Scheme 2.33) were synthesised by addition of Li-C≡C-TMS to the appropriate ynone **2.17A – C**. The TMS-dialkynols were obtained in excellent yields as oils; examination of the crude products' ^{1}H NMR spectra revealed trace amounts of the indolin-3-ols. Consequently, the dialkynols **2.19Ae, 2.19Be** and **2.19Ce** were not purified further and carried forward directly for the base-catalysed cyclisations. The desilyldialkynols (Scheme 2.17, Table 2.4, page 59) were prepared by addition of ethynylmagnesium bromide (0.5 M in THF) to the appropriate ynone **2.17A – C** (Scheme 2.36).



(i) THF, 40 °C to Δ; (ii) *n*-BuLi (2.1 equiv.), THF, -78 °C to r.t.

Scheme 2.36

Base-mediated cyclisations of the unsymmetrical dialkynols **2.19Ai – 2.19Ci** and **2.19Ae – 2.19Ce** was explored (Scheme 2.37). The outcomes from these cyclisations are collated in Table 2.7.



2.19Ai, R^1 = Ph
2.19Bi, R^1 = C_3H_7
2.19Ci, R^1 = 4-$MeOC_6H_4$

2.27, R^1 = H
2.30A, R^1 = Ph
2.30B, R^1 = C_3H_7
2.30C, R^1 = 4-$MeOC_6H_4$

2.5e, R^1 = TMS
2.19Ae, R^1 = Ph
2.19Be, R^1 = C_3H_7
2.19Ce, R^1 = 4-$MeOC_6H_4$

Scheme 2.37

Entry	R^1	Dialkynol	Time (h)	Base equiv.	Product	Yield (%)	δ_c =CH_2 (ppm)
1	TMS	**2.5e**	0.25	28.3	**2.27**	100	102.41
2	Ph	**2.19Ae**	24	11.2	**2.30A**	76	99.70
3	Ph	**2.19Ai**	1	59.5	**2.30A**	70*	
4	C_3H_7	**2.19Be**	24	10.1	**2.30B**	62	101.77
5	C_3H_7	**2.19Bi**	0.5	5.0	**2.30B**	91	
6	4-$MeOC_6H_4$	**2.19Ce**	24	22.9	**2.30C**	40	102.07
7	4-$MeOC_6H_4$	**2.19Ci**	24	60.4	**2.30C**	77	

Table 2.7 Yields of the base mediated cyclisation to **2.27** and **2.30.** *By ^{1}H NMR

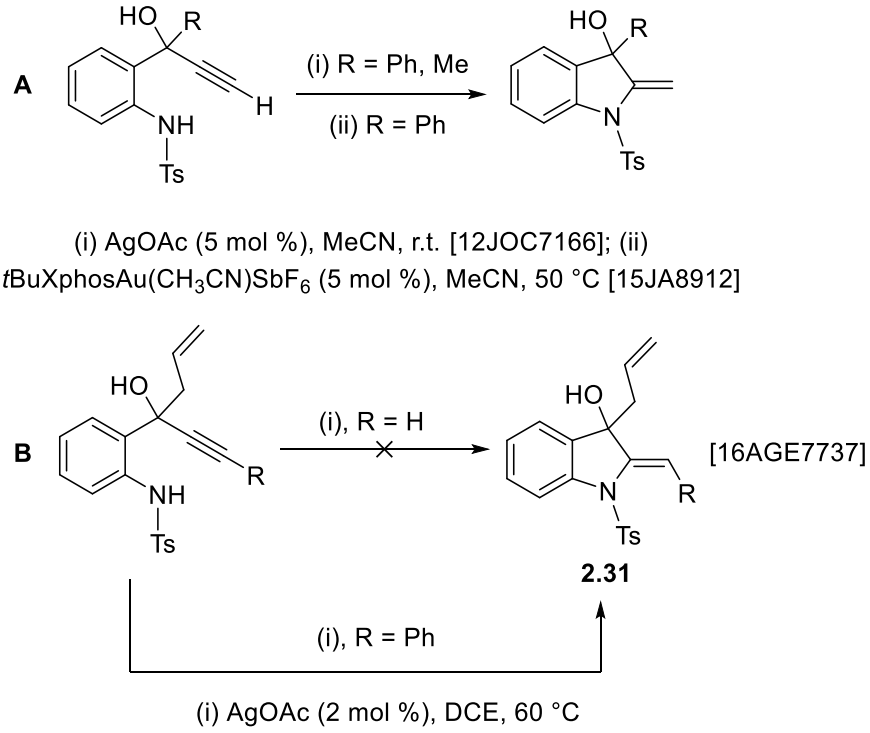
Table 2.7 indicates that in some cases a large excess of base was used to effect the ring closure. Generally, sufficient aqueous 5M NaOH was added to a methanolic solution of the dialkynol until TLC indicated that formation of the product had commenced or was complete.

The quantitative yield achieved from entry 1 (Table 2.7) in comparison to the other entries may indicate that the TMS group exerts a stabilising influence upon the cyclisation intermediate (anion), by the α-effect of the silyl group [93JOC1778, 94JA8304]. However this was not the case with the other silyl dialkynols and in general the terminal alkyne

derivatives produced better yields, with exception of **2.19Ai** (entry 3, Table 2.7). This difference is probably due to the difficulties in purification of the indoline **2.30A** from this substrate compared with the reaction of its TMS analogue **2.19Ae** (entry 2, Table 2.7).

All 2-methyleneindolines **2.27** and **2.30A – C** showed two characteristic doublets in the region of δ_H 5.80 – 5.90 ppm and 5.41 – 5.47 ppm with a *geminal* coupling of ^2J = 2.0 – 1.7 Hz, corresponding to the alkene protons.

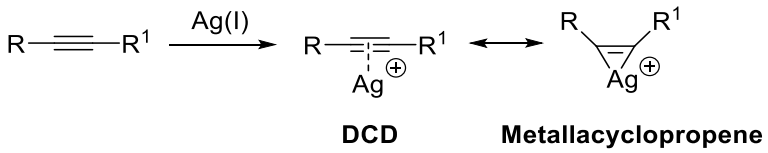
It is noteworthy that the 3-alkynyl-2-methylene-1-tosylindolin-3-ols **2.27** and **2.30A – C** are all novel compounds and thus represent the 'missing' examples in the series below (Scheme 2.38). Chan *et al.* synthesised the 3-phenyl- and 3-methyl- substituted indolin-3-ols from alkynols with the use of Ag(I) catalysis [12JOC7166]; the phenyl analogue (R = Ph) was also obtained in a poor yield with a Au(I) catalyst (**A**, Scheme 2.38) [15JA8912]. Ramasastry and co-workers could not access the 3-allylindoline **2.31** (R = H) but the benzylidene indolinol (R = Ph) was generated from a Ag(I) mediated cyclisation (**B**, Scheme 2.38) [16AGE7737].



Scheme 2.38

2.4 Silver(I) Catalysed 5-*Exo-Dig* Cyclisation of 3-[2-(Tosylamido)phenyl] penta-1,4-diyn-3-ols

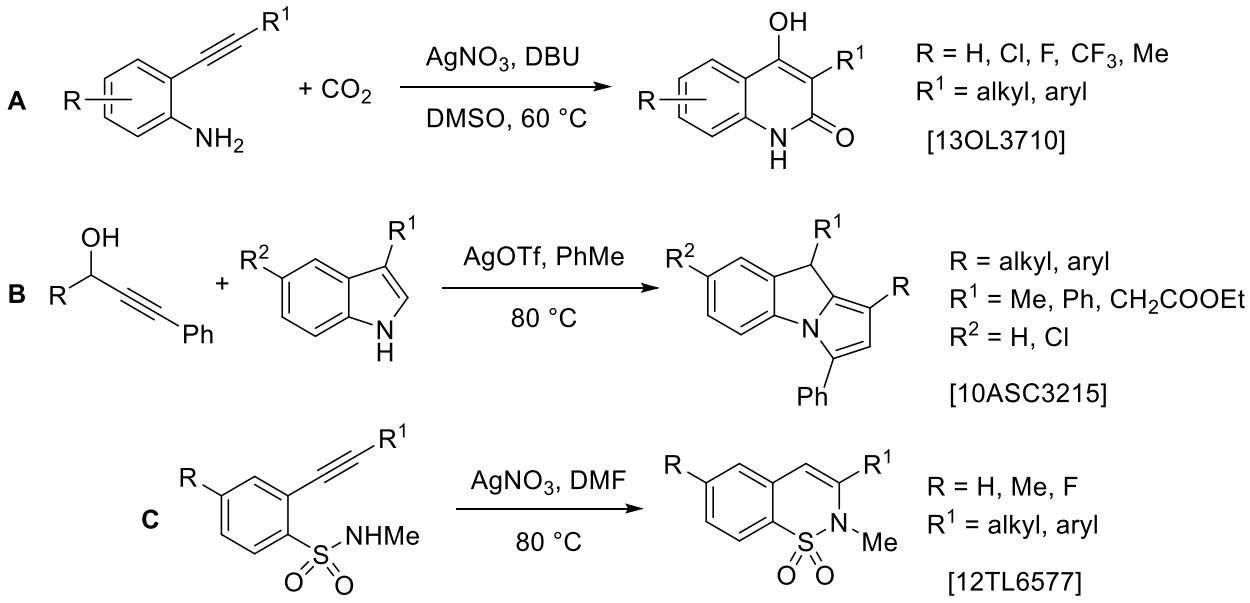
Many cyclisations of alkynes reported in the literature use silver(I) salts due to their affinity for triple bonds, the exploitation of this affinity has been reviewed numerous times [08CRV3174, 15CSR8124, 19AHC(127)1, 19MI1]. Silver has the electronic configuration [Kr]$4d^{10}5s^{1}$. The alkynophilicity of Ag(I) can be explained by invoking σ-overlap of a vacant orbital on the metal with the C≡C π-system (M ← L) with simultaneous, but weaker, back-donation from a silver 4d orbital to an alkyne π* orbital (M → L). Overall, the decrease in the electron density in the triple bond (with a decrease in bond order) renders it susceptible to nucleophilic attack. Detailed discussion of the nature of alkyne-metal π-complexation for silver and related metals is available. The Dewar-Chatt-Duncanson (DCD) and Metallacyclopropene models have been used to rationalise Ag(I)-alkyne interactions with an alkyne (Scheme 2.39) [14MI134, 15CSR8124, 19MI1]. Alkynophilicity has also been attributed to electrostatic forces between the metal salt and the triple bond [07AGE3140, 04JCP3134].



Scheme 2.39

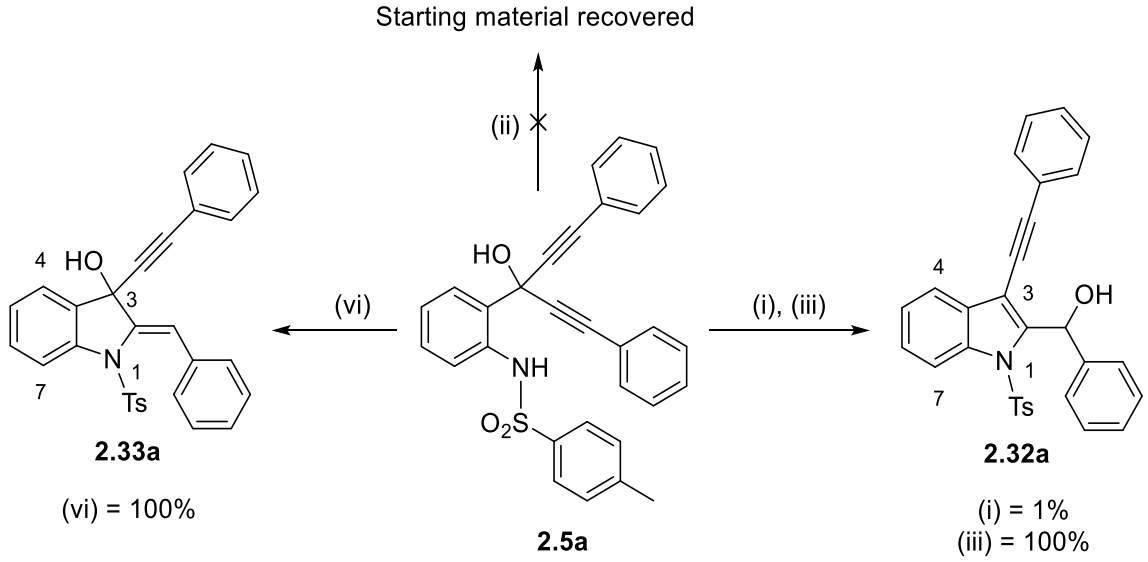
Some examples in which silver(I) salts have been used to catalyse the cyclisation of alkynes to various heterocycles are shown in Scheme 2.40. 4-Hydroxyquinoline2(1*H*)-ones can be synthesised by the Ag(I) catalysed intramolecular rearrangement of 4-alkylidene-3,1-benzoxazin-2-ones generated *in situ* form 2-alkynylanilines in the presence of CO_2 (**A**, Scheme 2.40) [13OL3710]. Hao *et al.* accessed pyrrolo[1,2-*a*]indoles from the silver(I) catalysed reaction of a variety of propargyl alcohols and 3,5-disubstitued indoles in varying yields (32 – 96%). It was found that the reaction pathway proceeded *via* two different routes, for secondary alcohols C2-propargylation followed by 5-*endo-dig* cyclisation, whilst with tertiary alcohols a C2-allenylation was followed by a 5-*endo-trig* cyclisation (**B**, Scheme 2.40) [10ASC3215]. 3-Substituted-1,2-benzothiazines were obtained from the Ag(I)

mediated cyclisations of *o*-(1-alkynyl)benzenesulfonamides in high yields 75 – 80% (**C**, Scheme 2.40) [12TL6577].



Scheme 2.40

A selection of conditions were evaluated with dialkynol **2.5a** to investigate its reactivity towards silver(I) and its potential for cyclisation, by activating the alkyne unit towards intramolecular nucleophilic attack from the sulfonamide nitrogen Scheme 2.41.



(i) AgOTf (5 mol %), PhMe, 90 °C, 2 h
(ii) AgOTf (10 mol %), DCM, r.t., 2.5 h
(iii) AgOAc (5 mol %), MeCN, Δ, 21 h
(vi) $AgNO_3$ on silica (5 mol %, 10 % w/w), MeCN, Δ, 18 h

Scheme 2.41

Reactions of the dialkynol **2.5a** with either AgOTf 5 mol % in PhMe (i), or with AgOTf 10 mol % in DCM (ii), provided only a complex mixture of products (i, Scheme 2.41) or recovery of starting material (ii, Scheme 2.41) respectively. On the other hand, AgOAc (5 mol %) in MeCN (iii, Scheme 2.41) resulted in a more successful outcome and provided a quantitative yield of the novel indole **2.32a** as a brown oil. The structure of **2.32a** was established from its NMR spectra, which is discussed on page 90 (Figure 2.10). Treatment of **2.5a** with $AgNO_3$ on silica (5 mol %) in MeCN (vi, Scheme 2.41) followed a different course to give (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol **2.33a** in a quantitative yield. The constitution of the indol-3-ol **2.33a** was established principally from its ^{1}H spectrum which exhibited broadened doublets at δ_H 7.86 and 7.54 ppm corresponding to the 4-*H* and 7-*H* protons respectively (Figure 2.7). The signals for these protons were assigned from the HMBC spectrum. The 7-*H* proton exhibits an interaction with the 7a carbon. The benzylidene proton (blue star, Figure 2.7) absorbs at δ_H 6.99 ppm, however it overlaps with the tolyl ring protons.

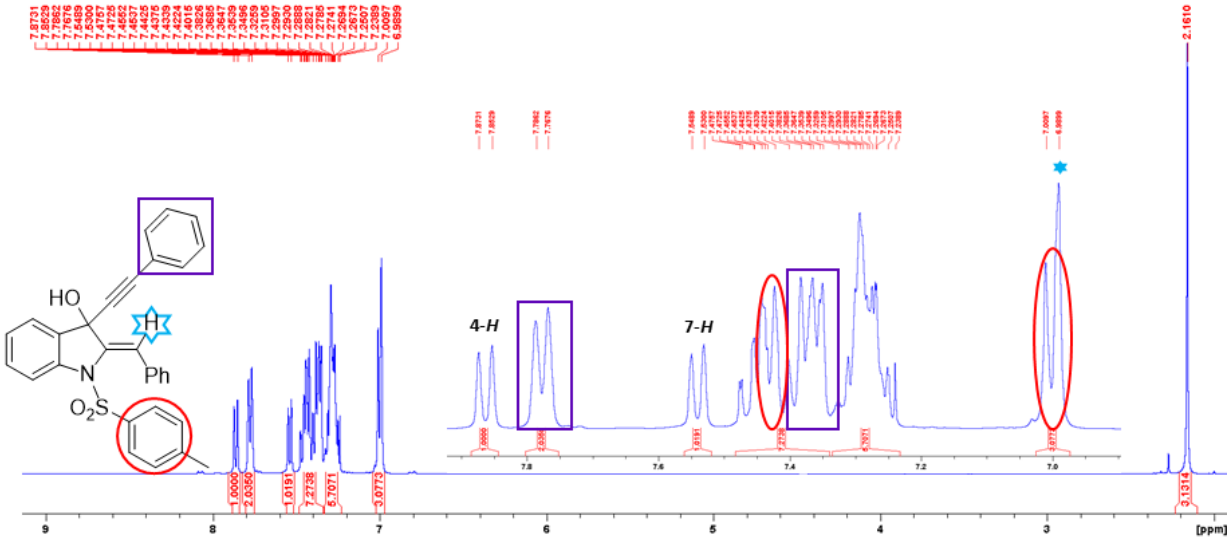


Figure 2.7 400 MHz ^{1}H NMR spectrum of (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol **2.33a** in $CDCl_3$

Confirmation of the stereochemistry of (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol **2.33a** was established by the NOESY spectrum. Figure 2.8 shows the energy minimised Chem3D structure of **2.33a** and its likely conformation. This structure reveals that the *p*-tolyl group is by virtue of attachment to the tetrahedral sulfone unit, inclined towards the C-3 phenylethynyl group. There is a through-space interaction of the phenylethynyl group *ortho*-

protons and the methine proton (blue star, interaction **Z**, Figure 2.8). Another means by which the NOESY spectrum confirmed the (*Z*)-stereochemistry was the absence of a through-space interaction of the phenyl groups from the benzylidene moiety and the PhC≡C- unit, which would be consistent with (*E*)-sterochemistry.

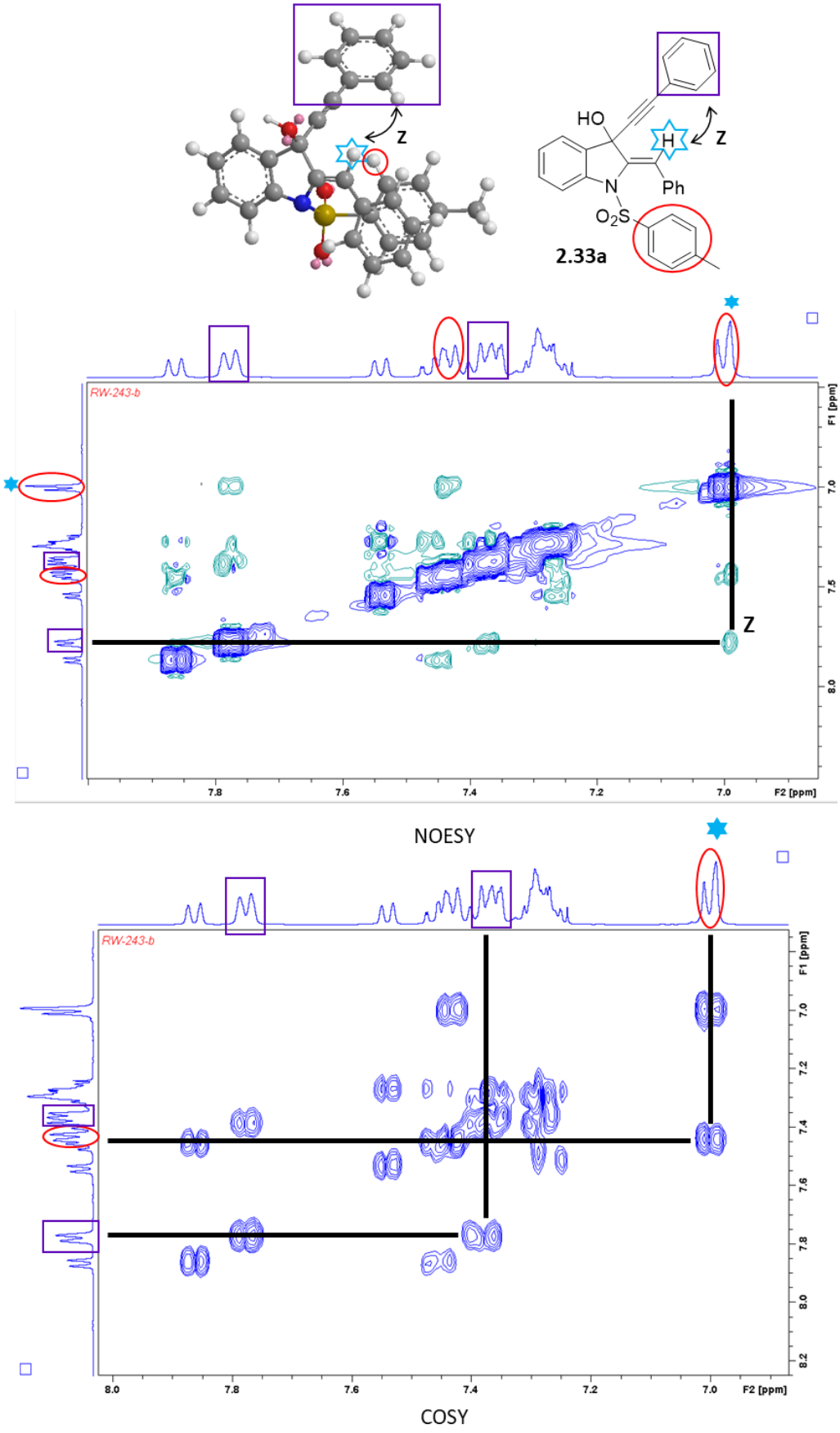
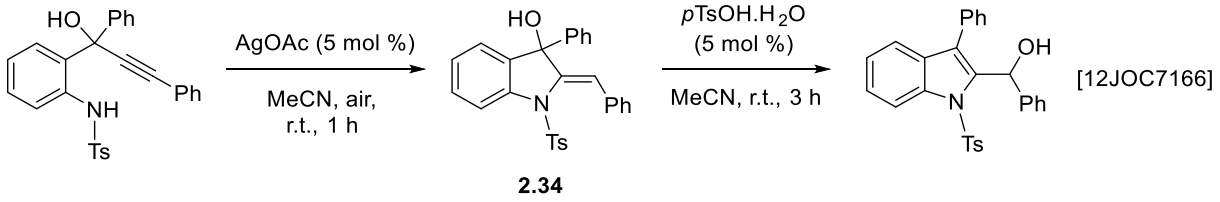


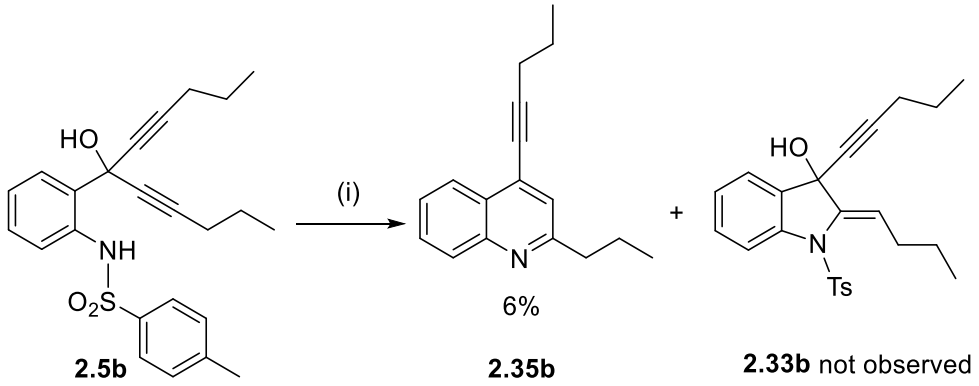
Figure 2.8 Chem 3D structure, NOESY and COSY spectra of **2.33a**

Chan and co-workers also found that when 1-[2-(tosylamino)phenyl]prop-2-yn-1-ol was treated with AgOAc in MeCN, 2-benzylidene-3-phenyl-1-tosylindolin-3-ol was obtained as the (*Z*)-stereoisomer exclusively (Scheme 2.42) [12JOC7166].



Scheme 2.42

It was of interest to investigate the course of the Ag-mediated dialkynol cyclisation when the terminal phenyl group in **2.5a** was replaced by alkyl groups. Thus, 6-(2-*p*-tosylamidophenyl)undeca-4,7-diyn-6-ol **2.5b** was subjected to the treatment with $AgNO_3$ on silica (Scheme 2.43).



(i) $AgNO_3$ on silica (5 mol %, 10 % w/w), MeCN, Δ, 18 h

Scheme 2.43

Unfortunately these conditions provided only a small amount of 4-(pent-1-yn-1-yl)-2-propylquinoline **2.35b** (6%). Formation of the latter is likely promoted by the Brønsted acidity of the silica rather than the Ag(I) salt (Scheme 2.44). The cyclisation of unsubstituted 1-(2-aminophenyl)propynols with PPTS to afford 2,4-disubstitued quinolines was also found to occur by Kumar *et al.* (page 33, Scheme 1.26). Consequently, $AgNO_3$ was not used for any further cyclisations.

The ^{1}H NMR spectrum of **2.35b** (Figure 2.9) exhibits a one proton singlet at δ_H 7.36 ppm corresponding to the C-3 position. Other features of 4-alkynylquinoline spectra are discussed in more detail in Section 3.1.

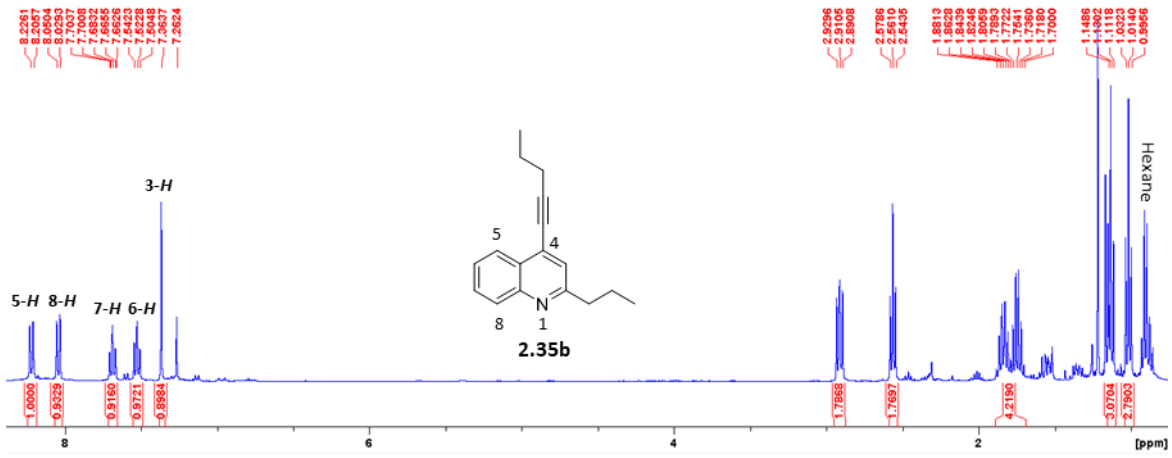
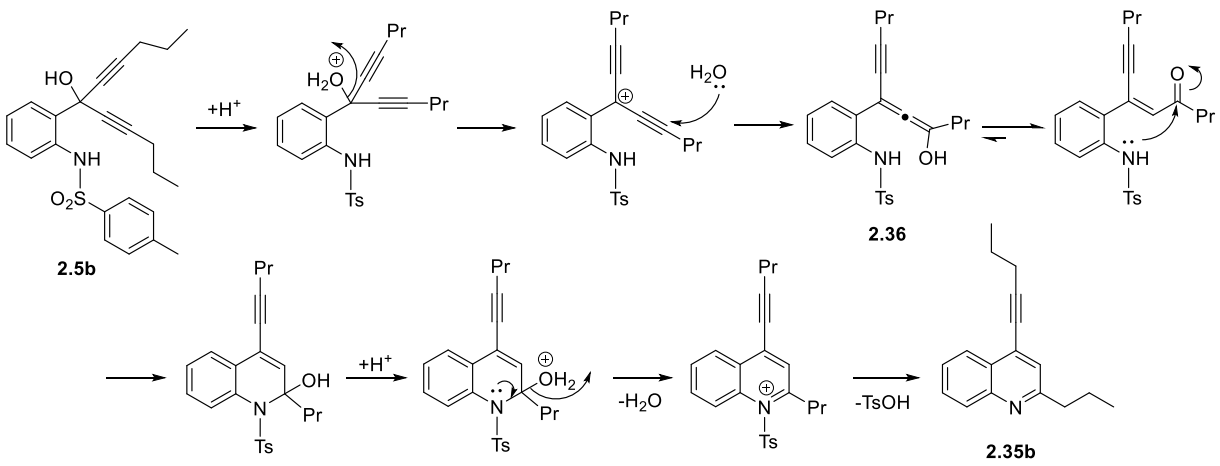


Figure 2.9 400 MHz ^{1}H NMR spectrum of **2.35b** in $CDCl_3$

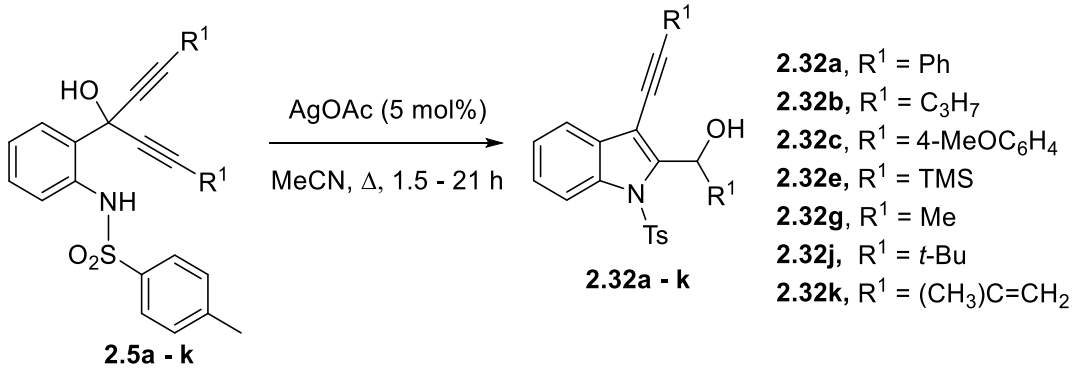
The formation of **2.35b** from **2.5b** and $AgNO_3$-silica is outlined in the proposed mechanism below (Scheme 2.44). In a Meyer-Schuster type reaction, initial loss of water generates the propargylic/allenic carbocation **2.36** that is susceptible to attack from water to afford an enone. Cyclisation by attack of the sulfonamide nitrogen ensues. Aromatisation by elimination of water and subsequently TsOH affords quinoline **2.35b**.



Scheme 2.44

Due to the failure of $AgNO_3$-silica to promote efficient cyclisations of the dialkynols **2.5a – b**, attention shifted to the use of AgOAc in refluxing MeCN, which proved effective for cyclisation of **2.5a** to the benzylic alcohol **2.32a** (iii, Scheme 2.41). Thus dialkynols **2.5a – k**

were subjected to AgOAc in refluxing MeCN (Scheme 2.45). The results of these reactions are collated in Table 2.8.



Scheme 2.45

Entry	R^1	Dialkynol	Time (h)	Indole	Yield (%)
1	Ph	**2.5a**	19	**2.32a**	100
2	C_3H_7	**2.5b**	1.5	**2.32b**[a]	62[a]
3	4-$MeOC_6H_4$	**2.5c**	21	**2.32c**	0
4	TMS	**2.5e**	19	**2.32e**[b]	0[b]
5	Me	**2.5g**	21	**2.32g**	0
6	*t*-Bu	**2.5j**	21	**2.32j**[c]	0[c]
7	$(CH_3)C=CH_2$	**2.5k**	21	**2.32k**	0

Table 2.8 Yields from the AgOAc cyclisations of **2.5a – k** to **2.32a – k**. a, b and c other products were isolated

Whilst the dilakynol **2.5a** provided the indole **2.32a** quantitatively and **2.5b** also gave the corresponding indole (62%) other products were isolated from this and some of the other substrates (entries 4 and 6) and these are discussed subsequently.

The ^1H spectrum of **2.32a** (Figure 2.10) exhibited a doublet at δ_H 6.95 ppm integrating for one proton with a *geminal* coupling constant of ^2J = 7.1 Hz, corresponding to the benzylic proton. The ^1H – ^1H COSY showed an interaction of the benzylic proton and the O*H* proton at δ_H 5.19 ppm.

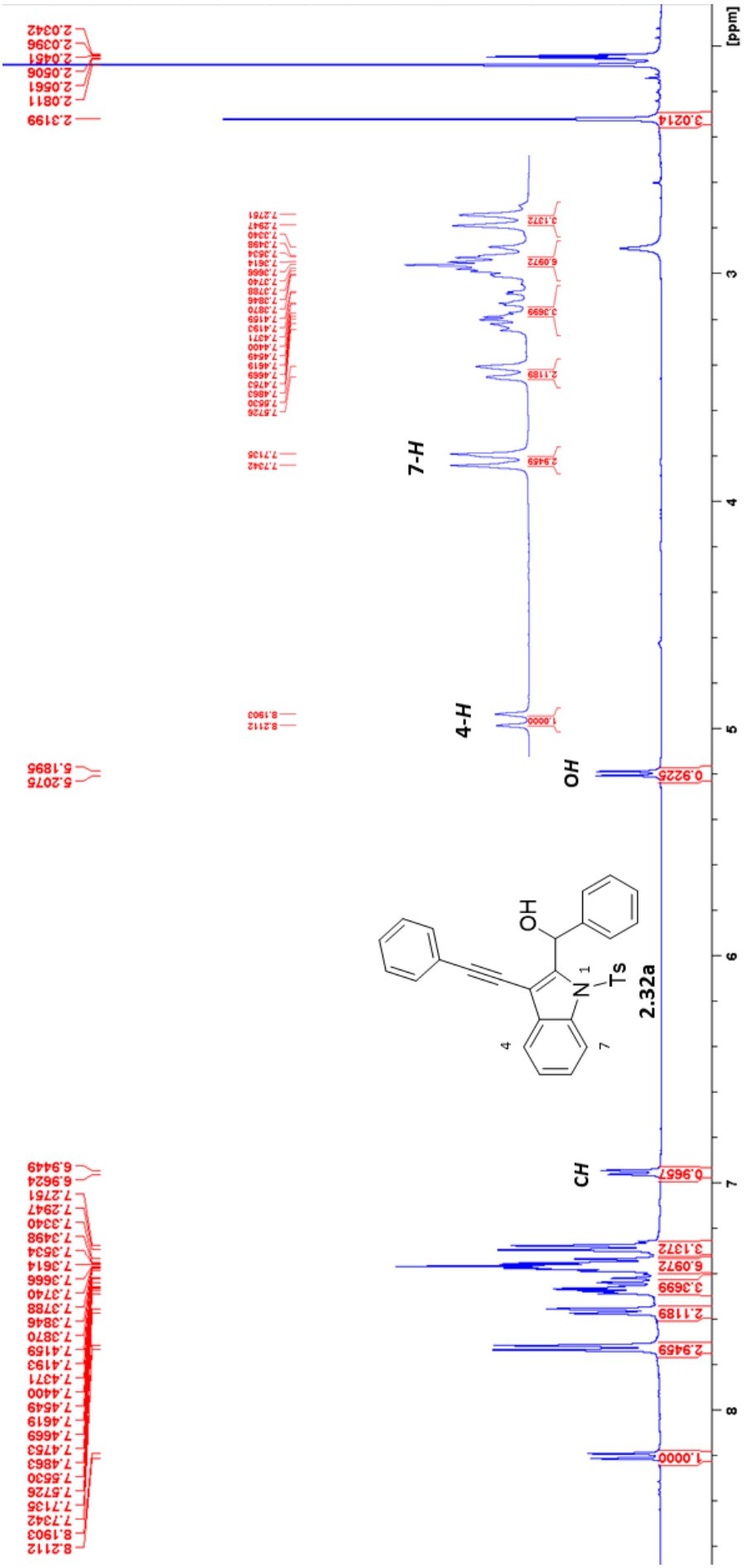
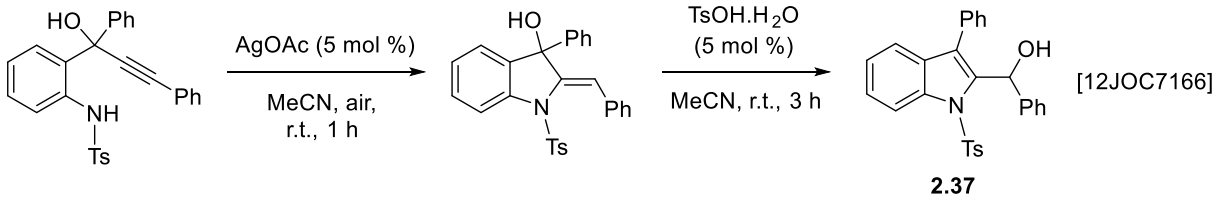


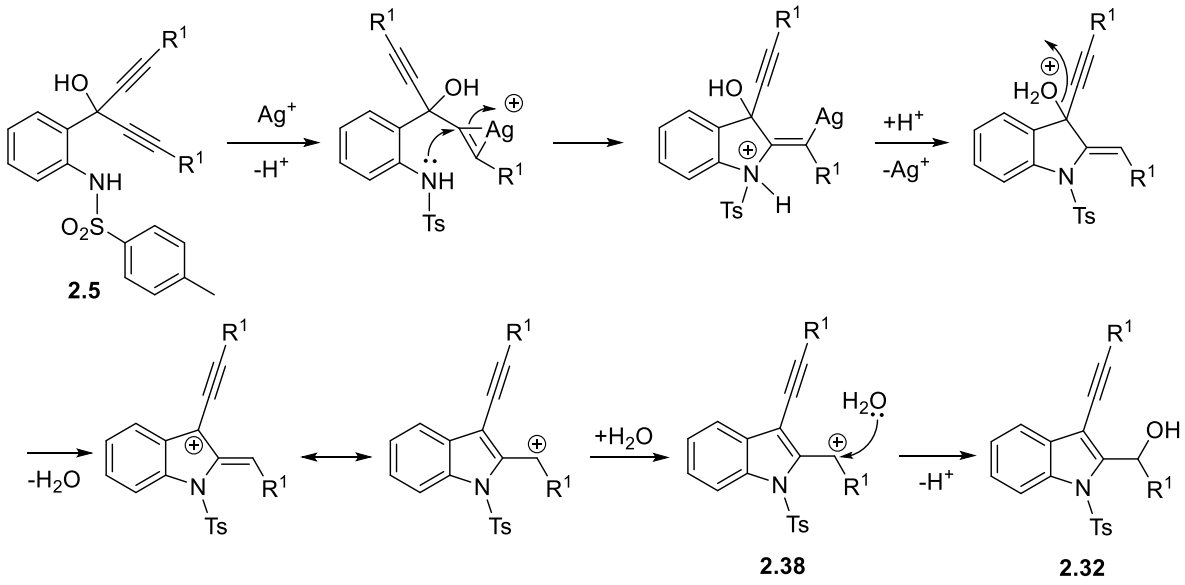
Figure 2.10 400 MHz ^{1}H NMR spectrum of phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methanol **2.32a** in acetone-d_6

Resonances for the benzylic and O*H* protons (δ_H 6.95 and 5.19 ppm, ^2J = 7.1 Hz) in **2.32a** are different to those reported (δ_H 6.30 and 4.72 ppm, ^2J = 11.84 Hz) by Chan *et al.* for **2.37** (Scheme 2.46) [12JOC7166]. On the other hand, the benzylic **C**H(OH) carbon resonance (^{13}C NMR) is nearly identical; δ_C 68.4 ppm for **2.32a** and δ_C 68.6 ppm for **2.37**. The downfield shift of the C*H* proton (benzylic) in the ^{1}H spectrum of **2.32a** is probably due to the anisotropic deshielding effect of the adjacent triple bond.



Scheme 2.46

A reasonable mechanism for the formation of indoles **2.32a – b** is shown in Scheme 2.47. Coordination of silver(I) to the triple bond will form the π-complex (metallacyclopropenium ion) which is susceptible to attack by the nucleophilic sulfonamide function and will cyclise accordingly, *via* a 5-*exo*-*dig* pathway. Following protodeargenation (loss of silver by attack of a proton) and protonation of the alcohol, dehydration (E_1) will lead to the carbocation **2.38**. Subsequent hydration of the alkene moiety and aromatisation will afford the corresponding 1-tosylindole **2.32a – b.**



Scheme 2.47

Flash column chromatography of the crude material from the reaction of 6-(2-*p*-tosylamidophenyl)undeca-4,7-diyn-6-ol **2.5b** with AgOAc afforded three products (fractions **A**, **B** and **C** in order of increasing polarity). The lowest yielding being 8% (fraction **B**), which was readily identified as 4-(pent-1-yn-1-yl)-2-propylquinoline **2.35b**. The ^{1}H NMR spectra of the fastest running fraction **A** (red spectrum, Figure 2.11) and slowest eluting fraction **C** from the column were similar (blue spectrum, Figure 2.11).

The ^{1}H and ^{13}C NMR spectra of fraction **A** confirmed the presence of a pentynyl substituent and a 1-tosylindole system. Fraction **A**, exhibited a doublet (signal **a**) at δ_H 6.99 ppm (J = 15.8 Hz) and a doublet of triplets (signal **b**) at δ_H 6.79 ppm (J = 15.8 and 6.5 Hz). Both chemical shifts and signal multiplicities were indicative of *trans*-alkene protons, in the case of signal **b**, additional coupling to an adjacent methylene group. When taken in conjunction with the integrations and multiplicities of the aliphatic proton signals these data indicated the presence of a but-1-enyl group i.e. C***H***=C***H***CH_2CH_3 unit. The absence of exchangeable protons was confirmed by addition of D_2O (red spectrum, Figure 2.12). Therefore the constitution of fraction **A** was established as (*E*)-2-(but-1-en-1-yl)-3-(pent-1-yn-1-yl)-1-tosyl-1*H*-indole **2.39**.

Fraction **C** provided the major product from the reaction and the presence of a 1-tosylindole core together with a pentynyl substituent was readily confirmed from the ^{1}H and ^{13}C NMR spectra. However, the side chain in fraction **C** was different to that of fraction **A** and gave

rise to a series of complex signals and splitting patterns. Discounting the aromatic signals the most downfield signal absorbed at δ_H 5.51 (*J* = 10.8, 7.2 Hz) as a doublet of triplets (**x**) corresponding to one proton. A higher field signal absorbed at at δ_H 3.72 ppm as a doublet(*J* = 10.8 Hz) (signal **y**) integrating for one proton.

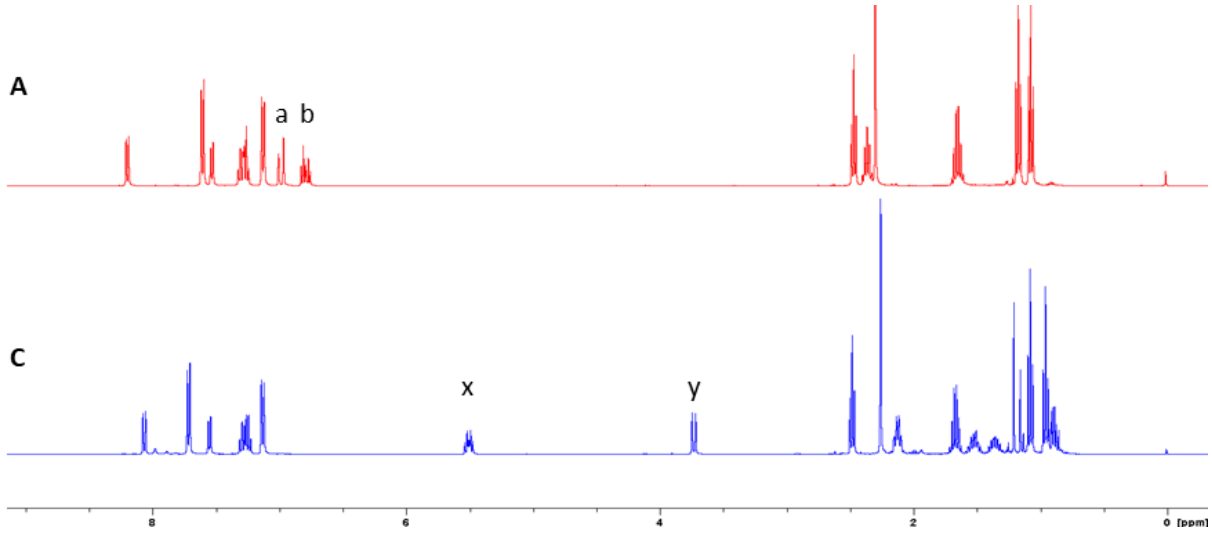


Figure 2.11 400 MHz ^{1}H NMR spectra of **2.39** (fraction **A**) and **2.32b** (fraction **C**) in $CDCl_3$

Although no signals disappeared upon addition of D_2O to fraction **A** (red spectrum, Figure 2.12) confirming the structure of **2.39**. In fraction **C** however, the doublet of triplets (signal **x**) collapsed to a triplet and the doublet (signal **y**) disappeared completely (blue spectrum, Figure 2.12), so indicating that the side chain contained a -C***H***(O***H***)C***H***$_2$- moiety. These data and the remaining aliphatic proton signals established the presence of a -CH(OH)$CH_2CH_2CH_3$ unit, so confirming that fraction **C** was 1-[3-(pent-1-yn-1-yl)-1-tosyl-1*H*-indol-2-yl]butan-1-ol **2.32b**.

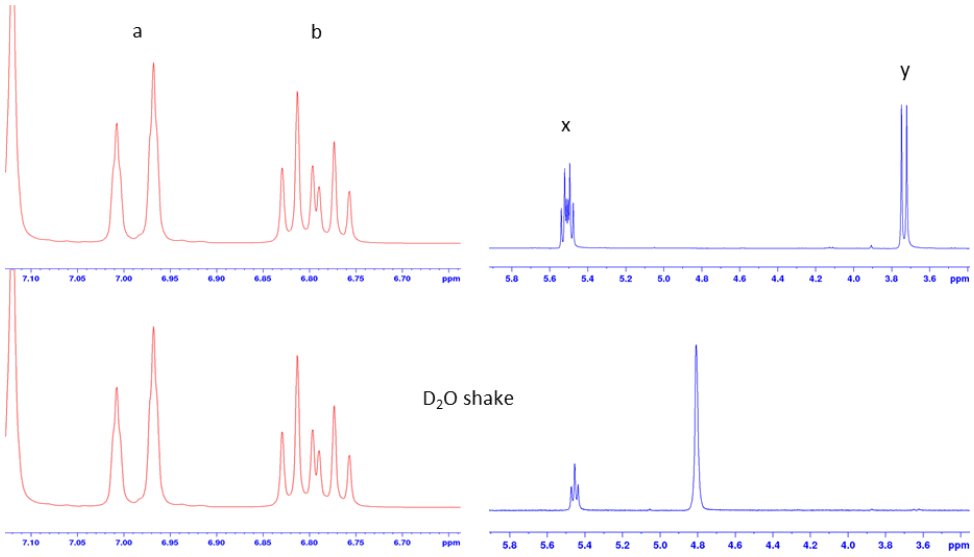
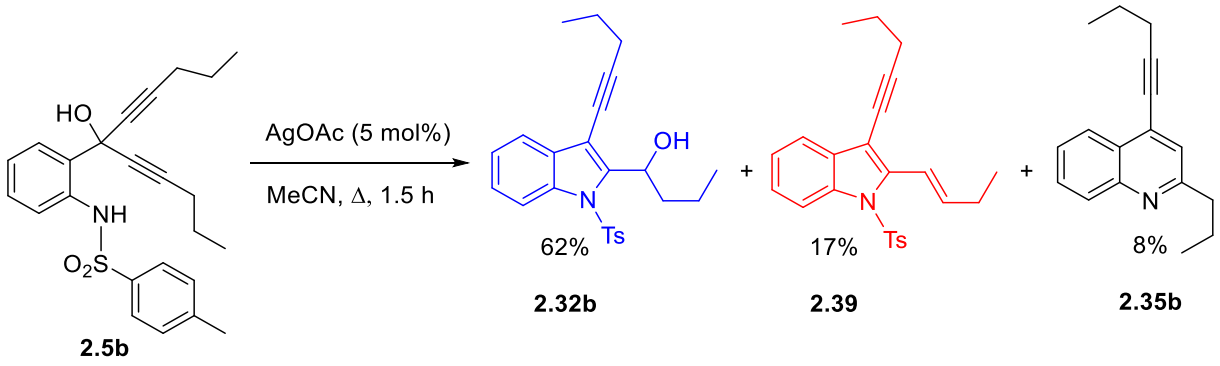


Figure 2.12 ^{1}H NMR spectra comparison of **2.39** and **2.32b** after D_2O shake

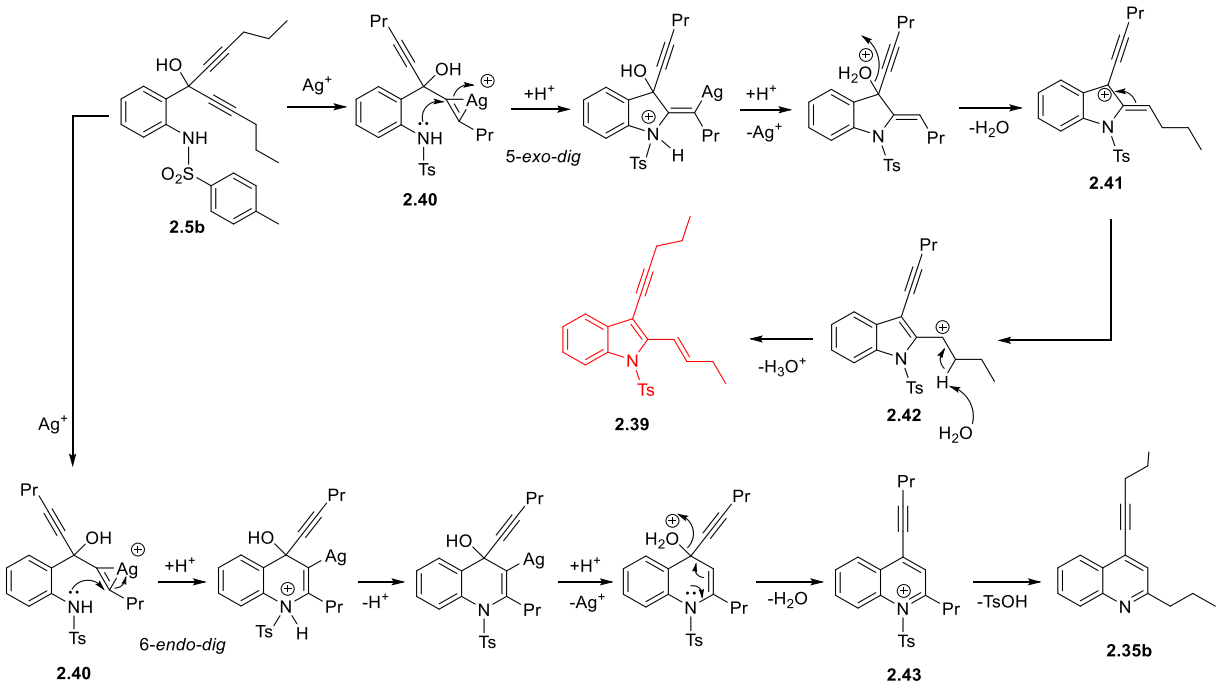
The cyclisation products from treatment of **2.5b** with AgOAc were thus the novel 3-alkynylindoles **2.32b** and **2.39** and the 4-alkynylquinoline **2.35b** (Scheme 2.48).



Scheme 2.48

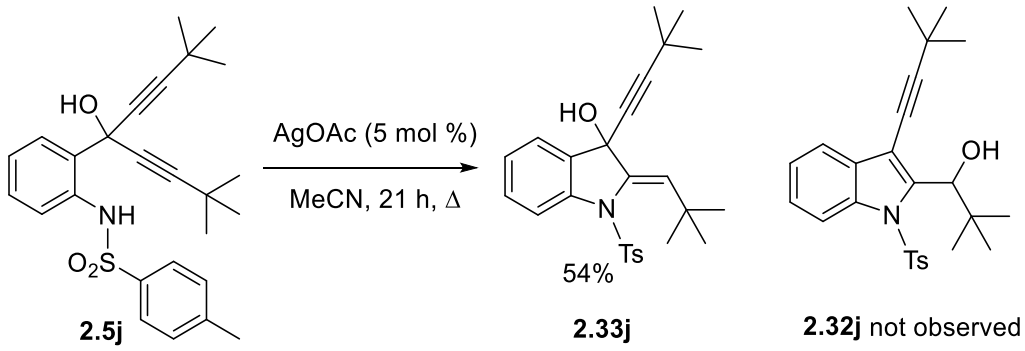
As with the formation of the 2-(α-hydroxyalkyl)indoles **2.32** (Scheme 2.47) a possible mechanism for the generation of the 2-buten-1-ylindole **2.39** (Scheme 2.49) involves initial coordination of silver(I) to the triple bond, forming the π-complex **2.40** which is then attacked by the nucleophilic sulfonamide function and intramolecular cyclisation *via* a 5-*exo-dig* pathway. Subsequent protodeargenation and protonation of the alcohol, followed by dehydration will lead to the highly delocalised carbocation **2.41**. Deprotonation of the aromatic species **2.42** will afford alkene **2.39**. Elimination from **2.42** occurs stereospecifically to afford the least sterically hindered (*E*)-alkene. In the case of the quinoline **2.35b** its formation proceeds by a 6-*endo-dig* cyclisation of the π-complex **2.40** and loss of water to

form the quinolinium salt **2.43**, which will facilitate displacement of tosyl the group to afford **2.35b** (Scheme 2.49).



Scheme 2.49

The reaction of the dilalkynol **2.5j** with AgOAc in MeCN (entry 6, Table 2.8) did not afford the expected indole **2.32j** Scheme 2.50. After careful consideration of the 1D (^{1}H and ^{13}C) and 2D (HSQC, HMBC, NOESY) NMR spectral data of the product, its structure was found to be the (*Z*)-3-(3,3-dimethylbut-1-yn-1-yl)-2-(2,2-dimethylpropylidene)-1-tosylindolin-3-ol **2.33j** (Scheme 2.50).



Scheme 2.50

The signals of interest in the ^{1}H spectrum of **2.33j** are the 4-*H* aromatic proton and methine proton. The 4-*H* proton for **2.33j** absorbs at δ_H 7.67 ppm as a doublet, whereas in the fully aromatic indole **2.32a** 4-*H* is deshielded and absorbs at δ_H 8.20 ppm. The methine proton in

tosylindolin-3-ol **2.33j** absorbs at δ_H 6.08 ppm as a singlet. However, it would be expected that the latter signal would be a doublet if the product from **2.5j** were the indole derivative **2.32j**, due to coupling of the methine proton with the OH moiety. Another indication that the product was the 2-(2,2-dimethylpropylidene)indoline **2.33j** accrued from comparison with the ^{13}C spectra of indole alcohols **2.32a** and **2.32b**. These latter compounds exhibited signals for the benzylic side-chain [Ar**C**H(OH)R] carbons at δ_C 68.38 and 68.74 ppm respectively. No similar resonance was observed for **2.33j**. The alkylidene carbon signal absorbed at δ_C 138.58 ppm as confirmed by a correlation in the HMBC spectrum (Figure 2.13) with the alkene proton signal at δ_H 6.08 ppm. These data confirmed that the C-2 side chain is sp^2 rather than sp^3 hybridised.

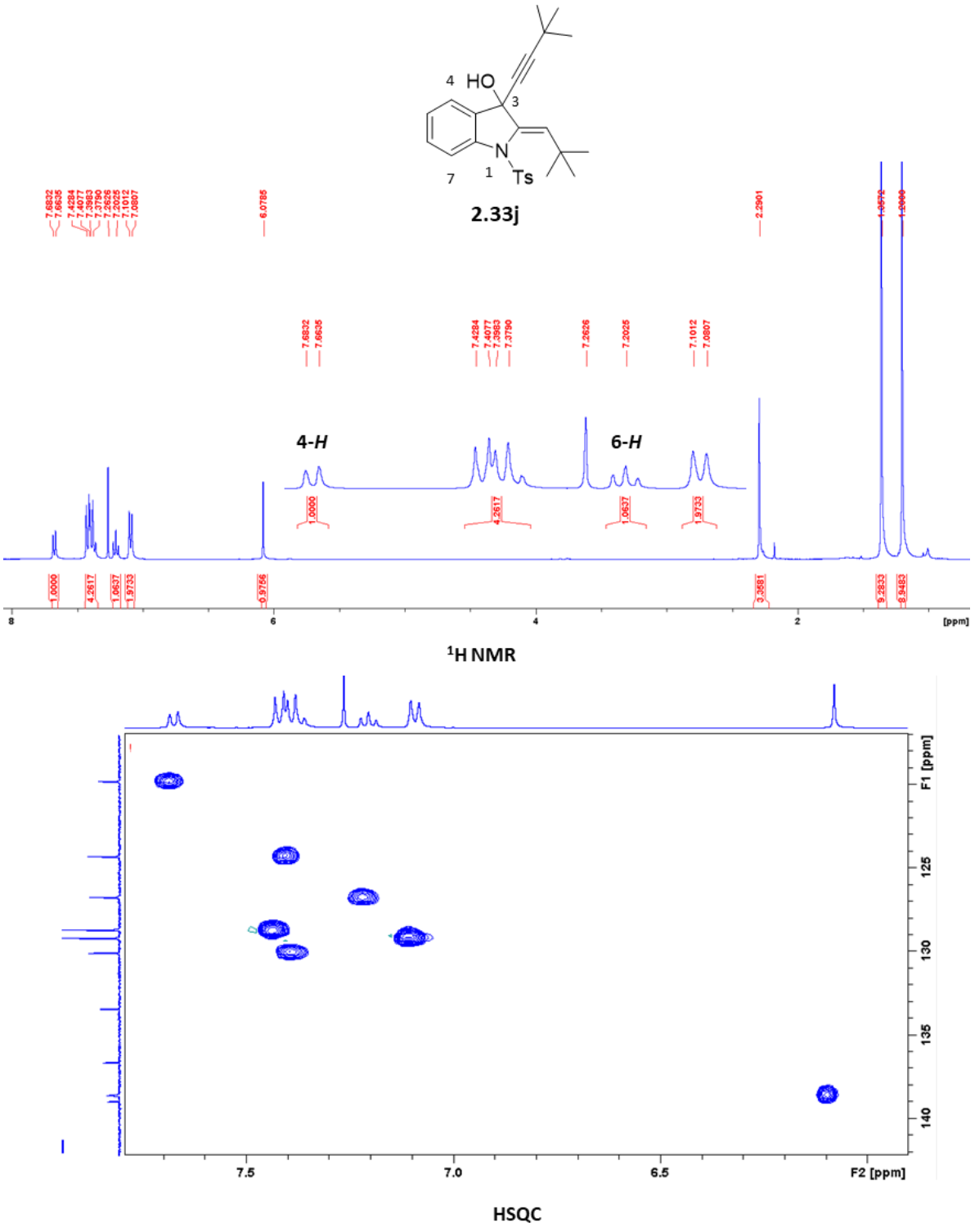
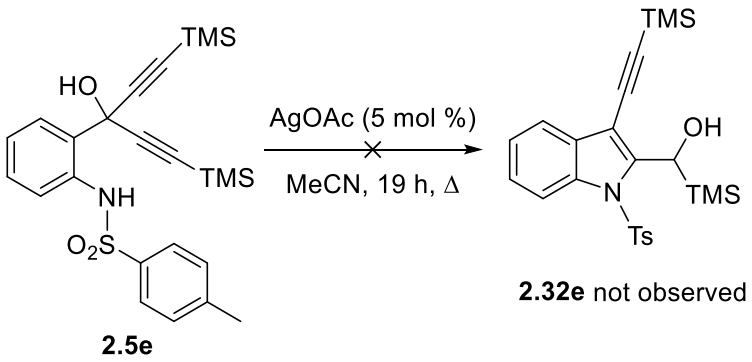


Figure 2.13 400 MHz ^{1}H NMR and HMBC spectra of **2.33j** in $CDCl_3$

Another example from this series of cyclisation reactions of 3-[2(tosylamido)phenyl]penta-1,4-diyn-3-ols **2.5a – k** with AgOAc which also provided different products to the expected indole was the dialkynol derivative **2.5a** (entry 4, Table 2.8) Scheme 2.51.

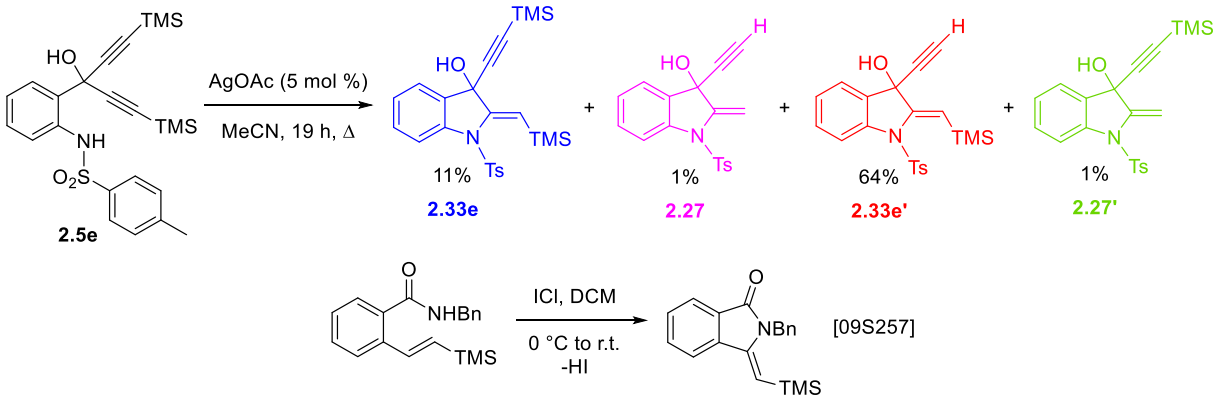


Scheme 2.51

However, treatment of **2.5e** with AgOAc in MeCN did not provide any of the α-(trimethylsilyl)arylmethanol **2.32e**. Despite their apparent simplicity, such compounds are generally only accessible *via* a Wittig-type rearrangement. For example, $PhCH(OH)SiMe_3$ has only been prepared *via* deprotonation of $PhCH_2OSiMe_3$ with *s*-BuLi in THF at r.t. [82JOC5051].

The reaction of *N*-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide **2.5e** with AgOAc, gave several products that could be separated by flash column chromatography on silica (10% EtOAc – petroleum ether) and obtained in varying yields (Scheme 2.52). The order in which the products eluted (left to right) is that as arranged in Scheme 2.52. Of note is that the major product was the vinylsilane **2.33e'**.

The formation of **2.33e** and **2.33e'** is of interest because it represents an unusual synthesis of an *exo*cyclic vinylsilane. Few examples of an analogous structural motif exist. An example is provided by the iodolactamisation of 2-[2-(trimethylsilyl)vinyl]-*N*-benzylbenzamide which proceeds with spontaneous elimination of HI to afford a phthalimide derivative (Scheme 2.52) [09S257].



Scheme 2.52

The structure of indolines **2.33e** and **2.33e'** were confirmed by their 1D (^{1}H and ^{13}C) and 2D NMR spectra (HSQC and HMBC) spectra. The ^{1}H and ^{13}C NMR data of significant signals in **2.33e** and **2.33e'** are shown in Table 2.9. The methine proton resonances are shielded in comparison to that in the indoline **2.33a** (δ_H 6.99 ppm) but similar to that of **2.33j** (δ_H 6.08 ppm). However the methine carbon resonances of **2.33e** and **2.33e'** are shielded compared with that of **2.33j** (δ_C 138.58 ppm) but similar to **2.33a** (δ_C 124.34 ppm). The shielding of the ^{1}H and ^{13}C signals seen in **2.33** and **2.33'** is probably due to the electron donating effect (+I) of the TMS group.

Indoline	4-*H* δ_H (ppm)	Methine Proton δ_H (ppm)	Methine Carbon δ_C (ppm)
2.33e	7.79	6.14	124.48
2.33e'	7.75	6.05	122.97

Table 2.9 ^{1}H and ^{13}C NMR data for **2.33e** and **2.33e'**

Comparative spectra for the four indolines generated from cyclisation of **2.5e** with AgOAc are presented in Figure 2.14.

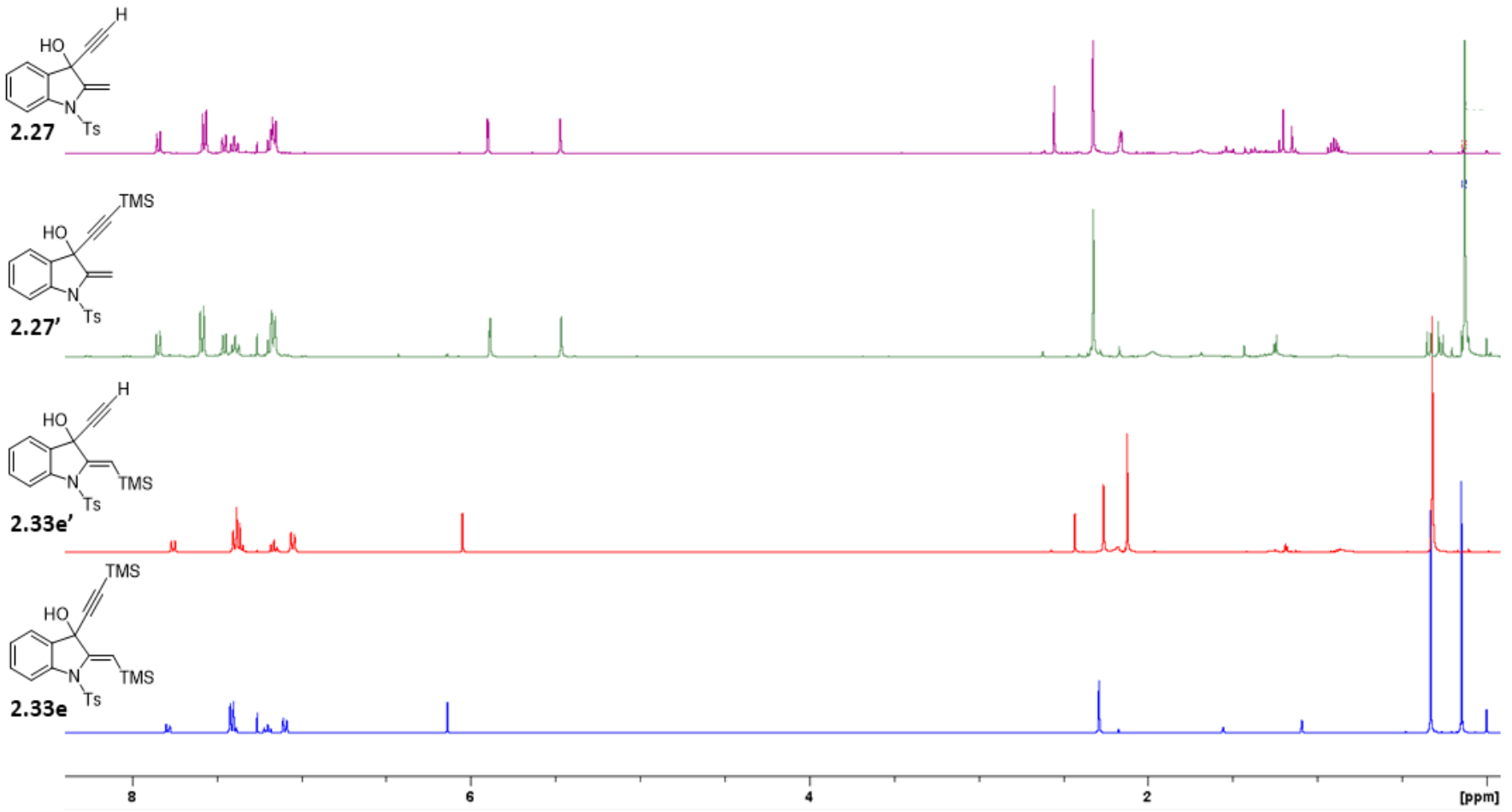
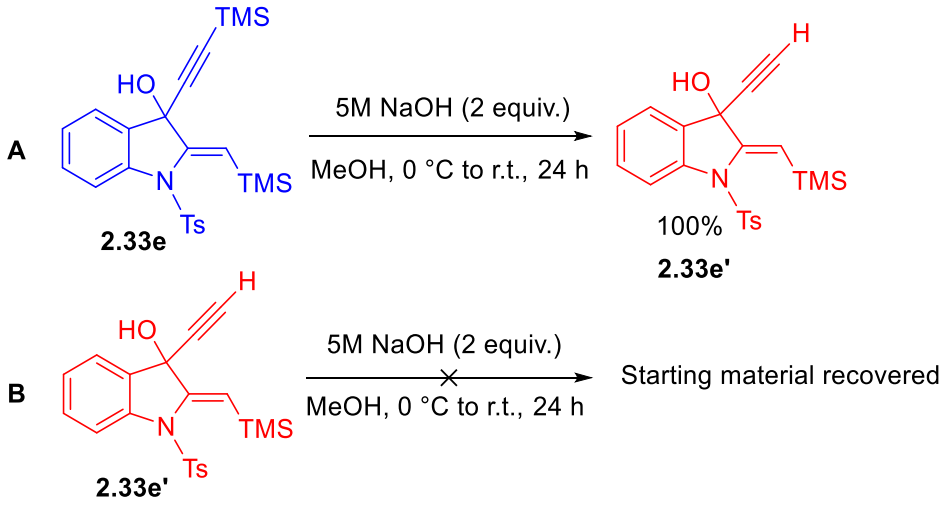


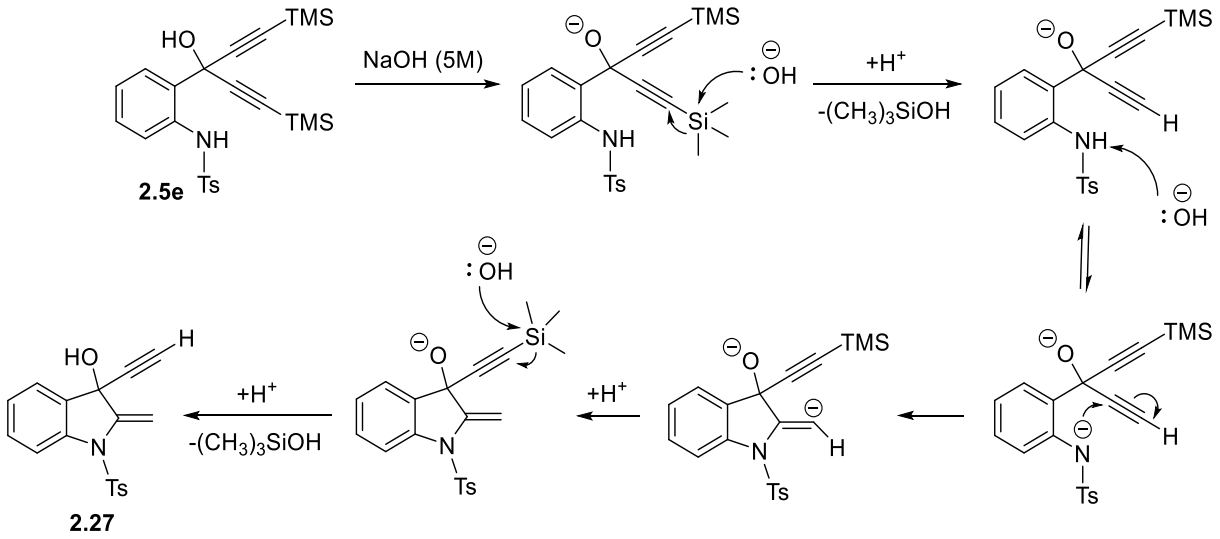
Figure 2.14 400 MHz ^{1}H NMR spectra comparison of **2.27, 2.27', 2.33e** and **2.33e'** in $CDCl_3$

To understand the nature of the cyclisation of **2.5e** further – both with base (Scheme 2.32) and Ag(I) catalysis – indolines **2.33e** and **2.33e'** were treated with 5M NaOH (2 equiv.) in MeOH for 24 h (Scheme 2.53). In the case of **2.33e** (**A**, Scheme 2.53) a quantitative yield of (*Z*)-3-ethynyl-1-tosyl-2-[(trimethylsilyl)methylene]indolin-3-ol **2.33e'** was obtained. However, use of excess base with **2.33e'** provided only unreacted starting material.



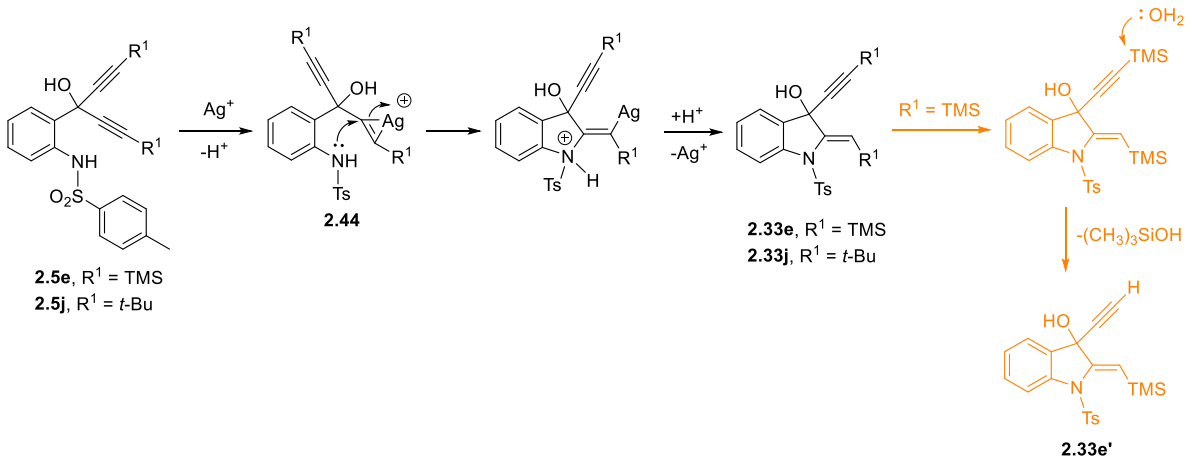
Scheme 2.53

The findings above provided an insight into the formation of indolines **2.27** and **2.27'**. Consequently, it can be envisaged that the reaction proceeds with removal of one of the TMS groups followed by cyclisation onto the ethynyl function. The remaining alkynylsilyl group will be deprotected. This sequence of events will also be applicable for the base-mediated 5-*exo-dig* cyclisation to **2.27** (Section 2.3, Scheme 2.32), Scheme 2.54 depicts the steps in the sequence.



Scheme 2.54

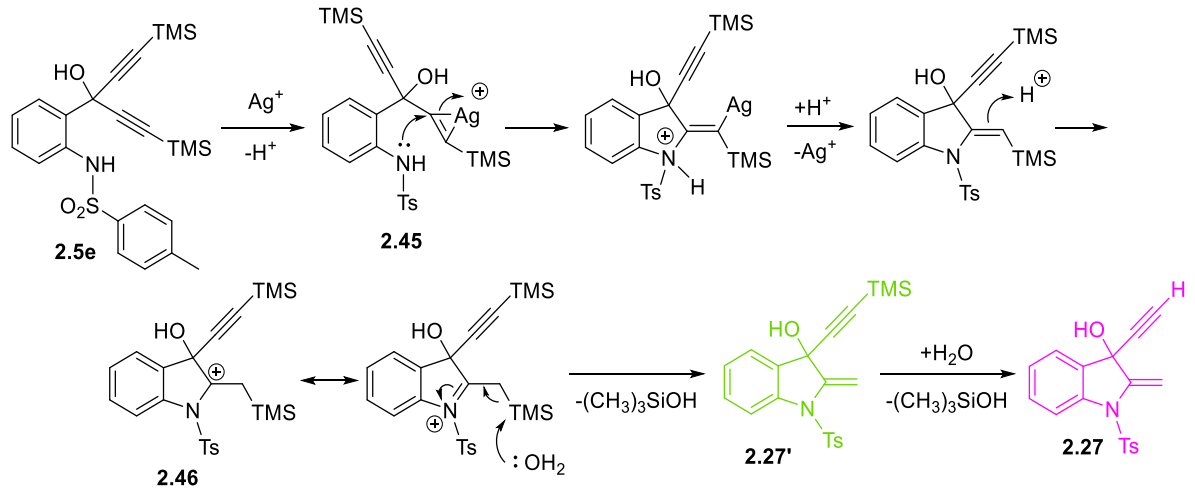
The formation of the indolines **2.33e, 2.33e'** and **2.33j** from the reaction of **2.5e – j** with AgOAc in MeCN can be postulated to proceed by the mechanism in Scheme 2.55. Coordination of silver(I) to the triple bond will form the π-complex (metallacyclopropenium ion) **2.44**, which is susceptible to attack by the nucleophilic nitrogen of the sulfonamide function and will cyclise accordingly *via* a 5-*exo*-*dig* pathway. Subsequent protodeargenation (loss of silver by attack of a proton) will afford the corresponding indoline **2.33e** and **2.33j.** In the case where R^1 = TMS the deprotection of the trimethylsilylethynyl group leads to **2.33e'** (Scheme2.55).



Scheme 2.55

The minor by-products from reaction of **2.5e** with AgOAc in MeCN (**2.27** and **2.27'**, Scheme 2.52) will procced by coordination of silver(I) to the triple bond will form the

metallacyclopropenium ion **2.45** which is susceptible to attack by the nucleophilic sulfonamide function and cyclisation *via* a 5-*exo*-*dig* pathway. However the vinylsilane will be protonated to form the carbocation **2.46** which can be stabilised by a combination of the β-silicon effect and electron release from the ring nitrogen. The carbocation is then susceptible to hydrolytic desilylation which in turn affords **2.27'**, further desilylation then affords **2.27** (Scheme 2.56).



Scheme 2.56

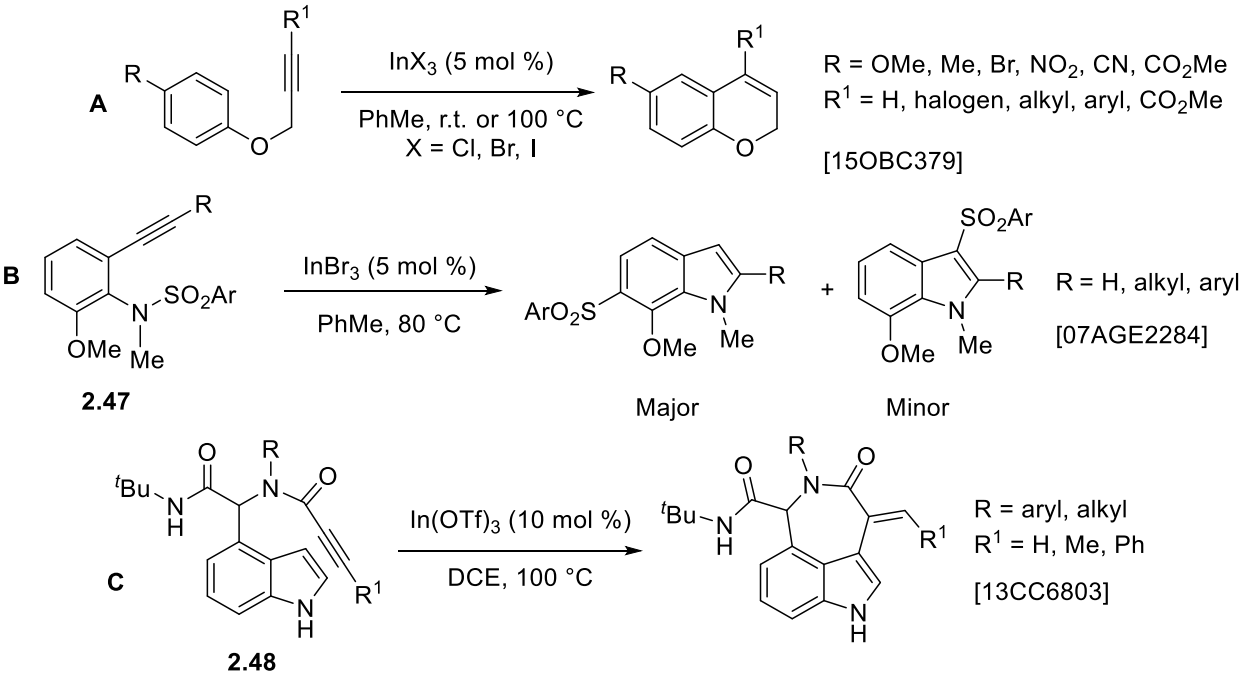
Thus, these findings parallel the report by Chan *et al.* [12JOC7166] that treatment 3-(2-*p*-tosylamidophenyl)penta-1,4-diyn-3-ols with AgOAc in MeCN, effects cyclisation *via* a 5-*exo*-*dig* pathway to indolines (Scheme 2.46) and not to indoles. Formation of indolines **2.33e** and **2.33j** in preference to the indoles **2.32e** and **2.32j** is possibly due to the presence of bulky groups (R^1 = *t*-Bu and TMS) hindering attack at the cationic centre. In the case of the TMS derivative, protonation of the indolin-3-ol and dehydration (E_1), will lead to a carbocation which cannot be stabilised by the β-silicon effect. Therefore, hydration of the alkene moiety (attack of H_2O) and aromatisation is very unlikely.

The reaction of dialkynols **2.5c, g** and **k** with AgOAc in MeCN failed to provide any tractable products (entries 3, 5 and 7 respectively, Table 2.8), only complex mixtures were obtained.

The reactions complied in Table 2.8 demonstrate that the product obtained from the AgOAc-mediated cyclisations of 3-[2(tosylamido)phenyl]penta-1,4-diyn-3-ols can be manipulated by the nature of the alkyne substituents.

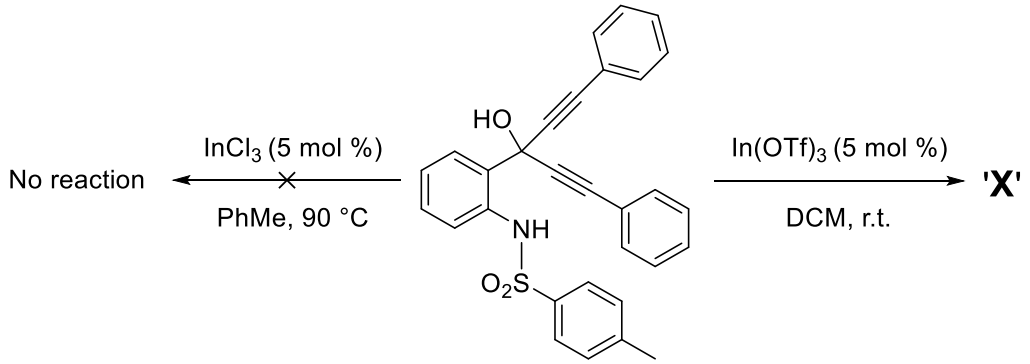
2.5 Indium(III) Promoted Cascade Cyclisation to a Furo[2,3-*c*]quinoline

In common with other group 13 elements In(III) exhibits Lewis acidity, albeit softer than other metal trihalides [63JA3533], such as $AlCl_3$ and BCl_3, due to its larger ionic radius. This Lewis acidity has been exploited for a variety of applications and In(III) use in synthesis to access a range of products has been reviewed a number of times [00EJO2347, 03S633, 07S1, 18OBC5733]. There are examples of In(III) reactivity towards alkynes in Scheme 2.57 and subsequent cyclisations to a variety of heterocycles [00EJO2347, 03S633, 07S1, 18OBC5733]. Indium-catalysed hydroarylation of aryl propargyl ethers proceeds efficiently to afford a range of 4-substituted 2*H*-chromenes (**A**, Scheme 2.57), including 4-halogenated chromenes (R^1 = Br, I) [15OBC379]. Nakamura and co-workers found that 2-alkynyl-6-methoxysulfonanilides **2.47** upon treatment with $InBr_3$, cyclised to indoles *via* a 5-*endo-dig* pathway (**B**, Scheme 2.57). Indium(III) also facilitated the migration of the arylsulfonyl group (1,3 and 1,7-migration) [07AGE2284]. Intramolecular hydroarylation of **2.48,** afforded azepinoindoles in high yields (60 – 89%) and could be initiated in the presence of $In(OTf)_3$ (**C**, Scheme 2.57) [13CC6803]. Surprisingly, there are no examples in the literature that describe the use of In(III) to cyclise propargylic alcohols, specifically analogues of 1-arylprop-2-yn-1-ols. It was therefore of interest to explore the behaviour towards the 3-arylpenta-1,4-diyn-3-ols.



Scheme 2.57

Initially **2.5a** was treated with indium(III) chloride in toluene at 90 °C for 20 h. TLC examination of the reaction mixture showed this to contain mostly unreacted starting material. Efforts to purify the mixture proved unsuccessful and only the starting material could be isolated. With this result, the reactivity of **2.5a** towards an alternative indium(III) salt – $In(OTf)_3$ – was investigated. Dialkynol **2.5a** was treated with $In(OTf)_3$ in DCM at room temperature for 2.5 h (Scheme 2.58). TLC examination again revealed the presence of mostly starting material, although a new faster running (non-polar) compound was also present. Purification of the reaction mixture by flash chromatography provided the faster running component, following recrystallisation from hexane – EtOAc, as a beige powder. The ^1H NMR spectrum of this unknown compound '**X**' showed an upfield shift of the aromatic protons compared to those of the indole systems but were similar to indoline **2.33a** as shown in Figure 2.15.



2.5a

Scheme 2.58

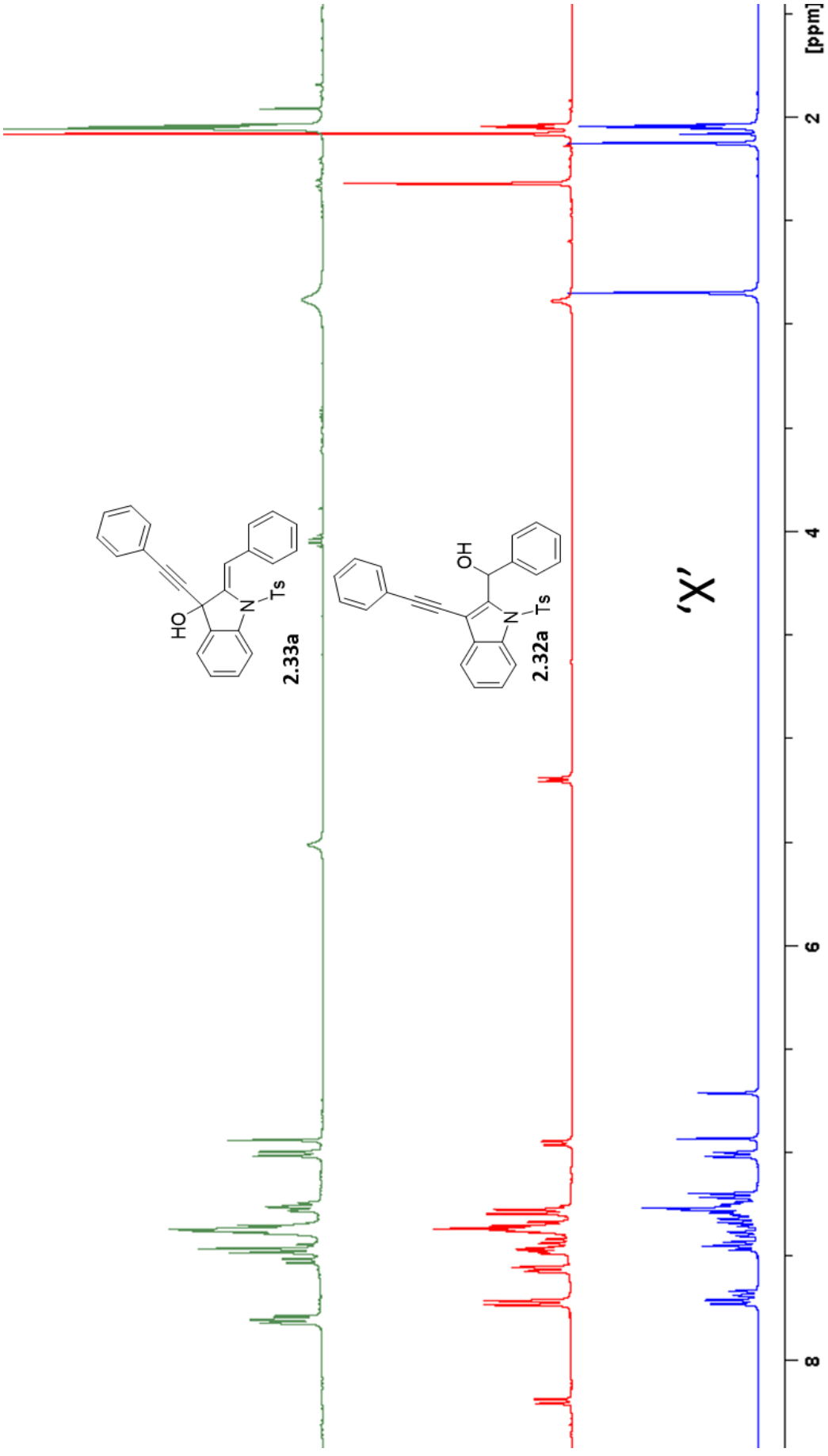


Figure 2.15 400 MHz ^{1}H NMR spectra comparison of **2.32a**, **2.33a** and '**X**' in acetone-d_6

Most surprising was the ^{13}C NMR spectrum (Figure 2.16), which revealed the absence of acetylenic carbon signals, evidently, both alkyne moieties had participated in this indium(III) catalysed reaction.

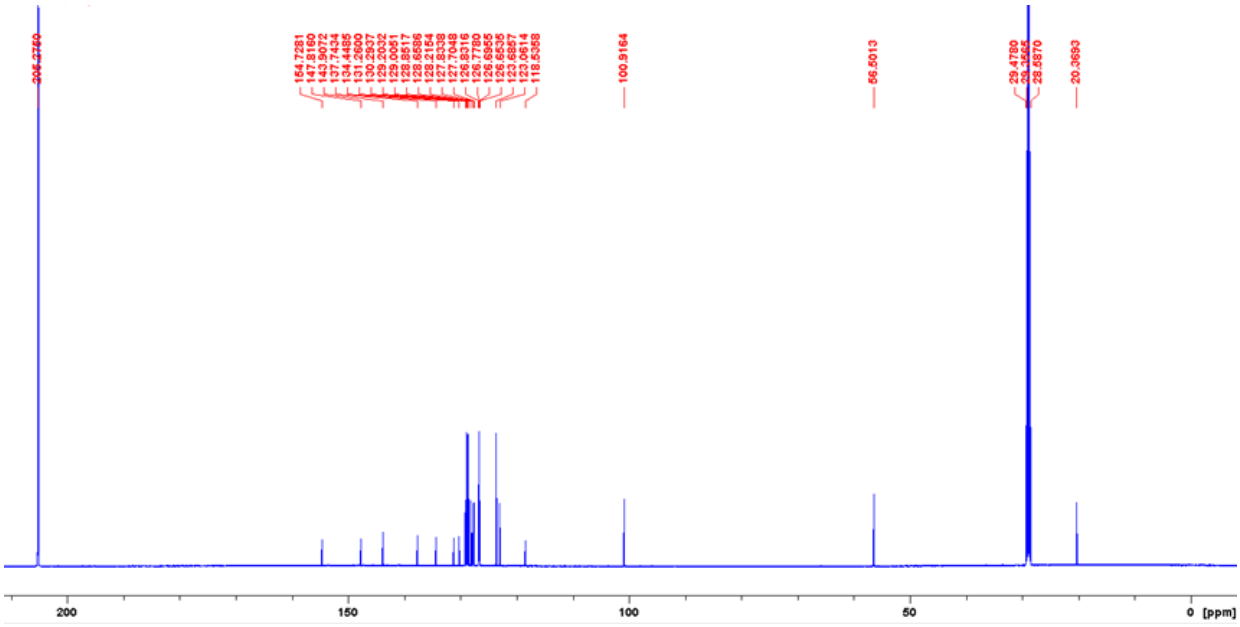
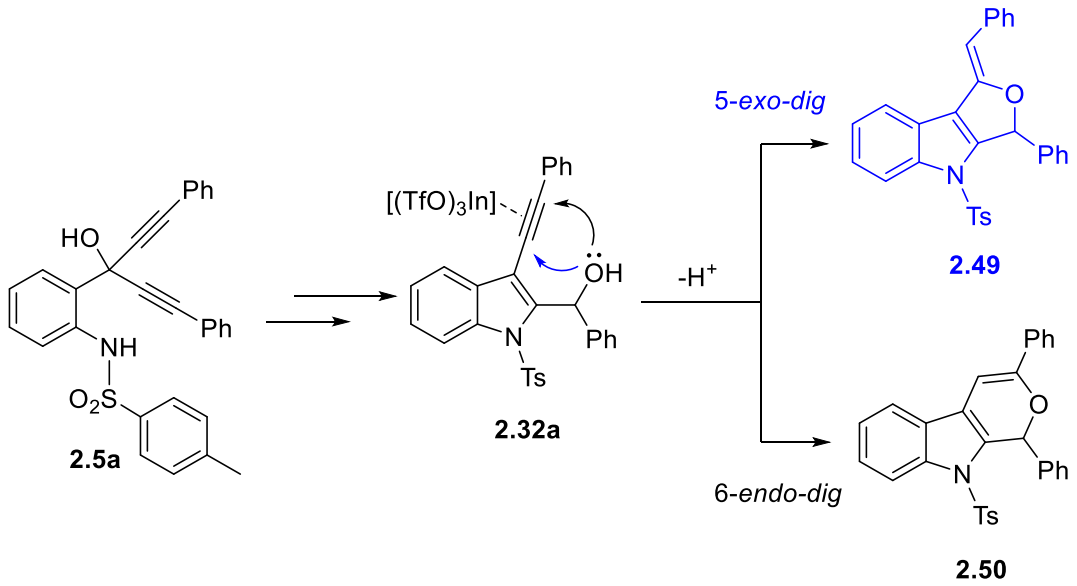


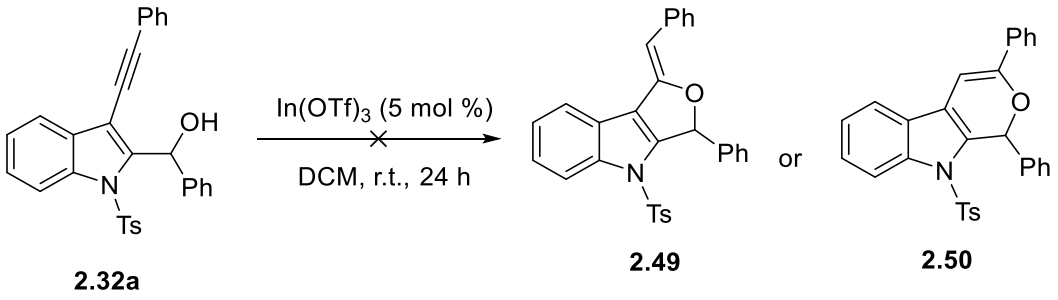
Figure 2.16 150 MHz ^{13}C NMR spectrum of unknown compound '**X**' in acetone-d_6

Two possible structures can be postulated from the NMR data, the furo[3,4-*b*]indole **2.49** or the pyrano[3,4-*c*]indole **2.50** which could have been derived from **2.32a** *via* a 5-*exo*-*dig* or 6-*endo*-*dig* cyclisation respectively (Scheme 2.59).



Scheme 2.59

However, treatment of the alcohol **2.32a** with $In(OTf)_3$ in DCM failed to effect cyclisation to '**X**'. TLC examination showed only starting material was present (Scheme 2.60).



Scheme 2.60

This finding established that neither **2.49** nor **2.50** was the product isolated from the reaction of **2.5a** with $In(OTf)_3$. Moreover, NMR data from similar fragments as the furo[3,4-*b*]indole **2.49** and pyrano[3,4-*c*]indole **2.50** – (*Z*)-2-benzylidene-5-phenyl-2,5-dihydrofuran **2.51** [09T1839] and 1,3-diphenyl-1*H*-isochromene **2.52** [17AGE5116] respectively – did not match the ^1H data of '**X**'. The chemical shift of the 3-*H* proton from 1,3-diphenyl-1*H*-isochromene (**2.52**), highlighted in red, is the only similar (δ_H 6.67 ppm, δ_C 100.4 ppm) aromatic resonance (Figure 2.17) [17AGE5116]. This data provided further confirmation that neither **2.49** nor **2.50** were the correct structure of '**X**'.

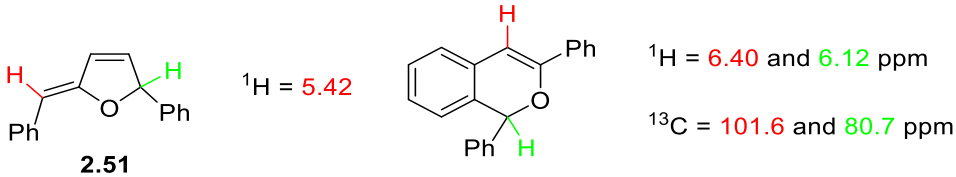


Figure 2.17 ^{1}H and ^{13}C NMR data for (*Z*)-2-benzylidene-5-phenyl-2,5-dihydrofuran **2.51** [09T1839] and 1,3-diphenyl-1*H*-isochromene **2.52** [17AGE5116]

After careful consideration, another possibility for the structure of '**X**' is the tricyclic 4,5-dihydrofuro[2,3-*c*]quinoline **2.53**, NMR data for this structure is a better fit with that of several model compounds and structural fragments shown below (Figure 2.18) [11JOC2379, 14CC8324, 17MI42168, 15AGE3116]. *N*-[Furan-2-yl(phenyl)methyl]-4-methylbenzenesulfonamide (structure **B**) is particularly informative due to the similar furan ^{1}H and ^{13}C shifts as well as the non-aromatic carbon ^{13}C (C-H) shift, with structure **C** also confirming that 2-C is saturated as the ^{13}C shift is identical. The shift of the methine proton in **D** is similar to that in '**X**' i.e. structure **2.53**.

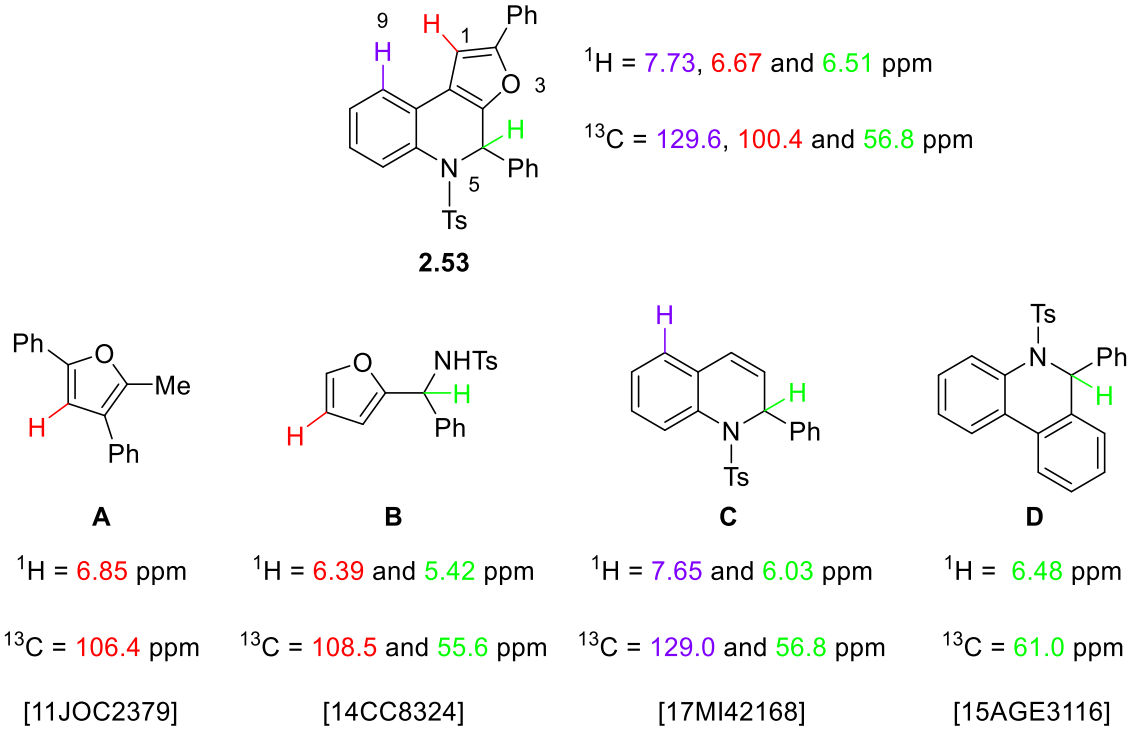
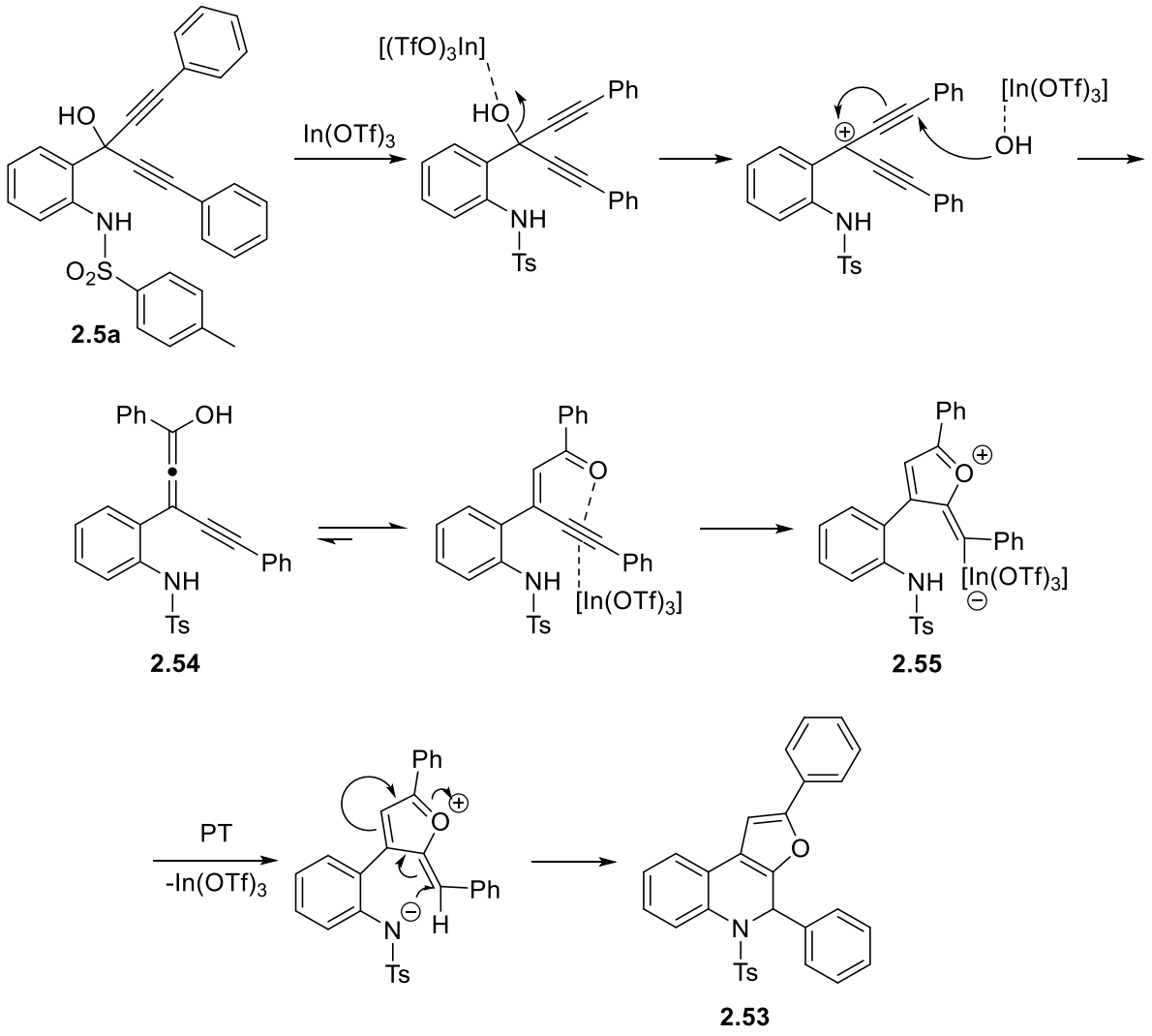


Figure 2.18 ^{1}H and ^{13}C data for structural fragments of **2.53**

The mechanism for the formation of this novel structure **2.53** is shown in Scheme 2.61. It can be postulated that dehydration of **2.5a** leads to the formation of a stabilised cation.

Hydroxide (or water) attack on one of the alkyne motifs, followed by tautomerization of this intermediate (**2.54**) produces an α,β-unsaturated ketone in a Meyer-Schuster rearrangement [00EJO2347, 03S633, 07S1, 16CC12147, 18OBC5733]. Indium activates the remaining alkyne function to attack from the carbonyl oxygen to form a conjugated oxonium cation **2.55**, nucleophilic attack of the sulfonamide nitrogen on this alkylidene intermediate will effect cyclisation to **2.53**.



Scheme 2.61

Reaction of indium(III) triflate with **2.5a** has therefore afforded a novel furoquinoline by an unprecedented cascade sequence. However the yield of **2.53** from the reaction was only 23%. In attempts to optimise the yield different solvents, catalysts and loadings were investigated (Table 2.10).

Entry	Catalyst	Loading (mol %)	Solvent	Temp (°C)	Time (h)	Yield of 2.53 (%) *
1	**$In(OTf)_3$**	**5**	**DCM**	**r.t.**	**2.5**	**23**
2	$In(OTf)_3$	10	DCM	r.t.	2.5	0
3	$In(OTf)_3$	15	DCM	r.t.	2.5	30
4	$In(OTf)_3$	2.5	DCM	r.t.	2.5	15
5	$In(OTf)_3$	5	MeOH	60	2.5	0
6	$In(OTf)_3$	5	MeCN	60	2.5	0
7	$In(OTf)_3$	5	EtOAc	60	2.5	0
8	$In(OTf)_3$	5	$CHCl_3$	60	2.5	0
9	$In(OTf)_3$	5	DCE	90	2.5	0
10	$In(OTf)_3$	5	70% EtOH aq.	90	2.5	0
11	$In(OTf)_3$	5	THF	66	22	0
12[a]	$In(OTf)_3$	5	DCM	r.t.	24	0
13[b]	$In(OTf)_3$	5	DCM	r.t.	24	0
14	$Ga(OTf)_3$	5	DCM	r.t.	24	0
15	$Sc(OTf)_3$	10	DCM	r.t.	24	0
16	AgOAc : $Sc(OTf)_3$	2 : 10	DCE	85	4	0
17[cd]	$AuPPh_3NTf_2$	2	Dry PhMe	110	20	0
18[d]	$Au(PPh)_3Cl$: AgOTf	5 : 2	Dry PhMe	110	22	0
19	$Cu(OTf)_2$	5	DCM	r.t.	24	0

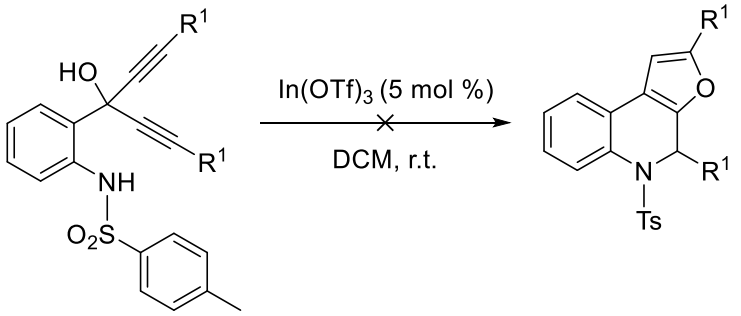
Table 2.10 Optimising conditions to **2.53**, *^{1}H NMR yields. a = 50 % w/w montmorillonite K-10 added, b = 10 equiv. of water added, c = 1 equiv. dry MeOH added, d = reaction carried out in the dark

All the yields in Table 2.10 (excluding entry 1) were derived from ^{1}H NMR data only, by the appearance and integration of two distinct signals present in the spectrum of **2.53** (δ_H 6.67 and 6.51 ppm, Figure 2.15). Scale may be a factor in the yields achieved, as the majority of the entries did not produce anything other than unreacted starting material.

The increased catalyst loading of In(III) (entry 3, Table 2.10) was scaled up to see if **2.53** could be isolated in a higher yield than the initial result with DCM. However at increased scale only 15% of 4,5-dihydrofuro[2,3-*c*]quinoline **2.53** could be isolated.

Changing the polarity of the solvent (DCM) to a more polar system (higher dielectric constant), could help stabilise the charged species formed (Scheme 2.61) and therefore increase the yield. However this modification did not enhance the reaction as envisaged. Other Lewis acids known for their alkynophilicity were investigated; Ga(III), Sc(III), Au(I) and Cu(II), [02JOC1414, 04T1959, 07AGE3140, 14AGE13532, 19OBC2663] unfortunately these reactions (entry 14 – 19, Table 2.10) only afforded unreacted starting material. Hence the conditions used initially (5 mol % $In(OTf)_3$ in DCM) were optimal. It is possible that purification of the crude reaction product plays a role in the yield obtained of **2.53**, thus the acidity of the silica used in flash column chromatography may cause degradation of the furoquinoline **2.53**.

Other dialkynols **2.5b** and **2.5c** were subjected to the conditions discussed above – $In(OTf)_3$ 5 mol % in DCM – but in each case only starting material was obtained (Scheme 2.62). The reasons for this outcome are unknown and it is proposed that the phenyl dialkynol analogue is a 'goldilocks' compound, because if the phenyl rings provide a stabilising effect then the 4-$MeOC_6H_4$ analogue **2.5c** should also have afforded the corresponding furo[2,3-*c*]quinoline.



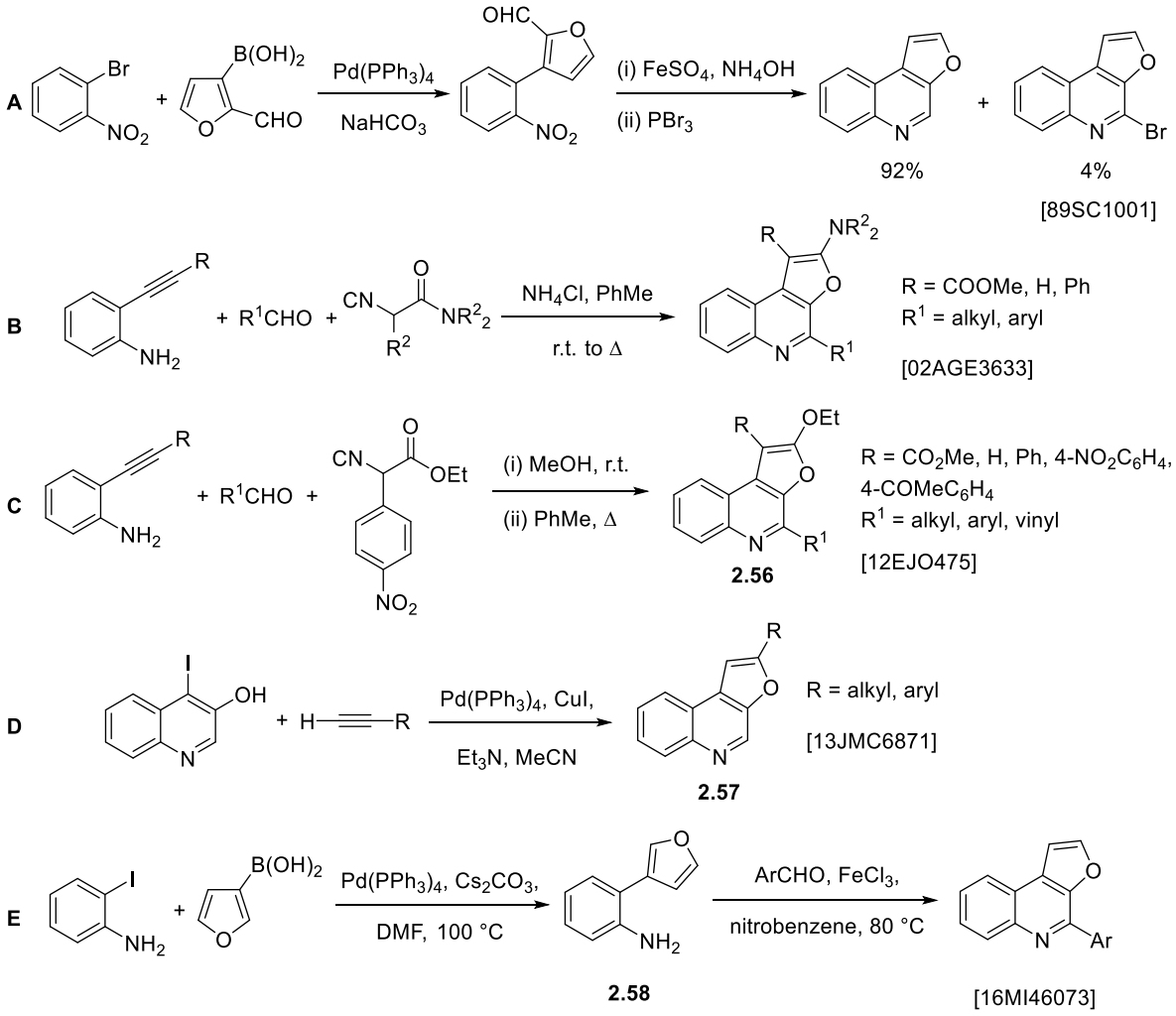
2.5b, $R^1 = C_3H_7$
2.5c, R^1 = 4-$MeOC_6H_4$

Scheme 2.62

The synthesis of the furoquinoline **2.53** is a remarkable result and warrants further investigation. Within the literature there is little work in relation to the synthesis of furo[2,3-*c*]quinolines, existing examples are shown in Scheme 2.63. Yang reported the coupling of 2-formyl-3-furanboronic acid with 2-bromonitrobenzene followed by reduction and deoxygenation with PBr_3 which yielded furo[2,3-*c*]quinoline in 92% yield together with 4-bromofuro[2,3-*c*]quinoline in 4% yield (**A**, Scheme 2.63) [89SC1001]. A one-pot reaction to 1,2,4-trisubstituted furo[2,3-*c*]quinolines involved the domino reaction of *ortho*-

alkynylanilines, aldehydes and an isocyanoacetamide (**B**, Scheme 2.63). The reactions provided the relevant furo[2,3-*c*]quinolines in fair to good yields (42 – 75%), and aryl, alkyl as well as electron withdrawing substituents can be introduced into the 4-position by this approach (derived from the aldehyde) [02AGE3633]. Scheme 2.63 **C** illustrates a similar method to afford 2-alkoxyfuro[2,3-*c*]quinolines **2.56** [12EJO475].

3-Hydroxyquinoline was utilised as a starting material for the synthesis of furo[2,3-*c*]quinolines by an initial iodination followed by a Sonogashira coupling, in which the Cu(I) also facilitates the 5-*endo-dig* cyclisation to **2.57** [13JME6871]. The coupling of a 3-furanylbornic acid with 2-iodoaniline affords **2.58**. Subsequent condensation with an aryl aldehyde in the presence of a catalyst results in the formation of the tricyclic system in a variant of the Pictet-Spengler reaction (**E**, Scheme 2.63). Both Lewis and Bønsted acids were employed, with iron(III) chloride found to be the most efficient (37 – 94% yield). By this method only 4-arylfuro[2,3-*c*]quinolines were synthesised, no other position of the ring system was substituted [16MI46073].

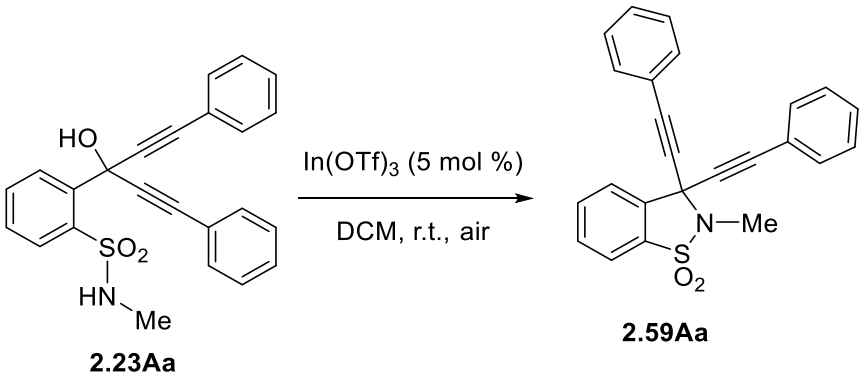


Scheme 2.63

With the novel furo[2,3-*c*]quinoline **2.53** being the only product obtained from the mild Lewis acid promoted dehydration of the sulfonamides **2.5a** – **2.5c**, attention now focussed on investigating the reactivity of 1,5-disubstituted-3-[2-(*N*-substituted sulfamoyl)phenyl]penta-1,4-diyn-3-ols (reversed sulfonamides **2.23Aa – Hb**) towards $In(OTf)_3$, using the conditions found to be optimum for the cyclisation of the dialkynol **2.5a** (entry 1, Table 2.10).

2.6 Indium(III) Mediated Synthesis of 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides

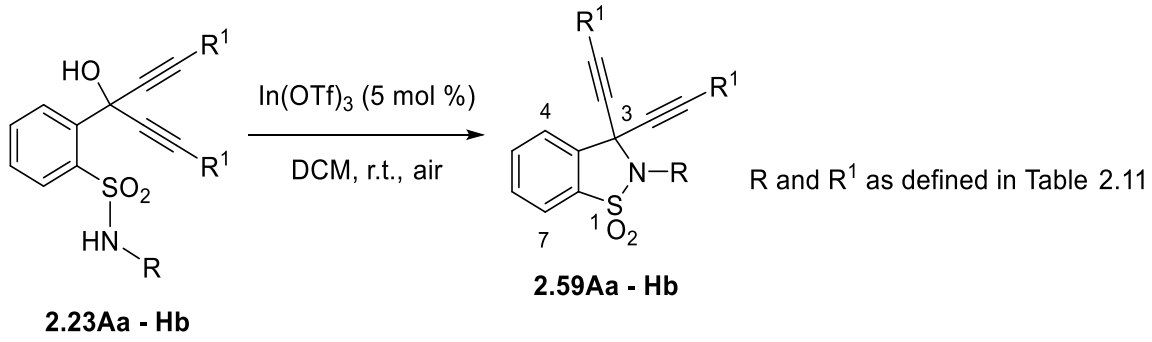
Initially a solution of the sulfonamide **2.23Aa** in DCM and 5 mol % $In(OTf)_3$ was stirred at room temperature (Scheme 2.64). TLC examination after 4 h showed no change, so the reaction mixture was left overnight. After this time the ^1H NMR spectrum of the crude reaction product revealed quantitative conversion to the novel 1,2-benzisothiazole 1,1-dioxide **2.59Aa**. Surprisingly both **2.23Aa** and **2.59Aa** have identical Rf values in a range of solvent systems, so the reaction may proceed to completion in less than 24 h.



2.23Aa **2.59Aa**

Scheme 2.64

The success of this novel cyclodehydration reaction prompted examination of the cyclisation of a range of the other reversed sulfonamides **2.23Aa – Hb** to these new 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb**, Scheme 2.65. The results are collated in Table 2.11.



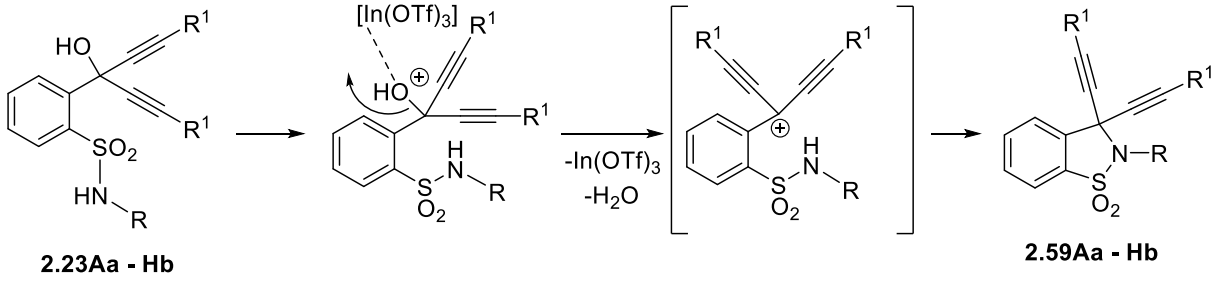
2.23Aa - Hb **2.59Aa - Hb**

Scheme 2.65

Entry	Dialkynol	R	R^1	1,2-Benzisothiazole 1,1-dioxide	Time (h)	Yield (%)
1	**2.23Aa**	Me	Ph	**2.59Aa**	24	100
2	**2.23Ab**	Me	C_3H_7	**2.59Ab**	5	92
3	**2.23Ba**	Tolyl	Ph	**2.59Ba**	24	100
4	**2.23Bb**	Tolyl	C_3H_7	**2.59Bb**	24	98
5	**2.23Bc**	Tolyl	4-$MeOC_6H_4$	**2.59Bc**	23	99
6	**2.23Be**	Tolyl	TMS	**2.59Be**	24	27
7	**2.23Bf**	Tolyl	CH_2OMe	**2.59Bf**	24	0
8	**2.23Ca**	3-MeC_6H_4	Ph	**2.59Ca**	24	53
9	**2.23Cb**	3-MeC_6H_4	C_3H_7	**2.59Cb**	24	82
10	**2.23Da**	2-$MeOC_6H_4$	Ph	**2.59Da**	22	37
11	**2.23Db**	2-$MeOC_6H_4$	C_3H_7	**2.59Db**	3	63
12	**2.23Ea**	3-$MeOC_6H_4$	Ph	**2.59Ea**	24	0
13	**2.23Eb**	3-$MeOC_6H_4$	C_3H_7	**2.59Eb**	24	100
14	**2.23Ga**	3-thienyl	Ph	**2.59Ga**	24	0
15	**2.23Gb**	3-thienyl	C_3H_7	**2.59Gb**	24	49
16	**2.23Ha**	2-naphthyl	Ph	**2.59Ha**	24	43
17	**2.23Hb**	2-naphthyl	C_3H_7	**2.59Hb**	7.3	45

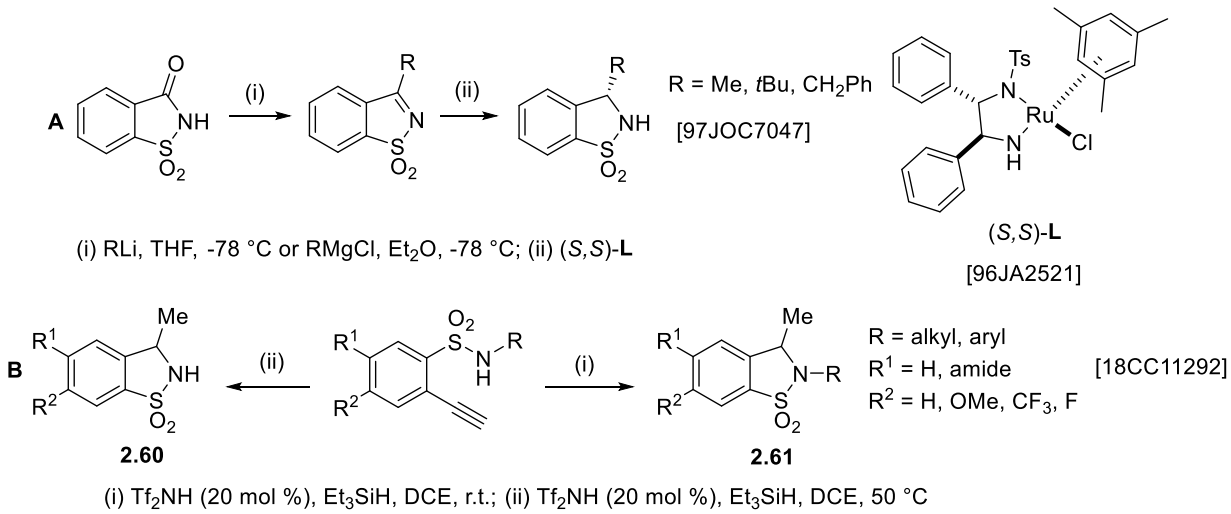
Table 2.11 Yields of $In(OTf)_3$ promoted cyclisation of **2.23Aa – Hb** to **2.59Aa – Hb**

Formation of **2.59Aa – Hb** is the result of an E_1 type elimination, facilitated by indium(III) coordination to the alcohol, the resulting carbocation will be highly stabilised but will be readily intercepted by the sulfonamide group (Scheme 2.66).



Scheme 2.66

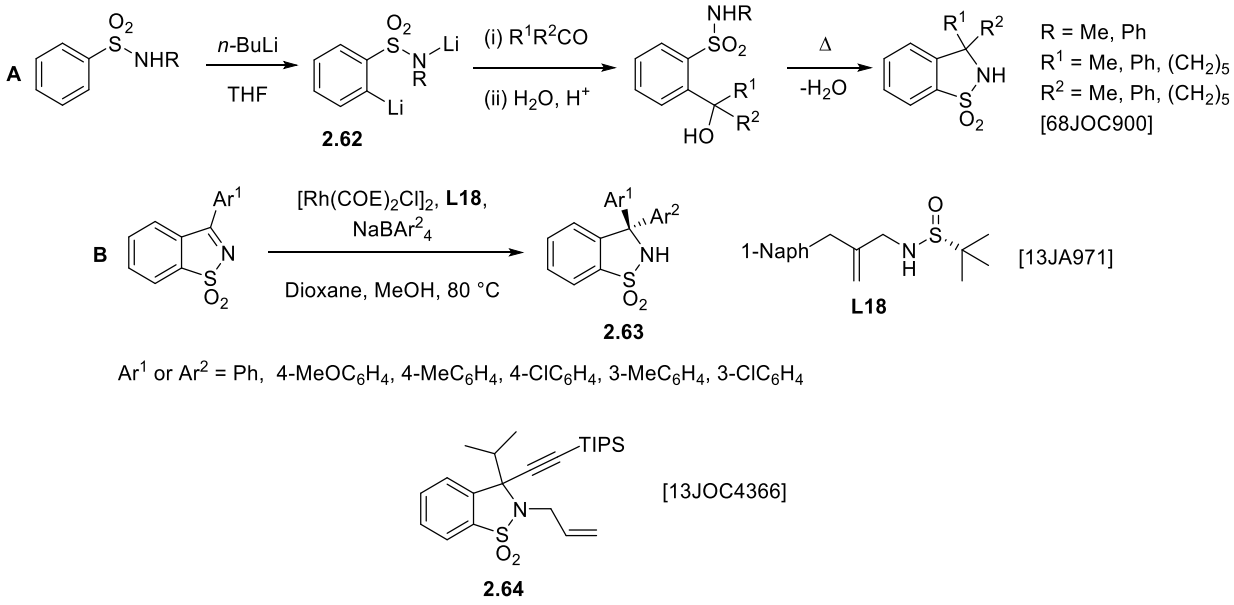
The foregoing cyclodehydration reaction constitutes a new approach to 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides although numerous routes to these systems exist (Scheme 2.67). For example, reduction of a 3-alkyl- or a 3-aryl-1,2-benzisothiazole 1,1-dioxide with a ruthenium(II) catalyst (**A**, Scheme 2.67) [96JA2521]. More recently, Tao and Gilbertson reported the Brønsted acid-mediated reductive cyclisation of an *ortho*-alkynyl sulfonamide to **2.60** (**B,** Scheme 2.67). It was also found that heating induces reductive cleavage of the sulfonamide *N*-substituent, resulting in the sultam **2.61** [18CC11292].



Scheme 2.67

However, less common are routes to 3,3-disubstitued-1,2-benzisothiazole 1,1-dioxides, some examples are shown in Scheme 2.68. The *N*-o*rtho* dilithiated benzenesulfonamides **2.62** have been intercepted with ketones and subsequent dehydration affords the

corresponding 1,2-benzisothiazole 1,1-dioxides (**A**, Scheme 2.68) [68JOC900, 79OR1]. Rhodium-promoted arylation of *N*-sulfonyl ketimines with sodium tetraarylborates in the presence of **L18** provided 3,3-diaryl-1,2-benzisothiazole 1,1-dioxides **2.63** with excellent enantioselectivity (94 – 98%) and high yields 72 – 90% (**B**, Scheme 2.68) [13JA971]. To date there is the only one example of a 3-alkynyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.64** (Scheme 2.68) however, Arai and co-workers did not report how it was synthesised [13JOC4366]. Therefore the results described above (Scheme 2.65) represents a novel pathway to the hitherto unknown 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb.**

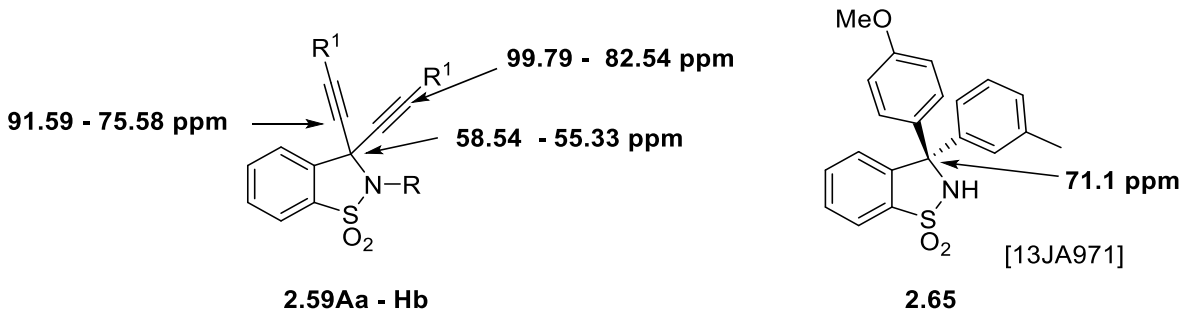


Scheme 2.68

The 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb** were characterised from their NMR spectra, which exhibited acetylene carbon resonances within the range of δ_C 99.79 – 75.58 ppm and the quaternary **C**-3 carbon absorbed in the range of δ_C 55.33 – 58.54 ppm (Figure 2.19). The most downfield acetylene carbon resonances (Figure 2.19) are from 2-(*p*-tolyl)-3,3-bis[(trimethylsilyl)ethynyl]-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide **2.59Be**.

The quaternary **C**-3 carbon exhibited the largest resonance change, being shifted upfield by up to 10 ppm in comparison to the starting dialkynols **2.23Aa – Hb** (Section 2.1, Table 2.6). This shift is not surprising after removal of the OH function. However, it is significantly different to that of **C**-3 in the 3,3-diaryl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.65**

(Figure 2.19) [13JA971]. Evidently the magnetic anistopy of the alkyne units in **2.59Aa – Hb** are responsible for this shielding.

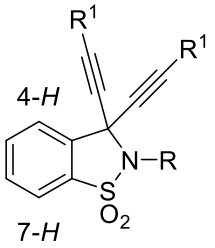


2.59Aa - Hb **2.65**

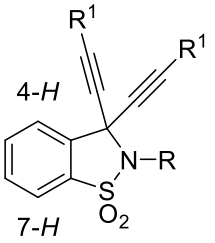
Figure 2.19 ^{13}C NMR data for **2.59Aa – Hb** and a derivative **2.65** [13JA971]

The reaction of 1,5-disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols (**2.23Bf**, **2.23Ea** and **2.23Ga**) with $In(OTf)_3$ in DCM, entries 7, 12 and 14 (Table 2.11) respectively, provided complex mixtures from which no identifiable products could be obtained. All the other reversed sulfonamides gave fair to excellent yields of the 1,2-benzisothiazole 1,1-dioxides. Where yields were poor the reaction failed to reach completion and unreacted starting material was recovered as the other component.

The aromatic 4-*H* protons signal of 3,3-di(arylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Ga** and **2.59Bc** are shifted further downfield than that of the 7-*H* protons (Table 2.12). However, in the 3,3-di(alkylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Ab – Gb, 2.59Be** and **2.59Bf** a differing trend in chemical shifts emerge, the 7-*H* signals are shifted downfield (Table 2.13). An exception of this trend is provided by the 2-(naphthalen-2-yl)-3,3-di(alkynyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxides **2.59Ha – b** where the chemical shifts are opposite to that described above. When R^1 = Ph (**2.59Ha**) 7-*H* proton resonance is shifted downfield and when $R^1 = C_3H_7$ (**2.59Hb**) 4-*H* proton is at lower field.



R = Tolyl, 3-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-thienyl
R^1 = Ph, 4-$MeOC_6H_4$



R = Tolyl, 3-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3-thienyl
R^1 = C_3H_7, TMS, CH_2OMe

	4-*H* **(ppm)**	**5-*H*** **(ppm)**	**6-*H*** **(ppm)**	**7-*H*** **(ppm)**
^{1}H	8.10 – 7.94	7.90 – 7.76	7.78 – 7.65	7.95 – 7.84

Table 2.12 ^{1}H NMR proton resonances of **2.59Aa – Ga** and **2.59Bc**

	4-*H* **(ppm)**	**5-*H*** **(ppm)**	**6-*H*** **(ppm)**	**7-*H*** **(ppm)**
^{1}H	7.74 – 7.82	7.75 – 7.50	7.65 – 7.56	7.87 – 7.72

Table 2.13 ^{1}H NMR proton resonances of **2.59Ab – Gb, 2.59Be** and **2.59Bf**

Assignments of protons signals in **2.59Aa – Hb** were established by their 2D NMR spectra (HSQC, HMBC and COSY). Figure 2.20 and Figure 2.21 show the HMBC spectra of **2.59Aa** and **2.59Bb** respectively. The HMBC spectrum 2-methyl-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Aa** (Figure 2.20) exhibits a through bond correlation between the 4-*H* proton at δ_H 7.90 ppm and the quaternary carbon **C**-3 at δ_C 57.01 ppm. The doublet at δ_H 7.84 ppm corresponding to 7-*H* shows a cross peak with the quaternary ring junction **C**-7a at δ_C 137.80 ppm. However, in 3,3-di(pent-1-yn-1-yl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Bb** the shifts of the 4-*H* and 7-*H* signals are reversed. Thus, Figure 2.21 exhibits a cross peak between the doublet (7-*H* proton) at δ_H 7.84 ppm and the ring junction carbon **C**-7a at δ_C 138.72 ppm. The 4-*H* proton resonates at δ_H 7.77 ppm and displays a through-bond correlation with the quaternary **C**-3 carbon at δ_C 57.93 ppm. These HMBC correlations allow the distinction between the 4-*H* and 7-*H* protons of the 3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb**.

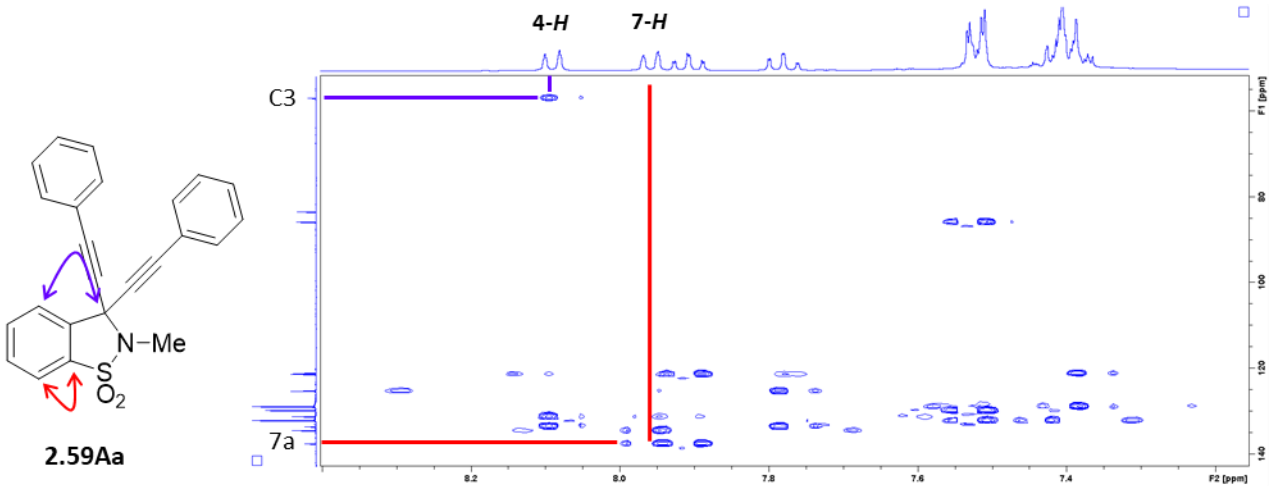


Figure 2.20 HMBC spectrum of **2.59Aa** in $CDCl_3$

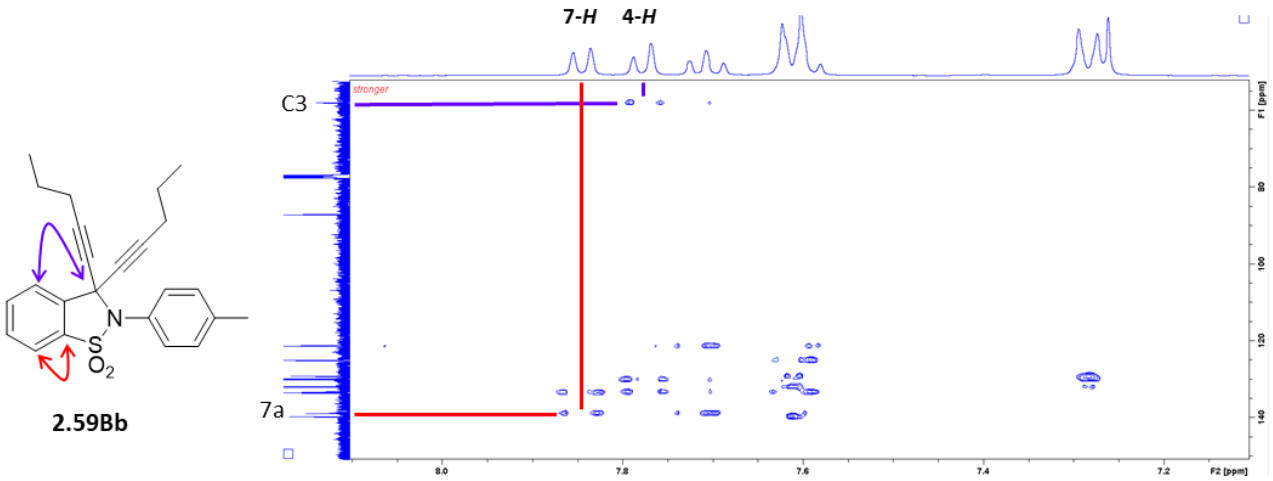
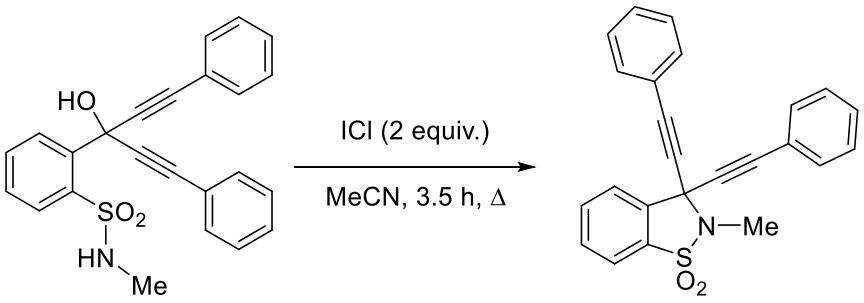


Figure 2.21 HMBC spectrum of **2.59Bb** in $CDCl_3$

2.7 Iodine-Mediated Cyclodehydration to 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides and 6-*Endo-Dig* Cyclisation to 1,2-Benzisothiazolo[2,3-*a*]quinolines

Other extensively used electrophilic activators that promote the cyclisation of alkynes and propargyl alcohols are iodine, iodine monochloride and NIS (Section 1.3) [14COS-II(4)412, 15S1961, 16OBC7639, 16MI49730]. They not only activate alkynes to nucleophilic attack and accompanying cyclisation, but an iodo-group can be incorporated into the structure, allowing further functionalisation of the ring.

With a selection of the reversed sulfonamide dialkynols **2.23Aa – Hb** to hand their reactivity towards an iodine electrophile was explored. Initially **2.23Aa** was subjected to optimised conditions found for another set of cyclisations (see Section 3.1); and was treated with 2 equiv. of ICl in MeCN. After 3.5 h at reflux the reaction mixture was quenched with aqueous sodium thiosulfate. Flash column chromatography (10% EtOAc – petroleum ether) of the crude material, provided 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxide **2.59Aa** in 48% yield as a brown oil (Scheme 2.69), a lower yield than that achieved with $In(OTf)_3$ in DCM (100%, entry 1, Table 2.11). However, this outcome is not too surprising as iodine monochloride (effectively I^+) is a softer Lewis acid compared to In(III) [63JA3533].



2.23Aa **2.59Aa**

Scheme 2.69

In order to investigate the scope of this iodine-promoted cyclisation the behaviour of the *N*-*p*-tolyl sulfonamide (**2.23Ba**) towards ICl was explored. Thus, treatment of **2.23Ba** with ICl (2 equiv.) in MeCN under reflux for 24 h gave a crude product that was purified by flash column chromatography (12% EtOAc – Pet ether). The ^{1}H NMR spectrum of the fast eluting fraction revealed the presence of 17 aromatic protons (Figure 2.22), one less than in the starting dialkynol **2.23Ba**, a high field broad singlet integrating for one proton at δ_H 6.68 ppm was also present. The ^{13}C NMR spectrum of this initial fraction showed that there was either only one alkyne unit intact or that both alkyne functions were in the same chemical environment (δ_C 86.82 and 83.99 ppm). In addition, a quaternary carbon signal at δ_C 64.97 was present. However these signals did not match those of the acetylenic and the **C**-3 quaternary carbons in the starting material **2.23Ba** (δ_C 67.05, 86.92 and 88.80 ppm), nor in 3,3-bis(phenylethynyl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Ba** (δ_C 86.19, 84.71 and 58.58 ppm). Another signal at δ_C 101.43 ppm suggested the presence of an alkenic carbon, perhaps indicating a C-I bond.

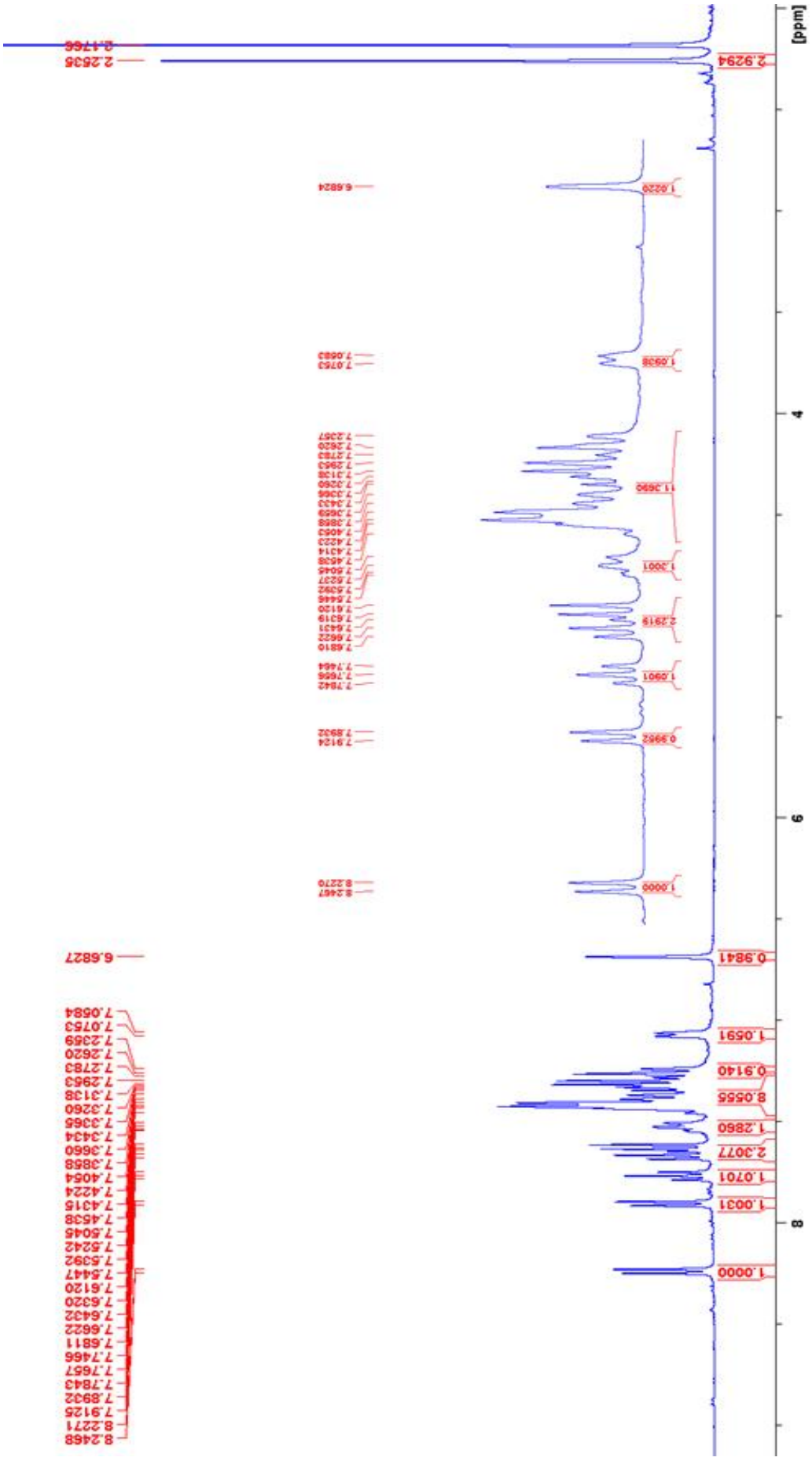


Figure 2.22 400 MHz ^{1}H NMR spectrum of the unknown iodocyclisation product in $CDCl_3$

The HRMS of this unknown compound revealed a molecular ion at *m/z* $[M+H]^+$ = 586.0328 corresponding to $C_{30}H_{20}INO_2S$. In order to definitely establish the constitution of this compound an X-ray crystal structure (Figure 2.23) was obtained and revealed the novel tetracyclic, 6a*H*-1,2-benzisothiazolo[2,3-*a*]quinoline structure **2.66Ba-3** (19% yield). The later eluting fraction from the column provided the 1,2-benzoisothiazole 1,1-dioxide **2.59Ba** in a 36% yield (Scheme 2.70).

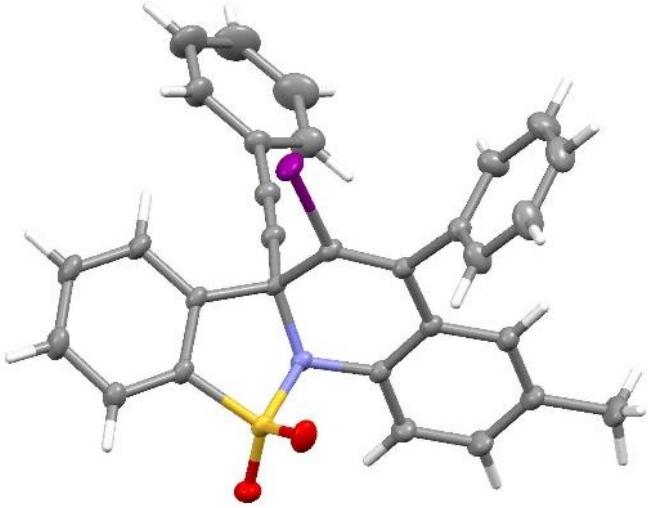
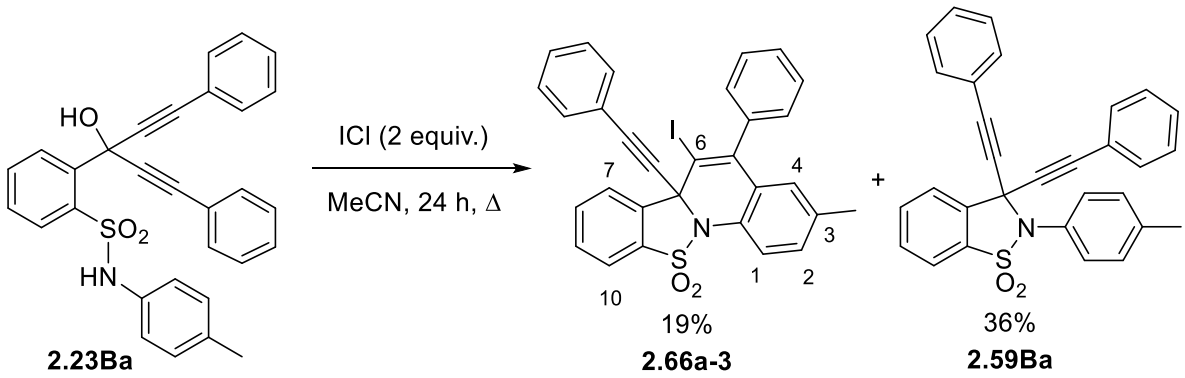


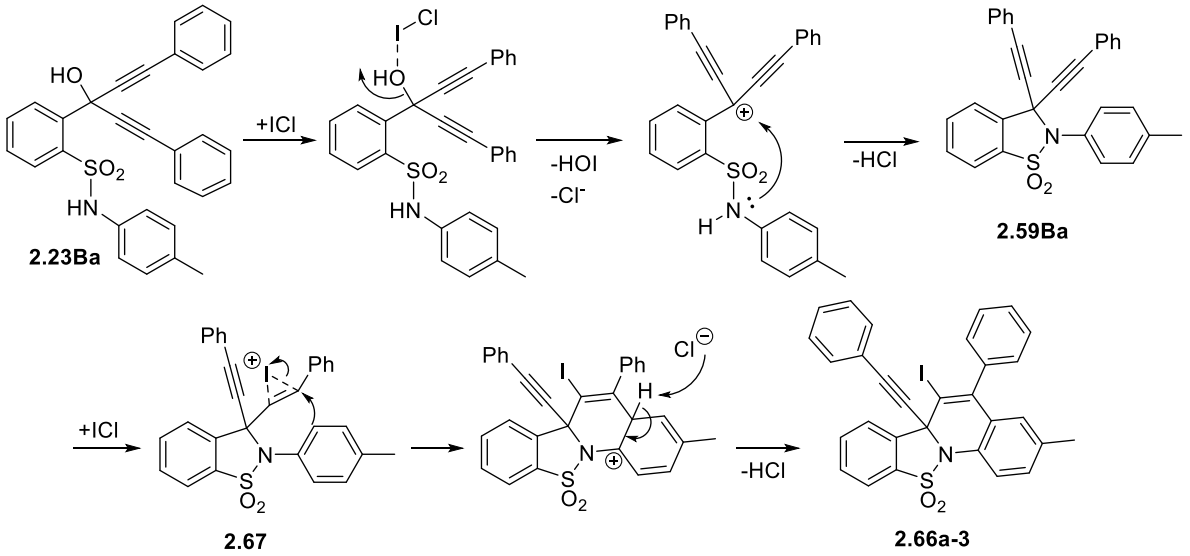
Figure 2.23 X-Ray crystal structure of 6-iodo-3-methyl-5-phenyl-6*a*-(phenylethynyl)-6*aH*-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide **2.66a-3**



Scheme 2.70

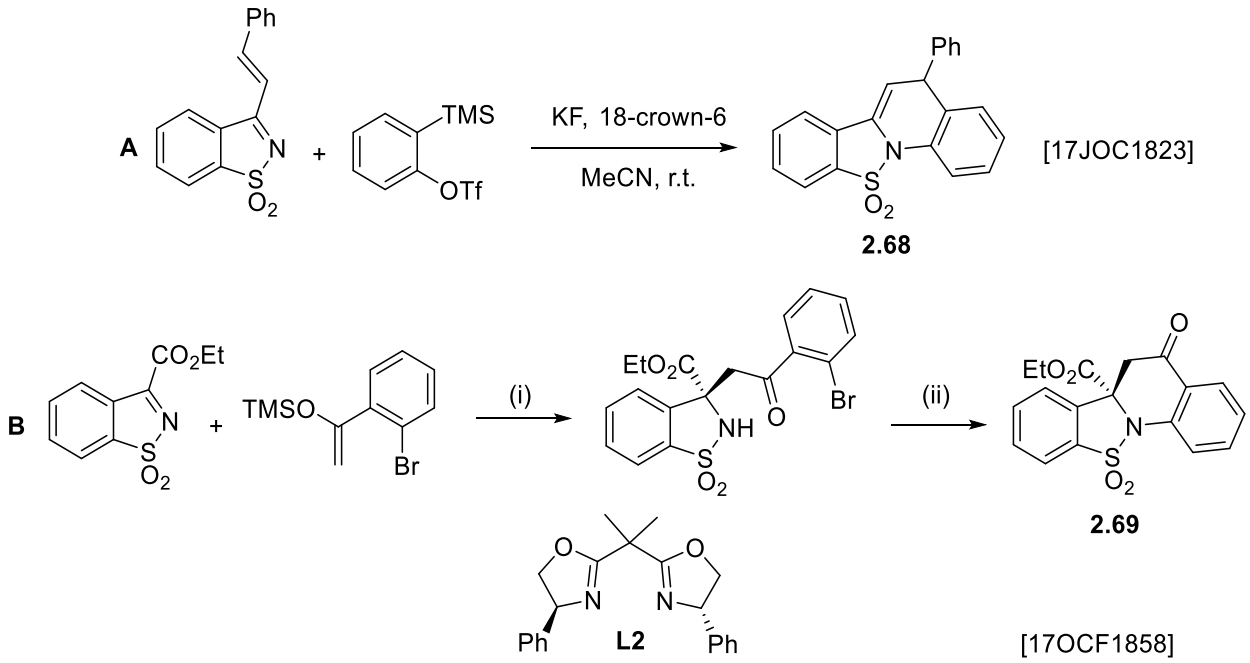
A plausible mechanism for the formation of **2.66a-3** is shown in Scheme 2.71. The initial step involves an E_1 elimination, from the alkynol facilitated by co-ordination of I^+. Following this, nucleophilic attack on the stabilised carbocation by the sulfonamide function will generate **2.59Ba** as an intermediate. Subsequent coordination of an iodine electrophile to

one of the alkyne moieties results in the formation of an iodonium ion (**2.67**). The latter is activated towards nucleophilic attack from the electron rich tolyl ring *via* a 6-*endo-dig* pathway, to give following completion of the S_EAr sequence, the 1,2-benzisothiazolo[2,3-*a*]quinoline **2.66a-3**.



Scheme 2.71

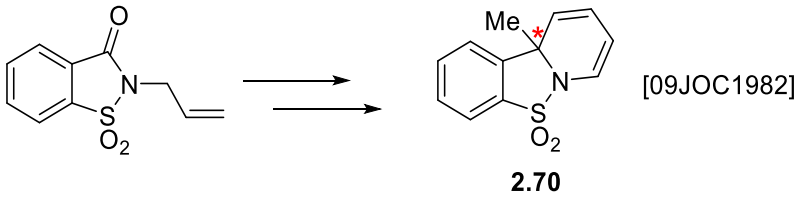
Ring systems such as **2.66a-3** possessing a 2,3-fused 1,2-benzisothiazole unit are unusual. Indeed, only two examples of the 1,2-benzisothiazolo[2,3-*a*]quinoline core have been reported (Scheme 2.72). Thus, Kiran *et al*. recently described the cycloaddition of 3-styryl-1,2-benzisothiazole 1,1-dioxide with benzyne, generated by the Kobayashi protocol, provided **2.68** in a 67% yield (**A**, Scheme 2.72) [17JOC1823]. A Ni-catalysed Mukaiyama-Mannich reaction between 3-(ethoxycarbonyl)-1,2-benzisothizole 1,1-dioxide and a silyl enol ether proceeds with a high degree of enantiocontrol and high yield (99% *ee*, 96% yield), in the presence of the chiral auxiliary **L2.** A subsequent intramolecular S_NAr reaction proceeds with displacement of bromide to provide the tetracycle **2.69** in an excellent yield 95% (**B**, Scheme 2.72) [17OCF1858].



(i) $Ni(ClO_4)_2 6H_2O$ (2 mol %), **L2** (2.2 mol %), $CHCl_3$, 0 °C; (ii) K_2CO_3, CuI, DMEDA, PhMe, 50 °C

Scheme 2.72

A tricyclic core closely related to **2.66a-3** was obtained from *N*-allylsaccharin *via* a five-step sequence by Modolo and co-workers [09JOC1982]. The starred quaternary carbon in Scheme 2.73 (**2.70**) resonates at δ_C 62.70 ppm, comparable to that observed for the teracycle **2.66a-3** which absorbs at δ_C 64.97 ppm.



Scheme 2.73

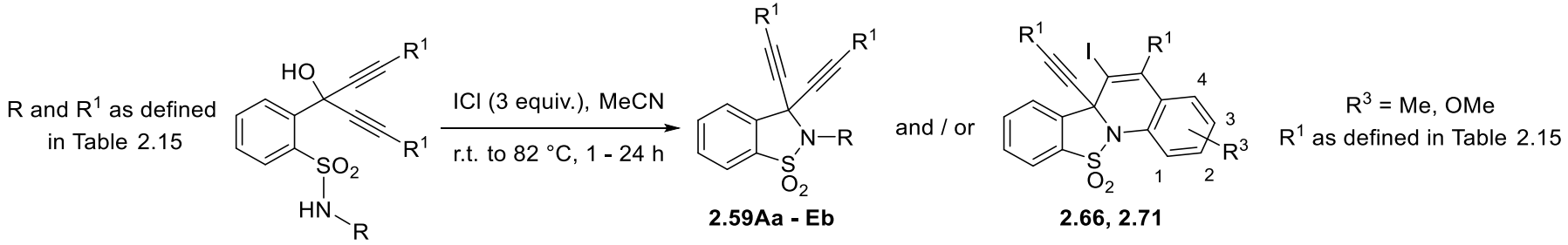
Attempts to optimise the yield of **2.66a-3** investigated the use of different solvents and electrophile ratios. The results are summarised in Table 2.14.

Entry	Electrophile	Equiv.	Solvent	Time (h)	2.59Ba Yield (%)	2.66a-3 Yield (%)
1	ICl	2	MeCN	24	36	19
2	**ICl**	**3**	**MeCN**	**24**	**45**	**35**
3	ICl	5	MeCN	24	36	33
4	I_2	3	MeOH	24	100	0

Table 2.14 Optimisation of iodocyclisation conditions to **2.66a-3**

Use of molecular iodine (entry 4, Table 2.14) provided only the 1,2-benzisothiazole **2.59Ba** in quantitative yield, none of the tetracycle **2.66a-3** was observed. Cyclisation to the latter proved to be most efficient with 3 equiv. ICl. Use of 5 equiv. did not increase the yield.

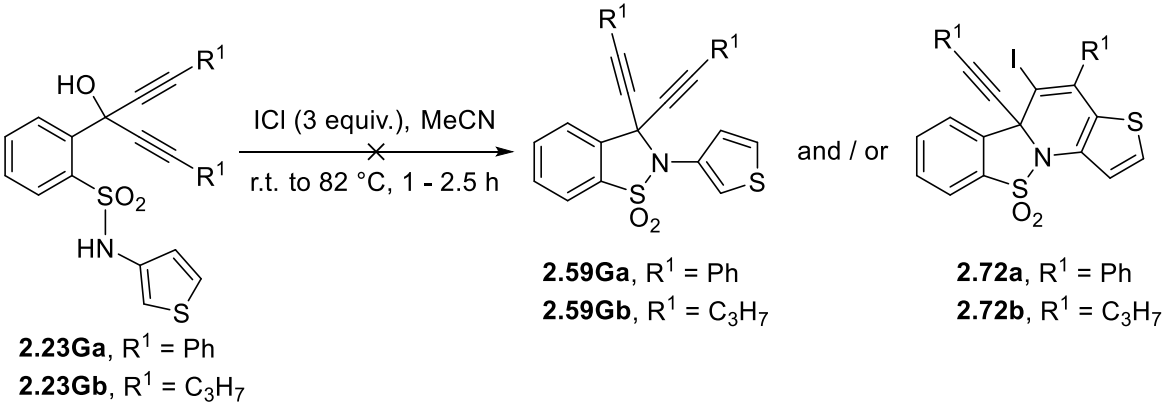
With the optimised iodocyclisation conditions at hand, their application to the propargyl alcohols **2.23Aa – Hb** was evaluated (Scheme 2.74 – 2.76). The results are compiled in Table 2.15 – 2.18.



Scheme 2.74

Entry	R	R^1	Dialkynol	Time (h)	Temp (°C)	1,2-Benzisothiazole	Yield (%)	Tetracycle	R^3	Yield (%)
1*	Me	Ph	**2.23Aa**	3.5	82	**2.59Aa**	48	**N/A**	N/A	N/A
2	Me	C_3H_7	**2.23Ab**	24	82	**2.59Ab**	0	**N/A**	N/A	N/A
3	Tolyl	Ph	**2.23Ba**	24	82	**2.59Ba**	45	**2.66a-3**	Me	35
4	Tolyl	C_3H_7	**2.23Bb**	3.5	r.t.	**2.59Bb**	36	**2.66b-3**	Me	33
5	Tolyl	4-$MeOC_6H_4$	**2.23Bc**	22	82	**2.59Bc**	0	**266c**	Me	0
6	Tolyl	CH_2OMe	**2.23Bf**	1	82	**2.59Bf**	40	**2.66f**	Me	0
7	3-MeC_6H_4	Ph	**2.23Ca**	4.5	82	**2.59Ca**	47	**2.66a**	Me	0
8	3-MeC_6H_4	C_3H_7	**2.23Cb**	1.5	82	**2.59Cb**	75	**2.66b**	Me	0
9	2-$MeOC_6H_4$	Ph	**2.23Da**	3	82	**2.59Da**	0	**2.71a**	OMe	0
10	2-$MeOC_6H_4$	C_3H_7	**2.23Db**	21	82	**2.59Db**	0	**2.71b**	OMe	0
11	3-$MeOC_6H_4$	Ph	**2.23Ea**	21	82	**2.59Ea**	0	**2.71a**	OMe	0
12	3-$MeOC_6H_4$	C_3H_7	**2.23Eb**	21	82	**2.59Eb**	54	**2.71b**	OMe	0

Table 2.15 Yields from the iodocyclisation of dialkynols **2.23Aa – Eb** with ICl. *2 equiv. of ICl used



2.23Ga, R^1 = Ph
2.23Gb, R^1 = C_3H_7

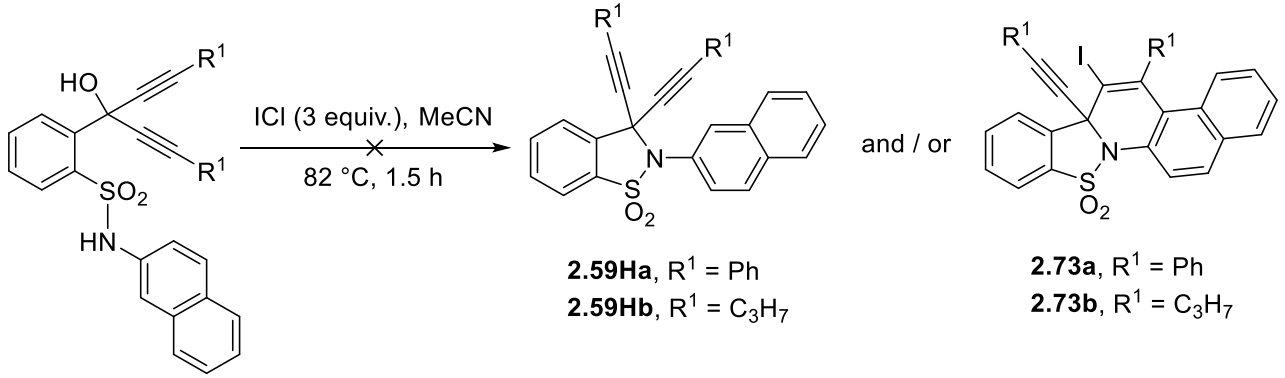
2.59Ga, R^1 = Ph
2.59Gb, R^1 = C_3H_7

2.72a, R^1 = Ph
2.72b, R^1 = C_3H_7

Scheme 2.75

Entry	R	R^1	Dialkynol	Time (h)	Temp (°C)	1,2-Benzisothiazole	Yield (%)	Tetracycle	Yield (%)
1	3-thienyl	Ph	**2.23Ga**	2.5	r.t.	**2.59Ga**	0	**2.72a**	0
2	3-thienyl	C_3H_7	**2.23Gb**	1.5	82	**2.59Gb**	0	**2.72b**	0

Table 2.16 Attempted iodocyclisations of dialkynols **2.23Ga – b** with ICl



2.23Ha, R^1 = Ph
2.23Hb, R^1 = C_3H_7

2.59Ha, R^1 = Ph
2.59Hb, R^1 = C_3H_7

2.73a, R^1 = Ph
2.73b, R^1 = C_3H_7

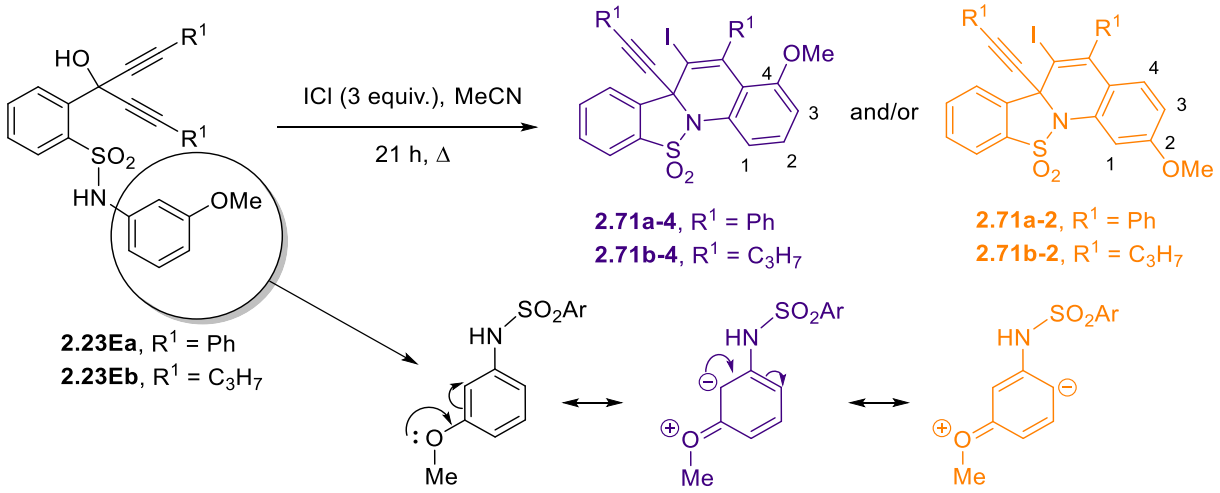
Scheme 2.76

Entry	R	R^1	Dialkynol	Time (h)	Temp (°C)	1,2-Benzisothiazole	Yield (%)	Tetracycle	Yield (%)
1	2-naphthyl	Ph	**2.23Ha**	1.5	82	**2.59Ha**	0	**2.73a**	0
2	2-naphthyl	C_3H_7	**2.23Hb**	1.5	82	**2.59Hb**	0	**2.73b**	0

Table 2.17 Attempted iodocyclisations of dialkynols **2.23Ha – b** with ICl

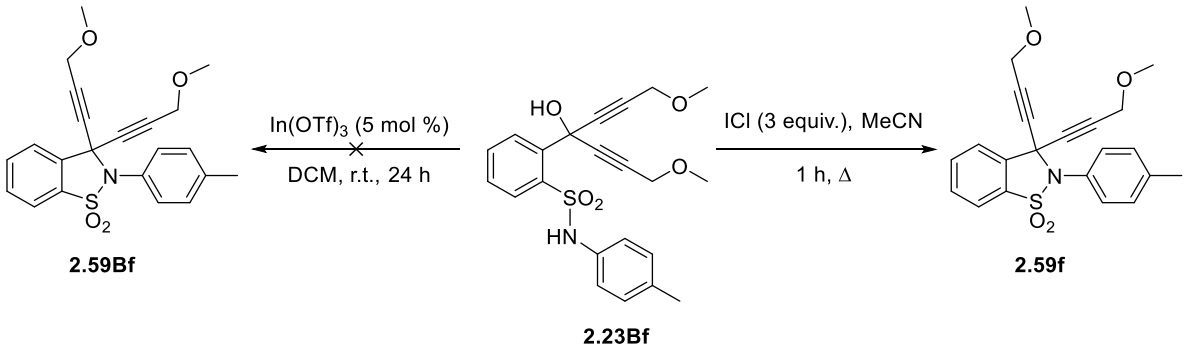
The majority of reactions, summarised in the entries in Table 2.15 – 2.17 gave complex mixtures from which no identifiable products could be isolated. Only *N*-*p*-tolyl (R^1 = Ph and C_3H_7 analogues) entries 3 and 4 (Table 2.15) gave the corresponding 1,2-benzisothiazolo[2,3-*a*]quinoline (**2.66a-3** and **2.66b-3**). It is surprising that the reversed sulfonamides with *N*-(3-thienyl) units (**2.23Ga – b**) entries 13 and 14 (Table 2.16) failed to give tractable products, as both the C-2 and C-5 positions on the 3-thienyl derivatives are activated for electrophilic attack.

Moreover, dialkynols **2.23Ea – b** should also be activated to attack from electrophiles in the *ortho* (to the nitrogen) position on the aromatic ring, due to the methoxy group being *ortho*/*para* directing (Scheme 2.77). It would be expected that cyclisation of **2.23Ea – b** would afford the 1,2-benzisothiazolo[2,3-*a*]quinolines **2.71a – b-2** as these would be the least hindered products.



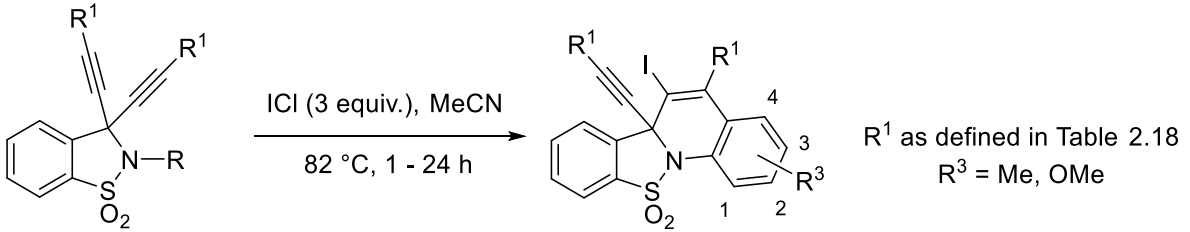
Scheme 2.77

Another interesting result from these ICl cyclisations is the formation of the 3,3-bis(3-methoxyprop-1-yn-1-yl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Bf** (entry 6, Table 2.15). When the reversed sulfonamide **2.23Bf** was treated with $In(OTf)_3$; which proved to be highly effective in the dehydration and cyclisation of the dialkynols **2.23Aa – Hb**, none of the corresponding 1,2-benzisothiazole (**2.59Bf**) was isolated (Scheme 2.78). The reasons for this are not known, it could be postulated that the alkynyl unit being terminated with a methoxymethyl group will change the reactivity of the species towards certain Lewis acids, possibly *via* coordination to a OMe group.



Scheme 2.78

In order to verify the intermediacy of 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Ba – Hb** in the formation of 1,2-benzisothiazolo[2,3-*a*]quinoline **2.66a – c, e** and **2.71a – 2.73b**, it was thought that addition of an iodine electrophile to preformed **2.59Ba – Hb** in a separate reaction would also give **2.66a – c, e** and **2.71a – 2.73b**. Accordingly, treatment of **2.59Ba** with 3 equiv. of ICl in MeCN at reflux was investigated. After 24 h TLC examination showed that the reaction had gone to completion and work-up provided **2.66a-3** in an excellent yield (91%, entry 1, Table 2.18), thereby reinforcing the suggested mechanism in Scheme 2.71. The reactivity of **2.59Ba – Hb** towards the optimised conditions (3 equiv. ICl in MeCN) were investigated as shown in Schemes 2.79 and 2.80, the results are collated in Tables 2.18 and 2.19.

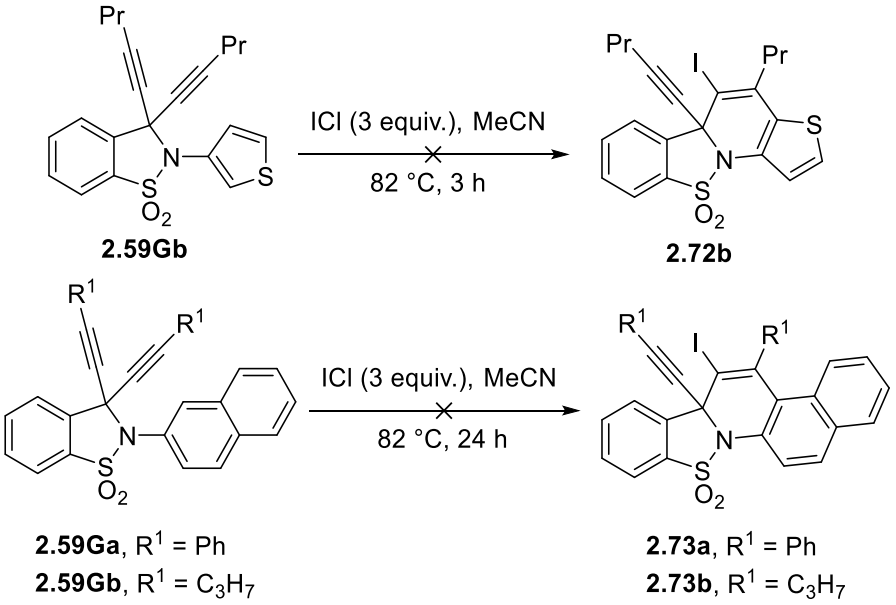


2.59Ba - Eb **2.66a - f** and **2.71a - b**

Scheme 2.79

Entry	R	R^1	1,2-Benzisothiazole	Time (h)	Temp (°C)	Tetracycle	R^3	Yield (%)
1	Tolyl	Ph	**2.59Ba**	24	82	**2.66a-3**	Me	91
2	Tolyl	C_3H_7	**2.59Bb**	21	82	**2.66b-3**	Me	40
3	Tolyl	4-$MeOC_6H_4$	**2.59Bc**	4	82	**2.66f**	Me	0
4	3-MeC_6H_4	Ph	**2.59Ca**	22	82	**2.66a**	Me	0
5	3-MeC_6H_4	C_3H_7	**2.59Cb**	22	82	**2.66b**	Me	0
6	2-$MeOC_6H_4$	C_3H_7	**2.59Db**	22	82	**2.71b**	OMe	0
7	3-$MeOC_6H_4$	Ph	**2.59Ea**	5	82	**2.71a**	OMe	0
8	3-$MeOC_6H_4$	C_3H_7	**2.59Eb**	1	82	**2.71b-2**	OMe	41

Table 2.18 Yields from iodocyclisations of 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Ba – Eb**



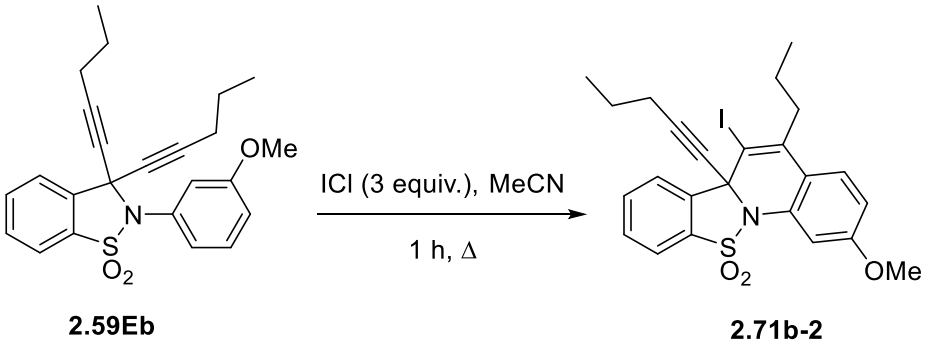
Scheme 2.80

Entry	R^1	R^2	1,2-Benzisothiazole	Time (h)	Temp (°C)	Tetracycle	Yield (%)
1	3-thienyl	C_3H_7	**2.59Gb**	3	82	**2.72b**	0
2	2-naphthyl	Ph	**2.59Ha**	24	82	**2.73a**	0
3	2-naphthyl	C_3H_7	**2.59Hb**	24	82	**2.73b**	0

Table 2.19 Attempted iodocyclisations of 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Gb – Hb**

Unfortunately the 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Ca – b** R = 3-MeC_6H_4, R^1 = Ph and C_3H_7 (entries 4 and 5, Table 2.18) and **2.59Ha – b** R = 2-naphthyl, R^1 = Ph and C_3H_7 (entries 2 and 3, Table 2.19) provided only starting material from the reaction with ICl in MeCN. The other substrates failed to yield any identifiable products and afforded only complex mixtures. The 1,2-benzisothiazolo[2,3-*a*]quinolines **2.66a-3** and **2.66b-3** (entries 1 and 2, Table 2.18), furnished higher yields from this stepwise sequence in comparison to the one-pot reaction Scheme 2.74 (entries 3 and 4, Table 2.15).

The 1,2-benzisothiazolo[2,3-*a*]quinoline **2.71b-2** was isolated in 41% yield (entry 8, Table 2.18); as discussed previously (Scheme 2.77) the 3-$MeOC_6H_4$ group should be significantly more reactive in the *ortho* positions of the aromatic ring to electrophilic attack from the alkyne derived iodonium ion. The 2-methoxy-1,2-benzisothiazolo[2,3-*a*]quinoline **2.71b-2** isolated from treatment of **2.59Eb** with ICl was found to be the expected regioisomer (Scheme 2.81). Cyclisation having occurred at the least hindered position *ortho* to nitrogen (i.e. para to OMe). None of the alternative regioisomer (the 1-methoxy derivative) arising from S_EAr *ortho* to the methoxy group was observed.



2.59Eb **2.71b-2**

Scheme 2.81

The structure of **2.71b-2** was confirmed by the ^1H NMR spectrum (Figure 2.24), and consideration of the splitting patterns and coupling constants of the aromatic ring protons.

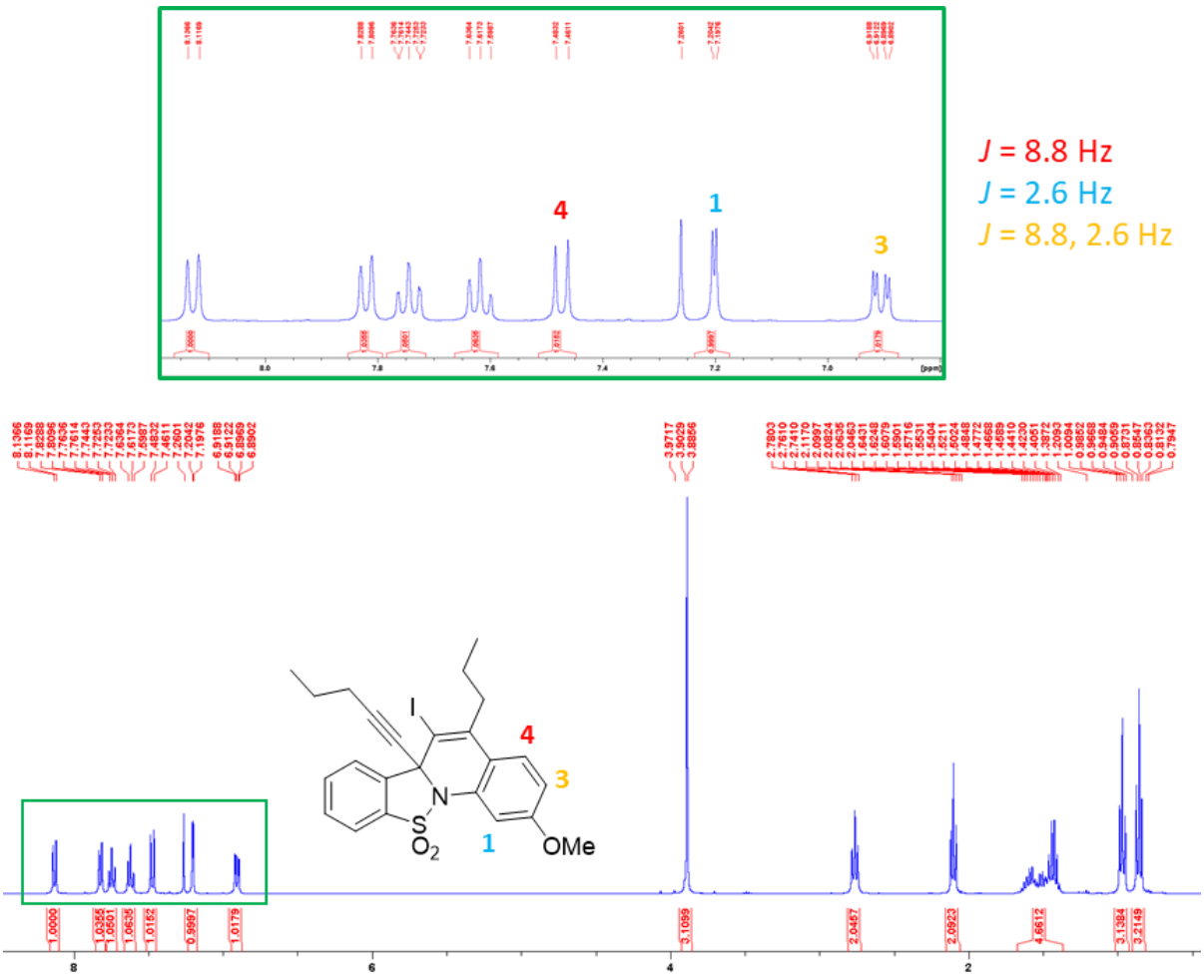


Figure 2.24 400 MHz ^{1}H NMR spectrum of **2.71b-2** in $CDCl_3$

The reaction of reversed sulfonamides **2.23Aa – Hb** and/or the 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides **2.59Aa – Hb** with ICl in MeCN provides a pathway to the novel ring system 1,2-benzisothiazolo[2,3-*a*]quinoline **2.66a – b** and **2.71a – 2.73b**. Iodocyclisation of a pre-formed 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxides appears to offer the most efficient route to these compounds, the chemistry of which merit further investigation.

Chapter 3

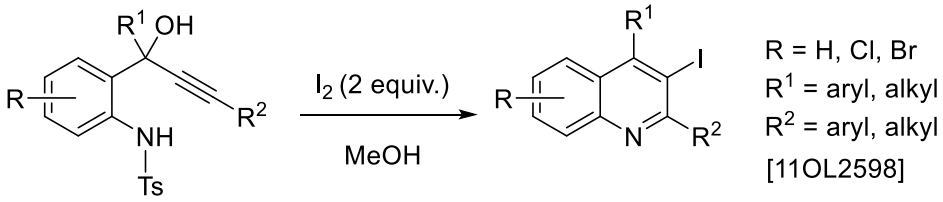
Electrophilic Cyclisations of 3-Arylpenta-1,4-diyn-3-ols *via* 6-*Endo*-dig or 6-E*xo*-*dig* Pathways

Chapter 3 Electrophilic Cyclisations of 3-Arylpenta-1,4-diyn-3-ols *via* 6-*Endo*-dig or 6-E*xo-dig* Pathways

3.1 Iodocyclisations of 3-[2-(Arenesulfonamido)phenyl]penta-1,4-diyn-3-ols to 4-Alkynyl-3-iodoquinoline and Derivatives

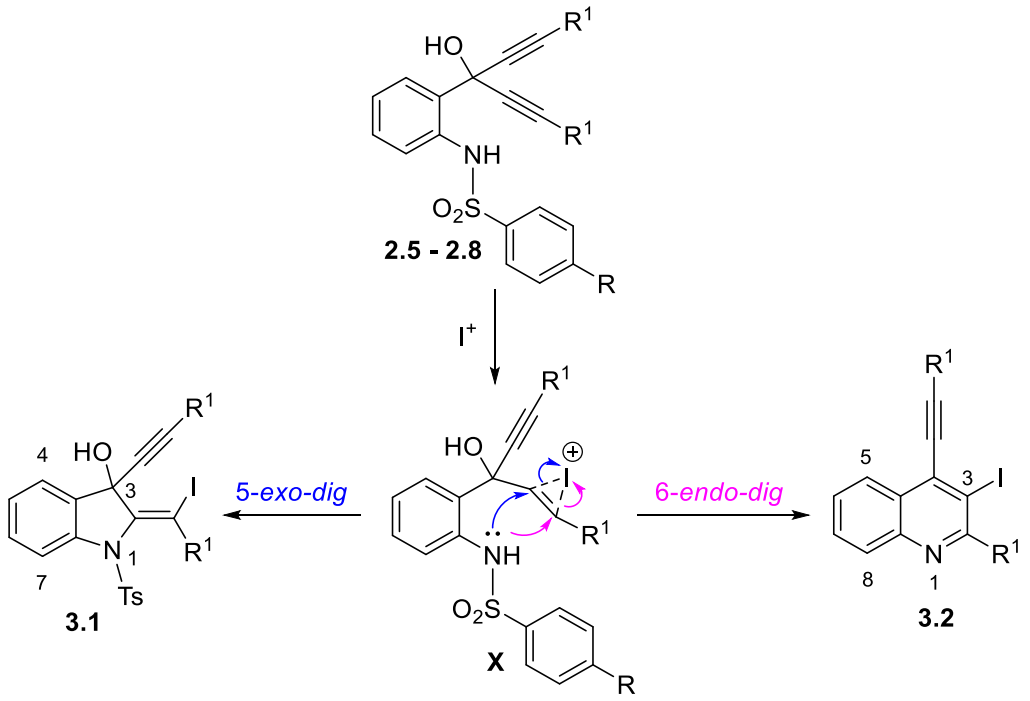
Iodine-mediated electrophilic cyclisations of alkynes have been exploited to generate a wide variety of different heterocycles (cf. Scheme 1.4). A significant advantage of this approach is that many of the resulting rings will possess an iodo substituent, allowing the further functionalisation or annulation of the ring. A number of reviews covering iodocyclisation reactions are available [14COS-II(4)412, 14MI251, 15S1961, 16OBC7639, 16MI49730].

Molecular iodine has been utilised to promote the cyclisation of 2-(tosylamino)phenylpropynols to afford 3-iodoquinolines. If nitromethane was used as the solvent the yields were poor. However, when replaced with methanol high yields (40 – 99%) of the 3-iodoquinoline were obtained (Scheme 3.1) [11OL2598].



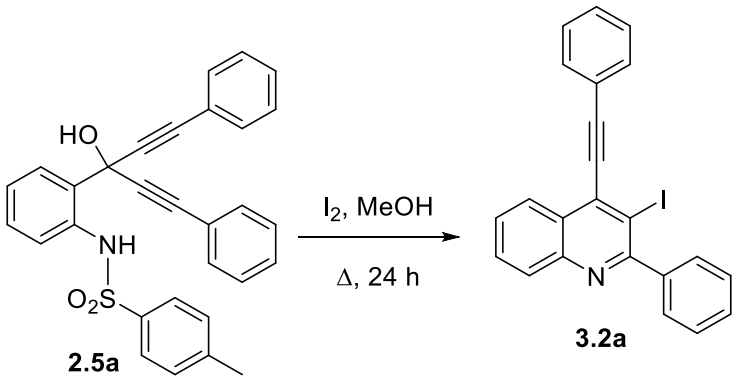
Scheme 3.1

To date, no example of the iodocylisations of alkynols in which R^1 = alkynyl have been reported. In the present work, initial experiments therefore focused on the behaviour of 1,5-disubstituted-3-[2-(arenesulfonylamido)phenyl]penta-1,4-diyn-3-ols **2.5 – 2.8** towards an electrophilic iodine source (iodenium ion I^+). It is pertinent to note that both 5-*exo-dig* (**3.1**) and 6-*endo-dig* (**3.2**) pathways are possible from the iodonium ion intermediate **X** affording indoles (**3.1**) or quinoline derivatives (**3.2**) respectively (Scheme 3.2).



Scheme 3.2

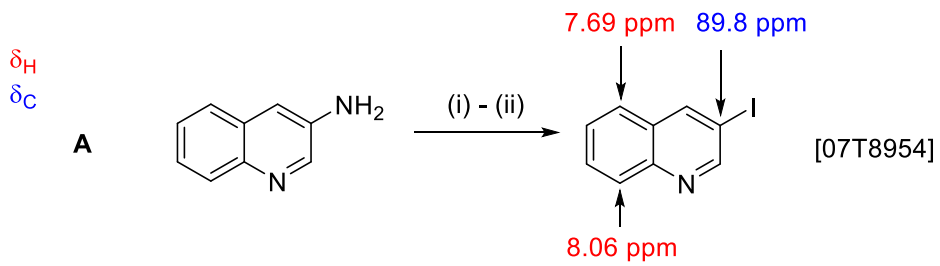
Preliminary work showed that when **2.5a** was treated with iodine in refluxing MeOH (Scheme 3.3), a good yield of iodoquinoline **3.2a** could be obtained (66%) [16UP1]. The product was characterised by its ^{1}H and ^{13}C NMR spectra (Figure 3.1) as well as by HMRS that exhibited a molecular ion at *m/z* $[M+H]^+$ = 432.0245 corresponding to $C_{23}H_{14}IN$.



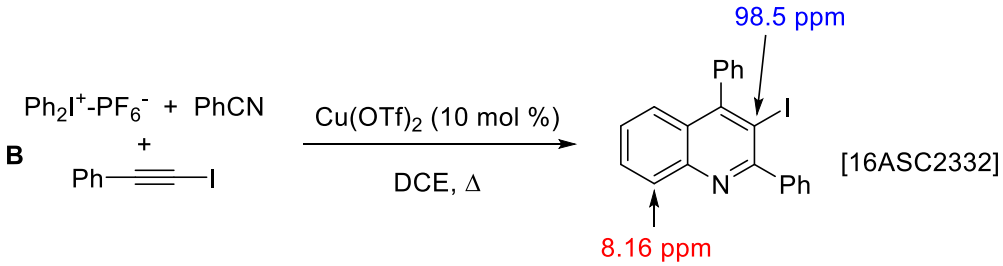
Scheme 3.3

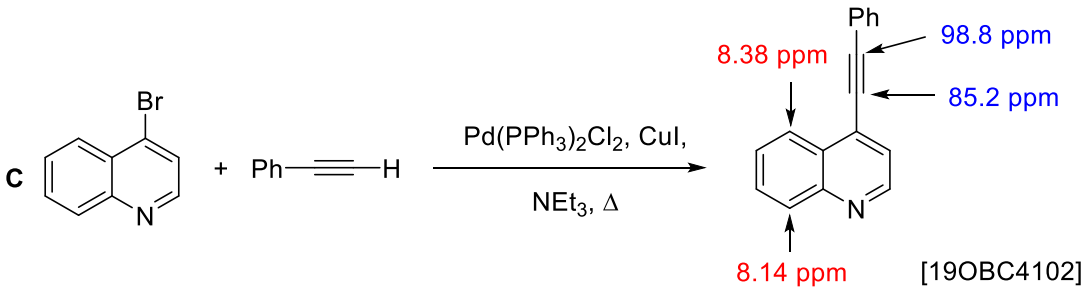
Various quinolines with similar structural features to 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** are shown in Scheme 3.4. 3-Iodoquinolines in Scheme 3.4 **A** and **B** have different ^{1}H NMR aromatic resonances for the benzo ring protons of the quinoline compared with those in **3.2a** (Figure 3.1). However, ^{1}H NMR data for 4-phenylethynylquinoline in **C** Scheme 3.4 reveals that upon incorporation of an alkyne unit in

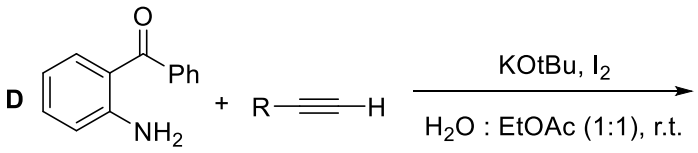
the 4-postion of the quinoline, the *peri* proton (5-*H*) is deshielded and moves downfield in comparison to 8-*H*. The ^{1}H NMR resonance for the 5-*H* proton on 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** (δ_H 8.39 ppm, Figure 3.1) is therefore similar to that of the 4-phenylethynyl quinoline shown in **C** Scheme 3.3 (δ_H 8.38 ppm). The quaternary 3-**C**-I ^{13}C NMR resonance of quinoline **3.2a** (δ_C 102.29 ppm) is comparable to that reported for 2,4-diphenyl-3-iodoquinoline δ_C 98.5ppm (**B**, Scheme 3.4) and for a number of other 2-substituted-3-iodo-4-phenylquinoline derivatives for which 3-**C**-I carbon resonates in the region of δ_C 100.2 – 101.6 ppm (**D**, Scheme 3.4). Addition of substituents to the quinoline ring clearly changes the shift of the ^{13}C NMR 3-**C**-I carbon resonance, as that in the 3-iodoquinoline (**A**, Scheme 3.4) is shielded by nearly 10 ppm in comparison to the 2,4-diphenyl-3-iodoquinoline in **B** Scheme 3.4.



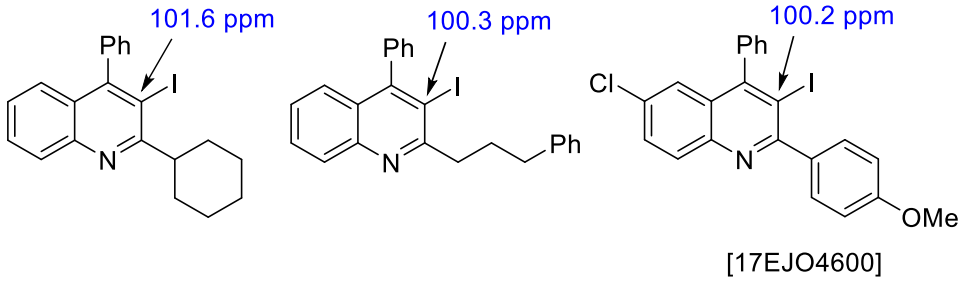
(i) HBF_4, *i*-amyl nitrite, acetone, -8 °C; (ii) KI, -8 °C to 10 °C







R = aryl, alkyl



Scheme 3.4

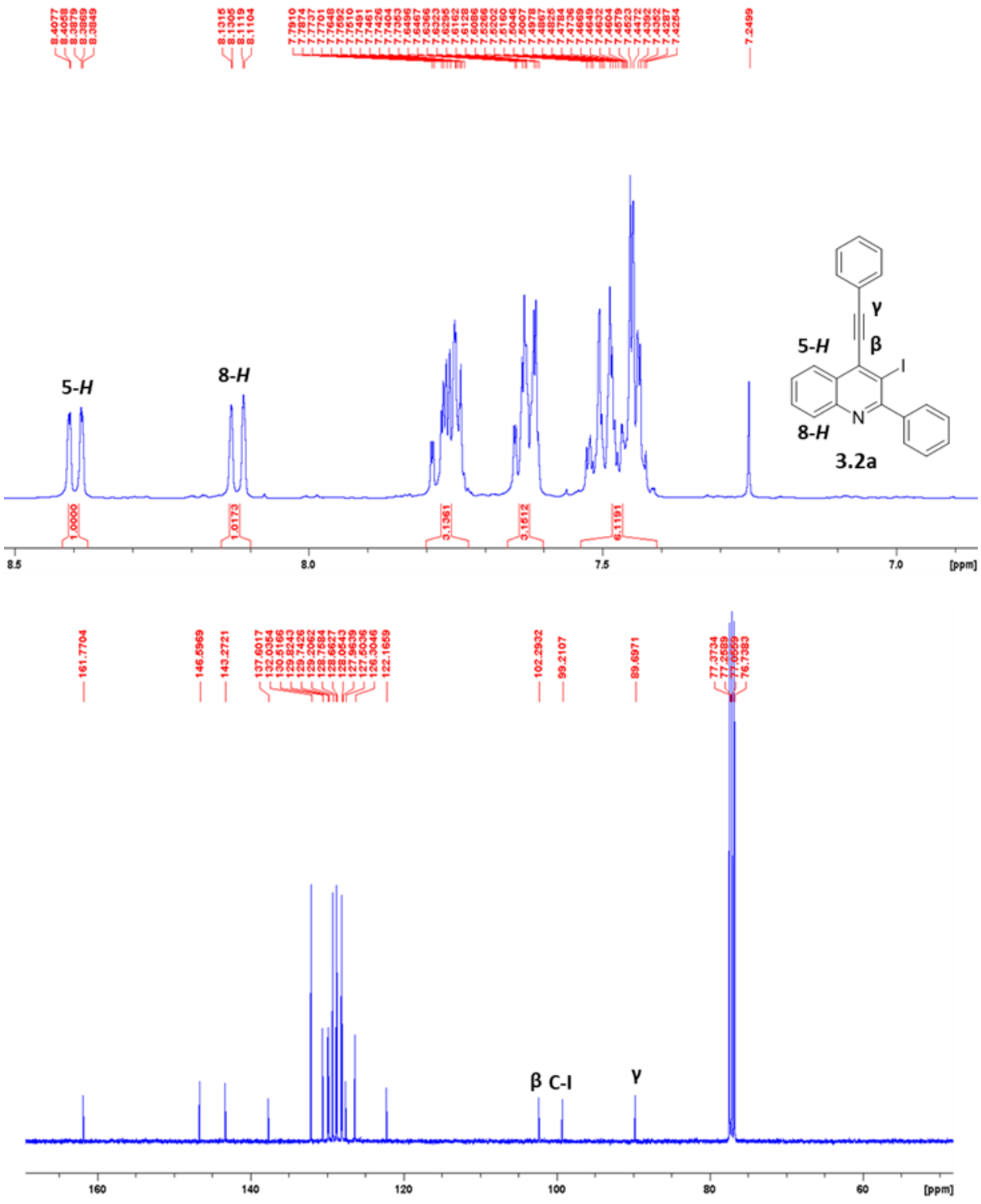
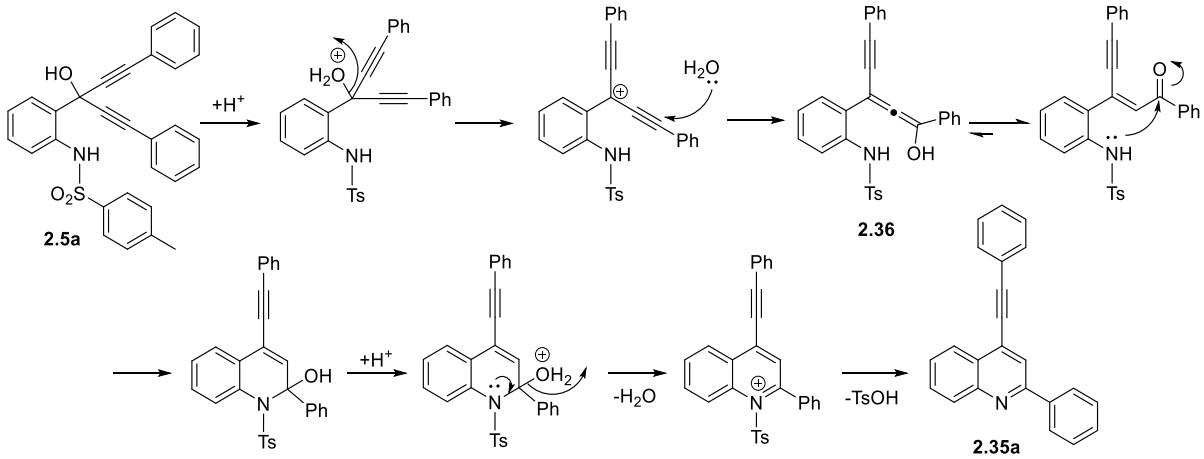


Figure 3.1 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra of **3.2a** in $CDCl_3$

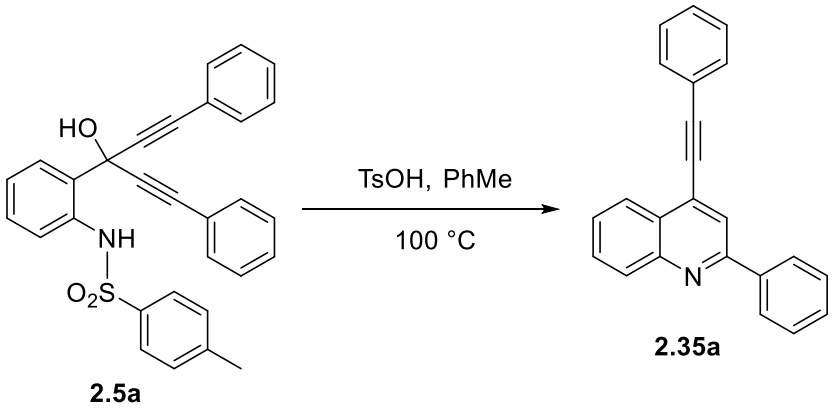
On repeating treatment of **2.5a** with iodine in refluxing MeOH (Scheme 3.3) was found that unfortunately the yield of **3.2a** was not as high nor as reproducible as previously achieved [16UP1]. However, an additional minor product was isolated by flash column chromatography from the reaction mixture. Both 1D and 2D NMR analysis (COSY, HSQC and HMBC) as well as HMRS confirmed the constitution of the product. The latter exhibited a molecular ion at *m/z* $[M+H]^+$ = 306.1285 corresponding to $C_{23}H_{15}N$. The compound was found to be the 2-phenyl-4-(phenylethynyl)quinoline **2.35a** but was only isolated in very low yields (6% - Table 3.1)**.**

Formation of **2.35a**, as described in Section 2.4 (Scheme 2.44) is generated *via* a Meyer-Schuster rearrangement and concomitant cyclisation of the intermediate enone (Scheme 3.5)



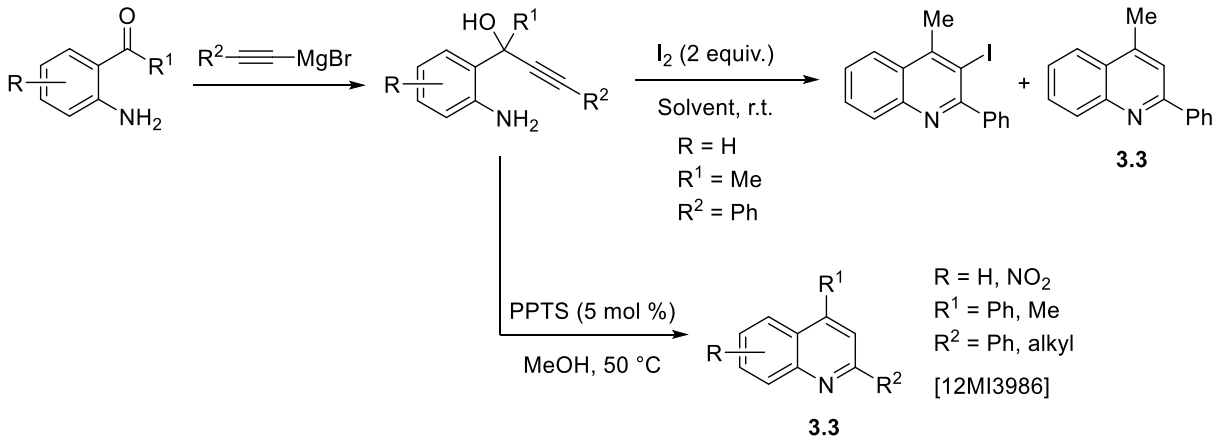
Scheme 3.5

To establish whether acidic conditions would effect cyclisation of the dialkynol **2.5a** to 2-phenyl-4-(phenylethynyl)quinoline **2.35a**, the former was treated with TsOH in toluene at 100 °C for 19 h (Scheme 3.6). The ^{1}H NMR spectrum of the crude material indicated that **2.35a** had indeed been formed and was 90% pure, however attempts to effect purification by column chromatography resulted in degradation. Nevertheless, this result confirmed that acidic conditions were the reason for the competing formation of the 4-alkynylquinoline **2.35a**.



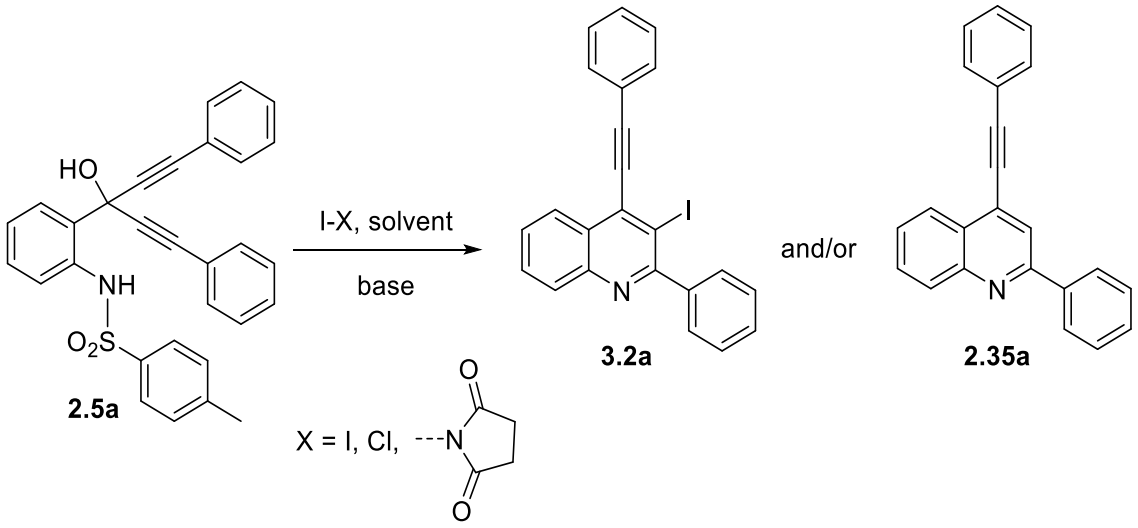
Scheme 3.6

Reddy *et al.* found that iodocyclisation (I_2) of alkynols to 3-iodoquinolines also afforded 2,4-substiuted quinolines (**3.3**) in up to 30% yield (Scheme 3.7). They did not allude to the formation of the latter but it is envisaged to proceed *via* a Meyer-Schuster rearrangement. It was found that high yields (70 – 90%) of the quinoline **3.3** could be obtained by treatment of the 1-(2-aminophenyl)propynols with PPTS [12MI3986].



Scheme 3.7

In efforts to optimise the yield of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** from dialkynol **2.5a** different solvents and positive iodine sources were investigated (Scheme 3.8); as well as the addition of base which should supress the acidic formation of the parent (uniodinated) quinoline **2.35a**. The results are collated in Table 3.1.



Scheme 3.8

Entry	I^+ source	Equiv.	Solvent	Time (h)	Temp (°C)	Base	Equiv.	Yield of 3.2a (%)	Yield of 2.35a (%)
1	I_2	2	MeOH	4.83	65	–	–	25	6
2	I_2	2	DCM	26.0	r.t.	–	–	0	0
3	I_2	2	MeOH	2.0	65	–	–	26	1
4	I_2	2	Dry MeOH	1.5	65	–	–	31	0
5	I_2	3	Dry MeOH	1.0	65	–	–	55	0
6	I_2	3	$MeNO_2$	1.5	80	–	–	25	8
7	I_2	2	Dry MeOH	4.0	65	Na_2HPO_4	2	0	0
8	I_2	3	Dry MeCN	3.5	60	Na_2HPO_4	3	10	0
9[a]	I_2	3	Dry MeOH	5.0	65	$NaHCO_3$	3	11	0
10	I_2	3	$MeNO_2$	1.5	80	$NaHCO_3$	3	17	0
11	NIS	3	H_2O:Me_2CO	4.67	100	–	–	0	0
12	NIS	3	$MeNO_2$	1.0	100	–	–	0	0
13[a]	NIS	3	Dry MeOH	2.0	65	–	–	7	0
14	NIS	3	MeCN	48.0	r.t.	–	–	0	0
15	**ICl**	**2**	**MeCN**	**1.0**	**r.t.**	**–**	**–**	**60**	**0**
16	ICl	2	$MeNO_2$	1.0	r.t.	–	–	24	0
17	ICl	2	DCM	1.0	r.t.	–	–	18	0
18	ICl	2	Toluene	5.0	r.t.	–	–	0	0
19	ICl	2.5	MeCN	0.67	r.t.	–	–	35	0
20	ICl	1.5	MeCN	24.0	r.t.	–	–	19	7

Table 3.1 Optimisation of conditions for the iodocyclisation of **2.5a** to **3.2a.** a = 3,6-diiodo-2-phenyl-4-(phenylethynyl)quinoline **3.4a** also isolated

With elemental iodine the use of dry solvents did not increase the yield of 3-iodoquinoline **3.2a** substantially, nor decrease the yield of the quinoline **2.35a**. However, increasing molar equivalents of the electrophile did exert a positive benefit (entry 5, Table 3.1). Iodocyclisations in which iodine was used in the absence of base (entries 1 – 6, Table 3.1), generated 2-phenyl-4-(phenylethynyl)quinoline **2.35a** (TLC) but separation from the 3-iodoquinoline **3.2a** was not always achievable, due to very similar Rf values in various solvent systems.

Treatment of **2.5a** with of I_2 and Na_2HPO_4 (entries 7 and 8, Table 3.1) produced very complex reaction mixtures, it was thought that the base strength of Na_2HPO_4 may have an adverse influence, therefore a weaker base ($NaHCO_3$) was employed. A less complex reaction mixture was obtained, however yields of the desired compound **3.2a** were still low. Although, as predicted no 2-phenyl-4-(phenylethynyl)quinoline **2.35a** appeared to be present (TLC).

Interestingly, with $NaHCO_3$ and I_2 in dry MeOH (entry 9, Table 3.1) in addition to 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a**, a faster running product was also isolated by flash column chromatography (5% EtOAc – hexane). This unknown material readily crystallised and when washed with cold hexane, produced white needles. The ^{1}H NMR spectrum of the compound exhibited a doublet at δ_H 8.75 ppm ($J_{5\text{-}7}$ = 1.9 Hz) and a doublet of doublets at δ_H 8.00 ppm ($J_{7\text{-}8}$ = 8.8 Hz, $J_{7\text{-}5}$ = 1.9 Hz), which implied that the quinoline benzo moiety was now substituted (Figure 3.2). Indeed, ESI-HRMS confirmed the constitution as a diiodinated species (**3.4a**) with a molecular ion at *m/z* $[M+H]^+$ = 557.9207 corresponding to $C_{23}H_{13}I_2N$.

Furthermore, the ^{13}C NMR spectrum exhibited high field signals in the region characteristic for an aromatic **C**-I bond, δ_C 102.90 ppm for the 3-**C**-I and at δ_C 100.03 ppm for another sp^2 **C**-I. These shifts are similar to those reported by Zhang for 3,6-diiodo-2,4-diphenylquinoline (δ_C 99.58 and 93.31 ppm, Scheme 3.10) [17OBC6901]. The diiodoquinoline was assigned the structure **3.4a** (Figure 3.2, 3,6-disubstituted) due to the electron releasing effect of the sulfonamide nitrogen at the *para* position in **2.5a** (Scheme 3.9), the yield of **3.4a** was 4% and that of the 3-iodoquinoline **3.2a** was 11%.

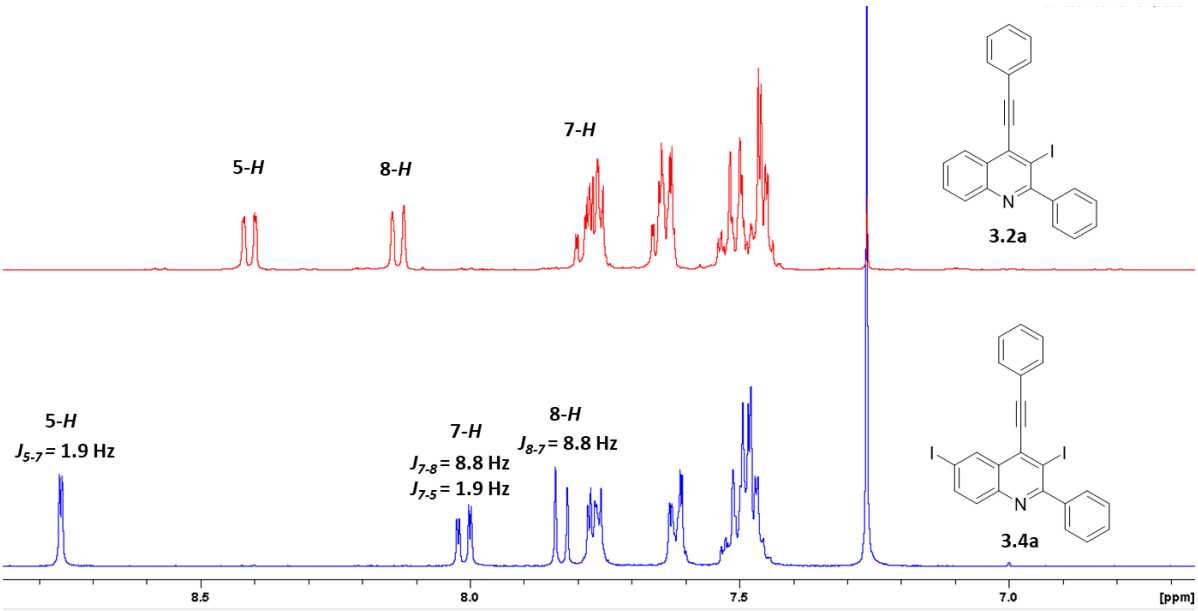
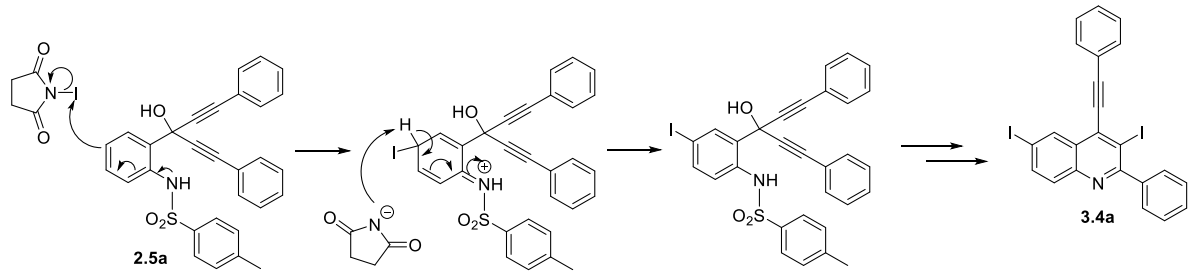


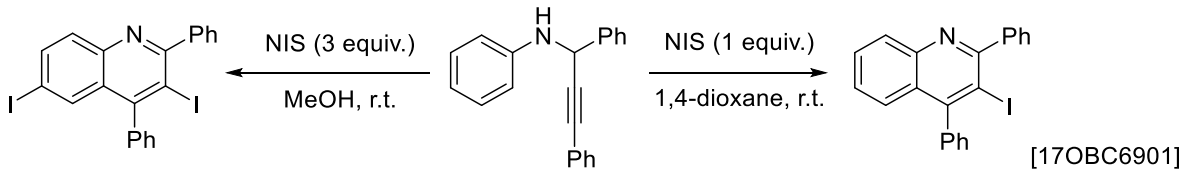
Figure 3.2 400 MHz ^{1}H NMR spectra comparison of quinolines **3.2a** and **3.4a** in $CDCl_3$

The mechanism for the formation of 3,6-diiodoquinoline **3.4a** is envisaged to be electrophilic aromatic substitution (S_EAr) of the benzo ring with an iodine electrophile, followed by the activation of the triple bond and subsequent cyclisation to the quinoline **3.4a** (Scheme 3.9).



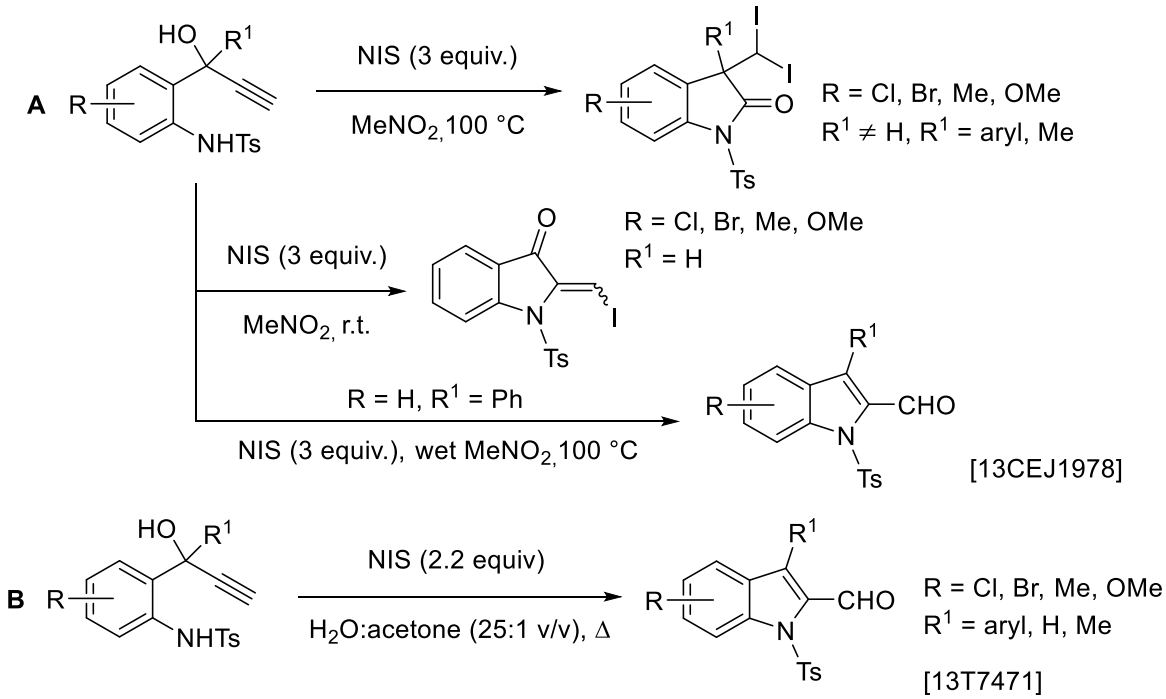
Scheme 3.9

Electrophilic cyclisation of dialkynol **2.5a** with NIS was also explored. As this positive iodine source has been reported to be highly effective for the synthesis of several heterocycles *via* iodocyclisation including but not limited to quinolines, indoles and dihydrofurans [14MI251, 19S1841]. Zhang *et al.* achieved good yields of 3-iodo-2,4-diphenylquinoline from an *N*-phenyl propargylamine with NIS in 1,4-dioxane, together with trace amounts of 3,6-diiodo-2,4-diphenylquinoline; whereas in MeOH the product distribution was reversed (Scheme 3.10) [17OBC6901].



Scheme 3.10

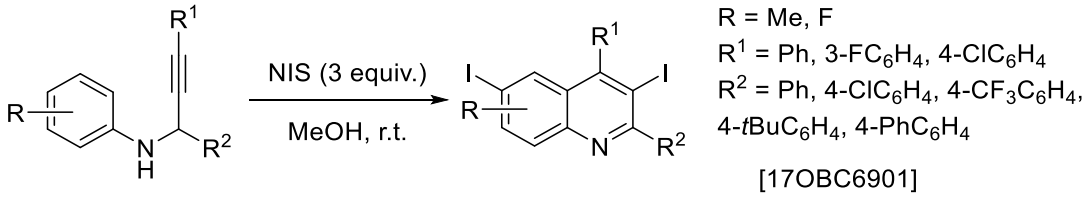
Chan and co-workers found that with NIS in dry $MeNO_2$ at reflux, 1-(2-tosylamidophenyl)prop-2-yn-1-ol in which $R^1 \neq H$ would cyclise easily to diiodomethyl-indolin-2-ones, but at ambient temperature when $R^1 = H$ iodomethylene-indolin-3-ones were be obtained. However, when non-distilled solvent was used 3-phenyl-1-tosyl-1*H*-indole-2-carbaldehyde was produced (**A**, Scheme 3.11) [13CEJ1978]. Similar behaviour was observed from treatment of the propynols with NIS in H_2O – acetone, this reaction also tolerated $R^1 = H$ (**B**, Scheme 3.11) [13T7471].



Scheme 3.11

Reactions of the dialkynol **2.5a** with NIS were not successful in a variety of solvents (entries 11 – 14, Table 3.1), providing little (7%, entry 13, Table 3.1) or no 3-iodoquinoline **3.2a**. Interestingly, NIS in dry MeOH (entry 13, Table 3.1) also provided the 3,6-diiodoquinoline **3.4a** in 14% yield. This finding is in line with that of Zhang *et al.* from the cyclisation of *N*-phenyl propargylamines with NIS in MeOH (Scheme 3.10) [17OBC6901]. We did not find 4-

alkynyl-3,6-diiodoquinoline **3.4a** to be generated in the same high yields as those reported by Zhang *et al.* for the 2,4-diaryl-3,6-diiodoquinoline (59 – 76% yield). The *N*-phenyl propargylamines are much more electron rich than the 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ol **2.5a** used in this work.



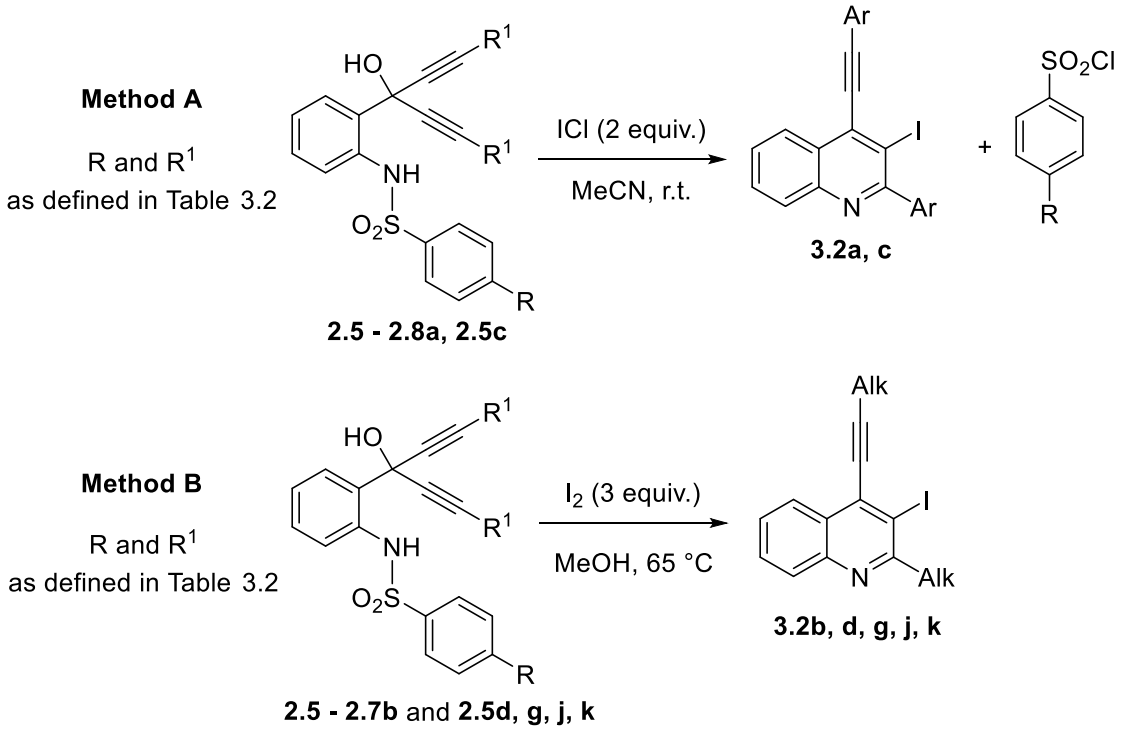
Scheme 3.12

Since NIS was not a favourable electrophile for the cyclisation of **2.5a** (entries 11 – 14, Table 3.1), the highly electrophilic species ICl was employed. With only a few papers describing its use as an electrophilic initiator to synthesise quinoline derivatives from arylacetylenes, arylpropynones and (most relevant) propynol derivatives (Scheme 3.17) [05OL763, 06JOC1626, 06OL243, 10JOC1266, 10T1177]. Iodine monochloride has found more extensive use for cyclisations leading to chromone and isocoumarins and the use of ICl to initiate electrophilic cyclisation has been reviewed [15S1961].

Thus treatment of dialkynol **2.5a** with ICl (2 equiv.) in acetonitrile (entry 15, Table 3.1) resulted in a rapid reaction and TLC indicated that after 1 h only a small amount of starting material remained. The mixture was purified by flash column chromatography. The initial fractions afforded TsCl whilst the main fractions provided a solid that was further purified by recrystallisation from EtOH – EtOAc to give 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** in 60% yield. With this being the highest yield achieved in the optimisation studies other 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ols **2.5 – 2.8** possessing a variety of substituents on the alkyne and benzenesulfonyl moieties, were then subjected to treatment with ICl in acetonitrile (Method **A**, Scheme 3.13, Table 3.2).

Unfortunately, exposure of the *N*-[2-(6-hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonamide **2.5b** to ICl in MeCN provided a complex mixture that could not be purified by flash column chromatography. Consequently, alkylacetylene-derived dialkynols (**2.5b, d, g, j, k** and **2.6b**, **2.7b**) were subjected to the 'next best' option in the screening procedure (Table 3.1), I_2 (3 equiv.) in MeOH at reflux (Method **B**, Scheme 3.13),

which allowed access to the 2-alkyl-4-alkynyl-3-iodoquinolines in yields ranging from 12 – 63% (Table 3.2).

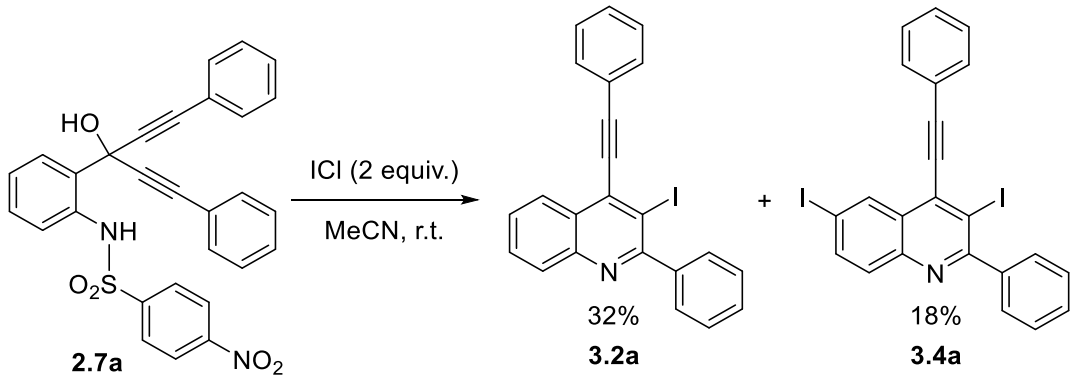


Scheme 3.13

Entry	R	R^1	Dialkynol	Method	Time (h)	Product	Yield (%)
1	Me	Ph	**2.5a**	A	1.0	**3.2a**	60
2	Me	C_3H_7	**2.5b**	B	1.0	**3.2b**	46
3	Me	4-$MeOC_6H_4$	**2.5c**	A	1.0	**3.2c**	40
4	Me	C_4H_9	**2.5d**	B	1.5	**3.2d**	63
5	Me	Me	**2.5g**	B	2.25	**3.2g**	26
6	Me	*t*-Bu	**2.5j**	B	1.25	**3.2j**	0
7	Me	$(CH_3)C=CH_2$	**2.5k**	B	1.25	**3.2k**	0
8	OMe	Ph	**2.6a**	A	1.0	**3.2a**	63
9	OMe	C_3H_7	**2.6b**	B	0.83	**3.2b**	50
10[a]	NO_2	Ph	**2.7a**	A	1.0	**3.2a**	32
11	NO_2	C_3H_7	**2.7b**	B	19.0	**3.2b**	12
12	H	Ph	**2.8a**	A	2.0	**3.2a**	41

Table 3.2 Yields from the iodocyclisation of dialkynols **2.5 – 2.8**. a = Reaction also afforded 3,6-diiodo-2-phenyl-4-(phenylethynyl)quinoline **3.4a**

N-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-nitrobenzenesulfonamide **2.7a** (entry 10, Table 3.2) reacted with ICl in MeCN to also afford the 3,6-diiodoquinoline **3.4a** in 18% yield (Scheme 3.14) and was the only dialkynol to do so under the optimised conditions. This observation can be ascribed to the diminished nucleophilicity of the sulfonamide nitrogen and subsequent slowing of its addition to the iodonium cation, allowing competitive electrophilic iodination of the aromatic ring.



Scheme 3.14

Dialkynols **2.5j** and **2.5k** (entries 6 and 7, Table 3.2) provided complex mixtures and no identifiable products could be isolated from these reactions. Dialkynols **2.5j** and **2.5k** were also subjected to Method **A** conditions (2 equiv. ICl in MeCN, r.t. for 24 h) but again only a complex mixture was obtained. However, with these two exceptions the other dialkynols provided access to a range of 4-alkynyl-3-iodoquinolines (Table 3.2).

Of the novel 4-alkynyl-3-iodoquinolines **3.2,** Figure 3.3 shows the ranges of ^{1}H and ^{13}C NMR resonances for 5-*H* – 8-*H* protons and for the 3-**C** carbon. The 3-**C**-I carbon bond is shielded in comparison to the normal range for an aromatic carbon (δ_C 120 – 160) due to the heavy-atom effect of the iodine substituent [98CEJ118, 16JTC199]. The ^{1}H NMR ranges of the benzo ring protons are similar to those reported by Batsyts *et al.* for 4-(phenylethynyl)quinoline (Scheme 3.3) [19OBC4102].

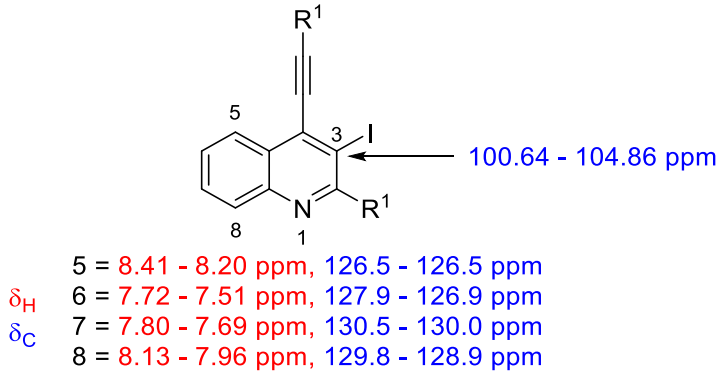
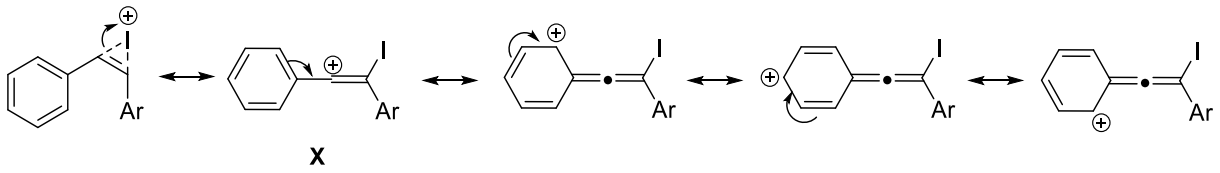


Figure 3.3 ^{1}H and ^{13}C NMR shifts of 4-alkynyl-3-iodoquinolines **3.2a – g**

Iodocylisations of 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ols **2.5 – 2.8** followed the expected trend; the benzenesulfonyl group containing the electron donating methoxy group (**2.6a – b**) provided better yields of 4-alkynyl-3-iodoquinolines in a faster time (entries 8 and 9, Table 3.2), whereas the dialkynols possessing the electron withdrawing 4-nitrobenzenesulfonyl group (**2.7a – b**) provided lower yields of 4-alkynyl-3-iodoquinolines and required a longer reaction time (entries 10 and 11, Table 3.2).

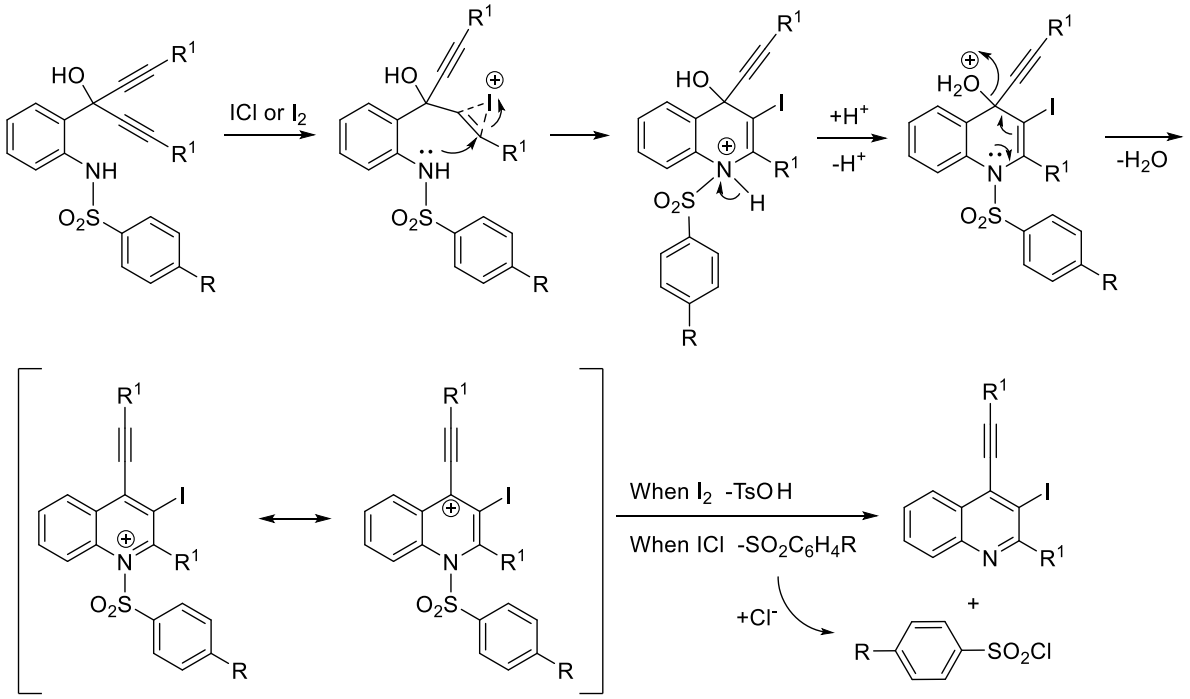
It is surprising that ICl did not react cleanly with the alkyl-terminated dialkynols **2.5b, d, g, j** and **k** as it is a better electrophile than iodine, due to the permanent dipole that exists and which facilitates electrophilic attack [07JOC977, 14MI251]. The phenyl ring will impart some stability to the intermediate iodonium ion, as in the strain-free ring-opened form, the vinyl carbocation **X,** there will be conjugation with the aryl group (Scheme 3.15) [93TL8205]. However, when the aryl substituent is replaced with an alkyl group only inductive stabilisation of the cation is possible. Presumably the lower yields of the 2-alkyl-4-alkynyl-3-iodoquinolines **3.2b, d, g, j** and **k**, compared to those of the 2-aryl-4-alkynyl-3-iodoquinoline derivatives **3.2a** and **3.2** are a reflection of the diminished stability of the cationic intermediate.



X

Scheme 3.15

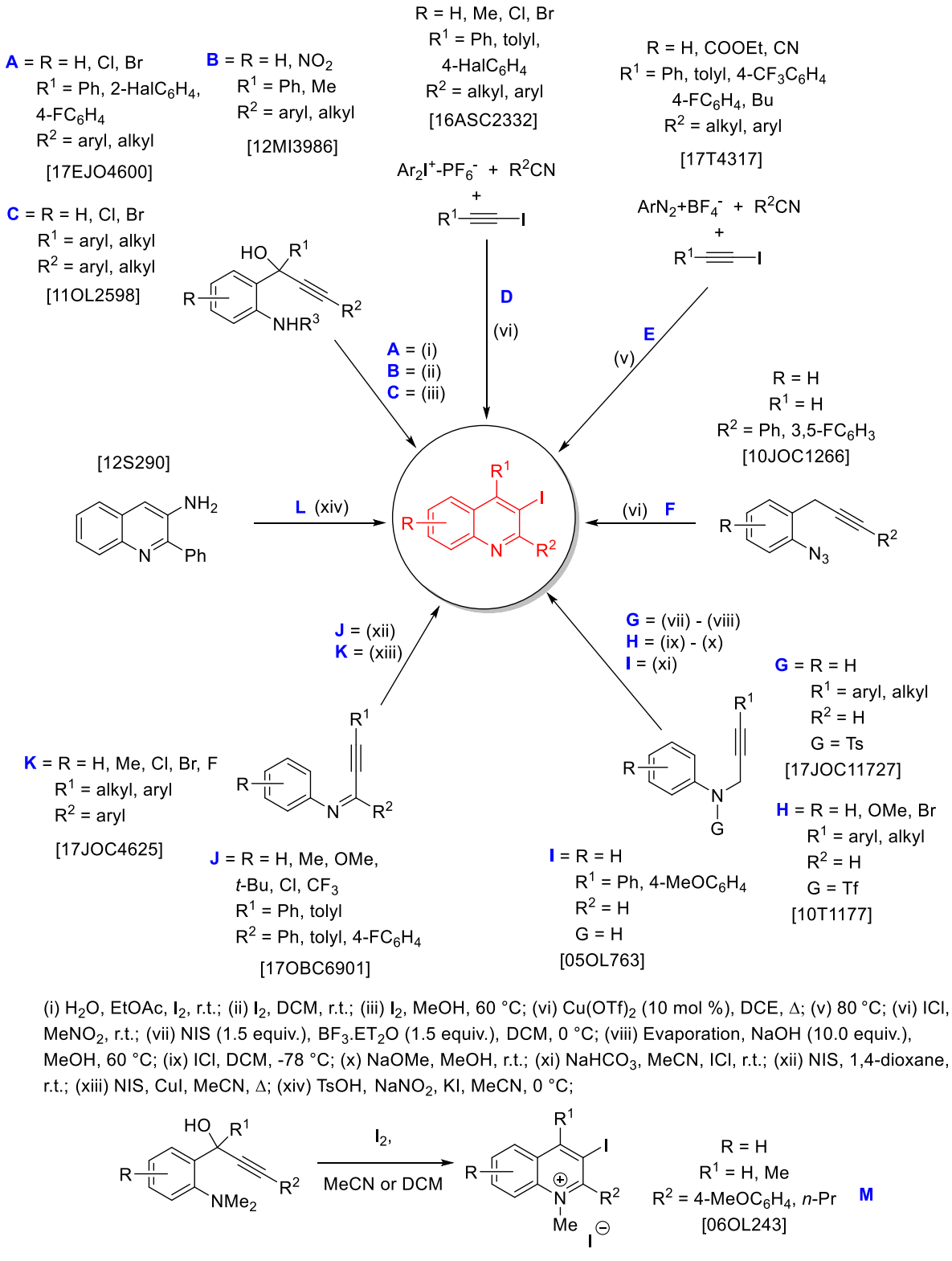
The mechanism for the formation of the 4-alkynyl-3-iodoquinolines **3.2** proceeds *via* an iodonium intermediate which was initially suggested by Larock and co-workers for the iodocyclisation of 1-(2-methoxyphenyl)prop-2-yn-1-ols to 3-iodochromones [06JOC1626], and subsequently for quinolines from 1-(2-tosylamindophenyl)prop-2-yn-1-ols by Ali and co-workers [11OL2598]. Overall, the reaction sequence can be envisaged as proceeding by *anti*-attack of the electrophile and the nitrogen on the alkyne moiety *via* a 6-*endo*-*dig* pathway to produce the intermediate quinolinium salt, which then dehydrates to afford the *N*-tosylquinolinium salt. Subsequent elimination of the arenesulfonyl moiety will be facile, to afford the product **3.2** (Scheme 3.16). When iodine monochloride is used the benzenesulfonyl chloride is isolated, it is expected that in the cases when molecular iodine is used TsOH will be lost.



Scheme 3.16

The 4-alkynyl-3-iodoquinolines (**3.2a – g**) obtained in this work are all novel compounds and as such represent a missing series of novel functionalised quinolines. Both the alkyne and the iodo functions allow the ring to be further elaborated, giving access to more complex heterocyclic systems *via* annulation reactions. With only a handful of literature examples of substituted 3-iodoquinolines and, as to date, only three papers accessing them *via* propargylic alcohols exist (**A**, **B** and **C**, Scheme 3.17) [11OL2598, 12MI3986, 17EJO4600]. In reaction **D** Scheme 3.17, no external iodine electrophile was utilised to afford the 3-

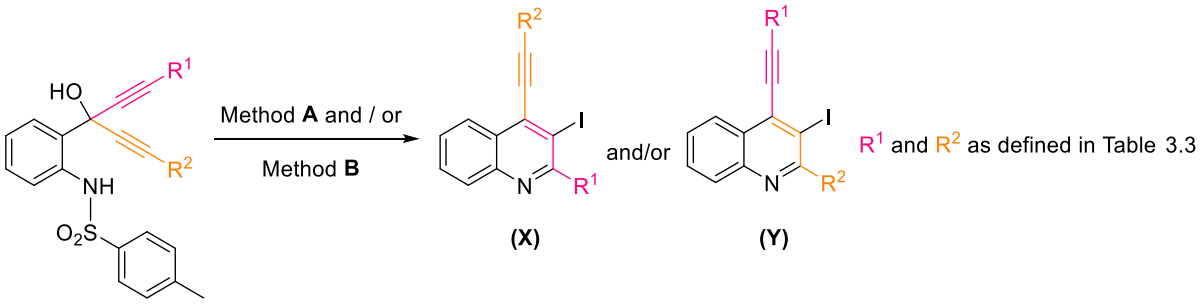
iodoquinoline. A copper(II) catalysed tandem reaction of diaryliodonium salts, nitriles and 1-haloalkynes afforded 2,4-disubstitued-3-haloquinolines with varying substituents, both aryl and alkyl groups are tolerated (**D**, Scheme 3.17) [16ASC2332]. Ramanathan and Liu utilised a similar set of starting materials to synthesise 2,4-disubstitued-3-iodoquinolines, from aryldiazonium salts with 1-iodoalkynes (**E**, Scheme 3.17) [17T4317]. 1-Azido-2-(2-propynyl)benzene cyclised with ICl in nitromethane at r.t. to afford 3-iodo-2-arylquinoline after the loss of N_2, only two examples were reported with this method (**F**, Scheme 3.17) [10JOC1266]. The majority of the other 3-iodoquinolines reported in the literature have been synthesised from the iodocyclisation of alkynylanilines (**G – K**, Scheme 3.17), with varying iodine electrophiles and solvents [04JOC8251, 05OL763, 10T1177, 17JOC4625, 17JOC11727, 17OBC6901]. Simple diazotisation of 3-aminoquinoline and substitution with KI afforded the 3-iodo-3-phenylquinoline (**L**, Scheme 3.17) [12S290]. The *N*-methylquinolinium salt (**M**, Scheme 3.17) was also afforded after the iodocyclisation of a dimethylaminoalkynol [06OL243].



(i) H_2O, EtOAc, I_2, r.t.; (ii) I_2, DCM, r.t.; (iii) I_2, MeOH, 60 °C; (vi) $Cu(OTf)_2$ (10 mol %), DCE, Δ; (v) 80 °C; (vi) ICl, $MeNO_2$, r.t.; (vii) NIS (1.5 equiv.), $BF_3.ET_2O$ (1.5 equiv.), DCM, 0 °C; (viii) Evaporation, NaOH (10.0 equiv.), MeOH, 60 °C; (ix) ICl, DCM, -78 °C; (x) NaOMe, MeOH, r.t.; (xi) $NaHCO_3$, MeCN, ICl, r.t.; (xii) NIS, 1,4-dioxane, r.t.; (xiii) NIS, CuI, MeCN, Δ; (xiv) TsOH, $NaNO_2$, KI, MeCN, 0 °C;

Scheme 3.17

The foregoing work demonstrated the successful iodocyclisation of 1,5-disubstituted-3-[2-(benzenesulfonylamido)phenyl]penta-1,4-diyn-3-ols **2.5 – 2.8** to novel 4-alkynyl-3-iodoquinolines **3.2**. Subsequent investigations were directed to exploring the regiochemical preferences in the iodocyclisations of the unsymmetrical dialkynols **2.19** with the optimised conditions; iodine monochloride in MeCN (Method **A**) or with elemental iodine in refluxing MeOH Method **B** (Scheme 3.18, Table 3.3).



Method **A**: ICl (2 equiv.), MeCN, r.t.
Method **B**: I_2 (3 equiv.), MeOH, Δ

Scheme 3.18

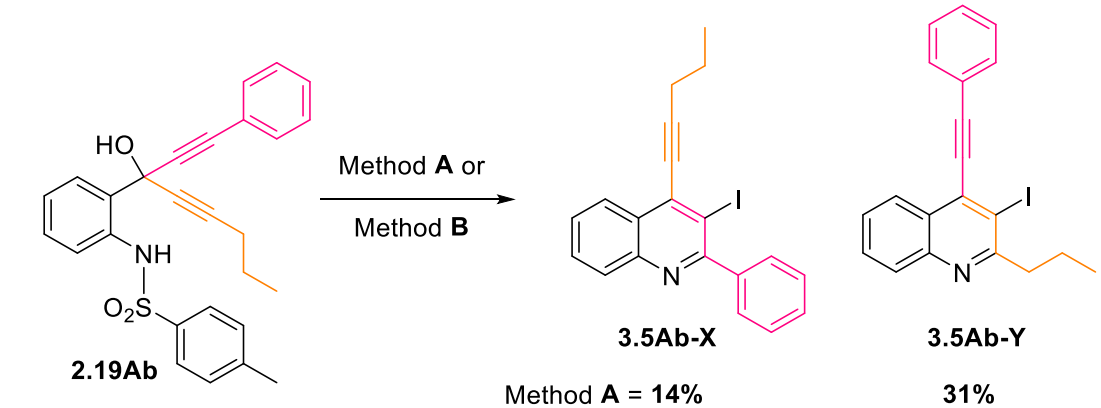
Entry	R^1	R^2	Dialkynol	Method	Time (h)	Quinoline	Quinoline-X yield	Quinoline	Quinoline-Y yield
1	Ph	C_3H_7	**2.19Ab**	A	4.3	**3.5Ab-X**	14	**3.5Ab-Y**	31
2	Ph	C_3H_7	**2.19Ab**	B	1	**3.5Ab-X**	0	**3.5Ab-Y**	15
3	Ph	4-$MeOC_6H_4$	**2.19Ac**	A	0.75	**3.5Ac-X**	0	**3.5Ac-Y**	32
4	Ph	CH_2OMe	**2.19Af**	A	2	**3.5Af-X**	0	**3.5Af-Y**	0
5	Ph	Me	**2.19Ag**	B	1.5	**3.5Ag-X**	8	**3.5Ag-Y**	17
6	Ph	*t*-Bu	**2.19Aj**	A	0.75	**3.5Aj-X**	19	**3.5Aj-Y**	0
7	Ph	$(CH_3)C=CH_2$	**2.19Ak**	A	19	**3.5Ak-X**	0	**3.5Ak-Y**	0
8	Ph	H	**2.19Ai**	A	1.5	**3.5Ai-X**	0	**3.5Ai-Y**	0
9	4-$MeOC_6H_4$	C_3H_7	**2.19Cb**	B	1.25	**3.5Cb-X**	28	**3.5Cb-Y**	0
10	4-$MeOC_6H_4$	CH_2OMe	**2.19Cf**	B	2.3	**3.5Cf-X**	0	**3.5Cf-Y**	0
11	4-$MeOC_6H_4$	H	**2.19Ci**	A	1.5	**3.5Ci-X**	0	**3.5Ci-Y**	0

Table 3.3 Yields from the iodocyclisations of unsymmetrical dialkynols **2.19**

It was difficult to isolate any pure products from the majority of the reactions because the compounds produced possessed very similar Rf values. In some cases, complex mixtures were produced from which no identifiable products could be isolated.

3-Iodo-4-(phenylethynyl)-2-propylquinoline **3.5Ab-Y** (entry 1 and 2, Table 3.3) was characterised by both 1D and 2D NMR (COSY, HSQC, HMBC) spectra, with the ^{1}H NMR data of 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline **3.2b** providing a useful comparison. The similarity of the CH_2 splitting pattern and the chemical shift of the C-2 propyl group in quinoline **3.2b** (δ_H 3.19 ppm, red spectrum, Figure 3.4), are comparable to that seen in **3.5Ab-Y** (δ_H 3.25 ppm, blue spectrum, Figure 3.4). Moreover, the HMBC spectrum of 3-iodo-4-(phenylethynyl)-2-propylquinoline **3.5Ab-Y** shows a correlation between the CH_2 protons of the 2-propyl group and the resonance corresponding to the 3-**C** carbon at δ_C 100.38 ppm (Figure 3.5). Surprisingly, the major isomer from the cyclisation of **2.19Ab** was the 2-propylquinoline **3.5Ab-Y**, using either Method **A** or Method **B** (entry 1 and 2, Table 3.3). The iodocylisation did not provide the 2-phenylquinoline **3.5Ab-X** as the major isomer. The latter would be expected because the phenyl ring should impart a stabilising effect on the intermediate iodonium ion (Scheme 3.15). The difference in the yields obtained maybe due to the difficulties in separating the two isomers (Scheme 3.19).

An indication that the cyclisation proceeds *via* cyclisation onto the more stabilised iodonium ion intermediate was obtained by consideration of the other entries in the table which gave the expected major isomer **3.5Ac-Y**, **3.5Aj-X** and **3.5Cb-X** (Table 3.3, entries 3, 6, and 9, respectively). Thus, **2.19Ac** provided the 3-iodo-2-(4-methoxyphenyl)quinoline **3.5Ac-Y** exclusively. In a similar manner **2.20Aj** and **2.20Cb** provided the 2-aryl-3-iodoquinoline as the only characterisable products, albeit in low yields.



Method **A**: ICl (2 equiv.), MeCN, r.t.
Method **B**: I_2 (3 equiv.), MeOH, 65 °C

Scheme 3.19

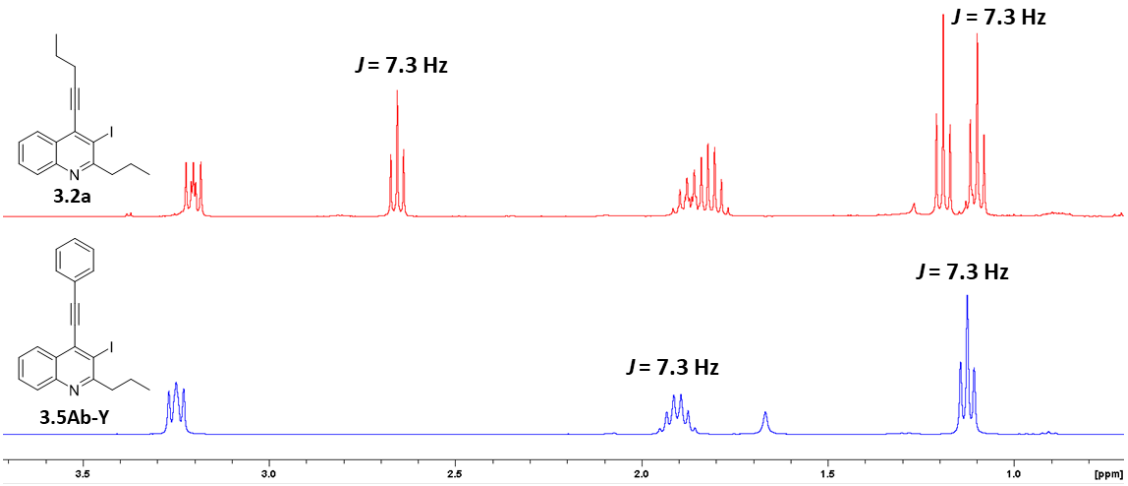


Figure 3.4 400 MHz ^{1}H NMR spectra comparison of **3.2a** and **3.5Ab-Y** in $CDCl_3$

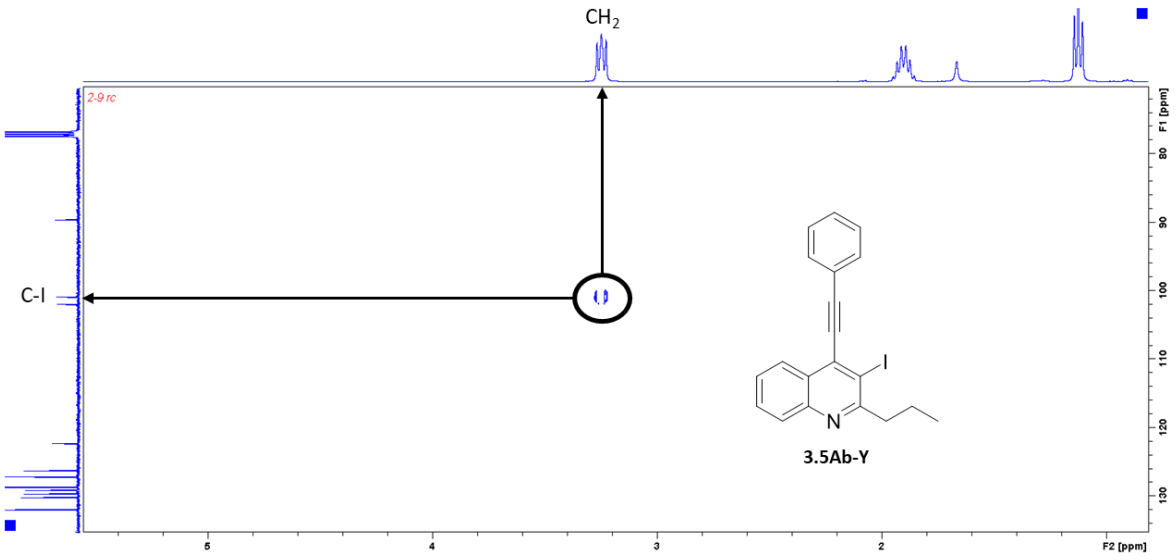


Figure 3.5 HMBC spectrum of **3.5Ab-Y**

The quinolines **3.5Ag-X, 3.5Ag-Y** and **3.5Aj-X** (entry 5 and 6, Table 3.3) were also characterised by their 1D and 2D NMR (COSY, HSQC, HMBC) spectra. In the case of 3-iodo-2-phenyl-4-(prop-1-yn-1-yl)quinoline **3.5Ag-X** (entry 5, Table 3.3) the alkynyl-linked methyl group exhibits a similar ^{1}H NMR chemical shift (δ_H 2.36 ppm) to the starting material **2.19Ag** (δ_H 1.92 ppm, Figure 3.6). Moreover, the ^{13}C NMR shift of the methyl carbon in **3.5Ag-X** (δ_C 5.18 ppm) is strongly shielded due to the anisotropic effect of the alkyne unit, thus confirming the structure as **3.5Ag-X**.

On the other hand, the next fraction (**3.5Ag-Y**) obtained from the iodocyclisation of **2.19Ag** exhibits a significant downfield shift of the methyl group both in the ^{1}H NMR (δ_H 3.03 ppm) and the ^{13}C NMR resonance (δ_C 31.20 ppm) as shown in Figure 3.6, in comparison to the starting material **2.19Ag** (δ_H 1.92 ppm and δ_C 2.64 ppm), implying that the methyl group is no longer shielded by the anisotropic effect of the alkyne, therefore supporting to the structure 3-iodo-2-methyl-4-(phenylethynyl)quinoline **3.5Ag-Y**. Moreover, the HMBC spectrum of **3.5Ag-Y** exhibits a correlation between the 2-methyl protons (δ_H 3.03 ppm) and the quaternary 3-**C** carbon (δ_C 100.90 ppm). The ^{1}H and ^{13}C NMR chemical shifts for the methyl groups in quinolines **3.5Ag-X** and **3.5Ag-Y** are nearly identical those that of the isomeric 3-iodo-2-methyl-4-(prop-1-yn-1-yl)quinoline **3.2g** (Figure 3.6), further confirming each assigned structure of quinolines **3.5Ag-X** and **3.5Ag-Y** (Figure 3.6).

The iodocyclisation reaction of dialkynol **2.19Ag** and molecular iodine in refluxing MeOH (entry 5, Table 3.3) provided the unexpected major isomer 2-methylquinoline **3.5Ag-Y** in a higher yield. As discussed previously this could be due to the difficulties in purifying the reaction mixture.

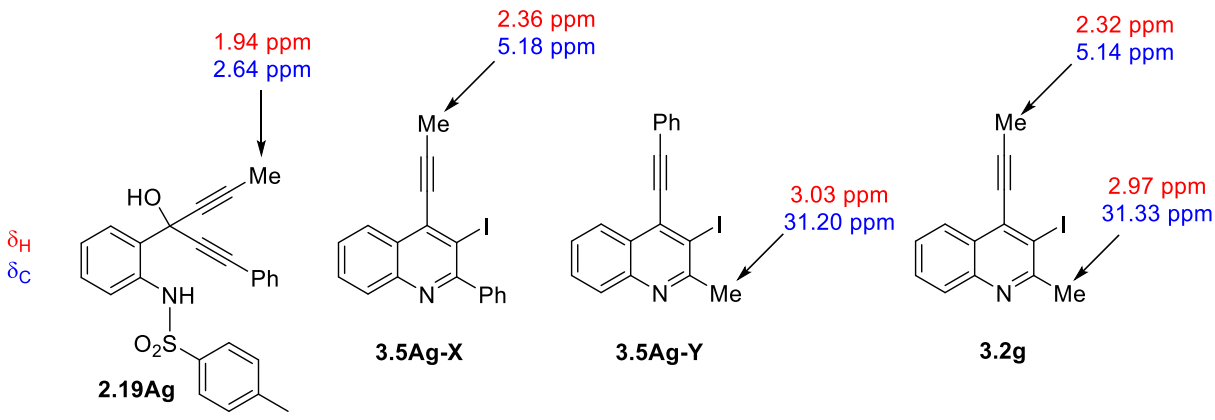
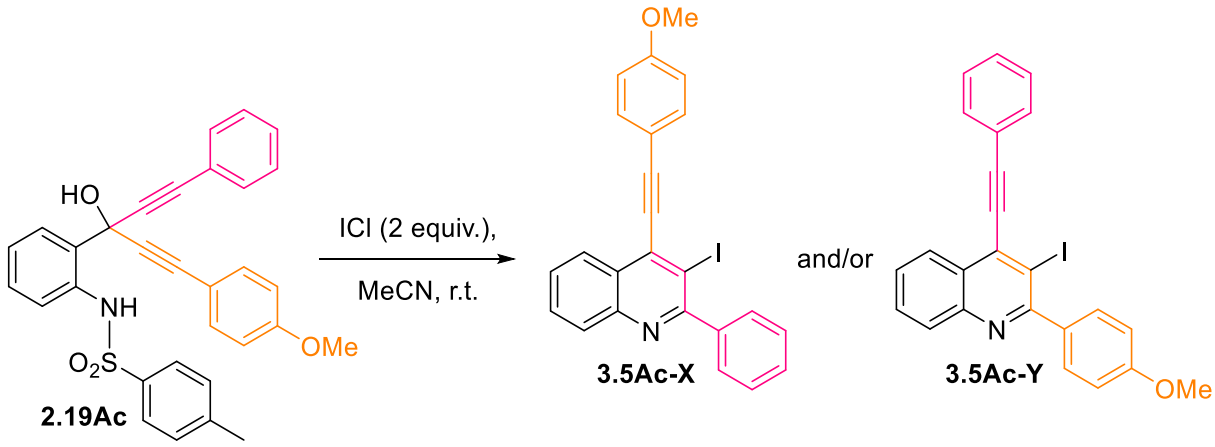


Figure 3.6 ^{1}H and ^{13}C NMR chemical shift comparison of **2.19Ag, 3.5Ag-X, 3.5Ag-Y** and **3.2g**

Of all the iodocyclisation products obtained from the unsymmetrical dialkynols (Table 3.3) the most challenging to characterise was that obtained form **2.19Ac** in which the two alkyne units are terminated by different aryl groups. Clearly the cyclisation could afford either the 2-phenylquinoline **3.5Ac-X** or the 2-(4-methoxyphenyl) derivative **3.5Ac-Y** (Scheme 3.20). It was anticipated that the latter would be generated preferentially because of the greater nucleophilicity of the (4-methoxyphenyl)ethynyl group towards ICl compared to the phenylethynyl functions. In addition, the enhanced stability of the iodonium cation bearing an electron donating 4-methoxyphenyl group (c.f. Scheme 3.15) should also assist in directing the cyclisation.



Scheme 3.20

Thus exposure of **2.19Ac** to ICl in MeCN afforded a single 3-iodoquinoline derivative in 32% yield (entry 3, Table 3.3). The constitution of this compound was established as the expected product i.e. 3-iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline **3.5Ac-Y** by comparison of its ^{1}H NMR spectrum, firstly with that of the 3-iodo-2-(4-methoxyphenyl)-4-(pent-1-yn-1-yl)quinoline **3.5Cb-X** which revealed that the ^{1}H NMR shifts of the 2-(4-methoxyphenyl) protons (red boxes, **B**, Figure 3.7, δ_H 7.57 ppm and 7.01 ppm) are similar to that found in **3.5Ac-Y** (red boxes, **A**, Figure 3.7, δ_H 7.60 ppm and 7.02 ppm). Furthermore the ^{1}H NMR resonances for the phenyl unit in 3-iodo-4-(phenylethynyl)-2-propylquinoline **3.5Ac-Y** (green boxes, **A**, Figure 3.7) have similar chemical shifts to that for quinoline **3.5Ab-Y** (green boxes, **C**, Figure 3.7), further confirming the assignment of entry 3 (Table 3.3) to quinoline **3.5Ac-X**.

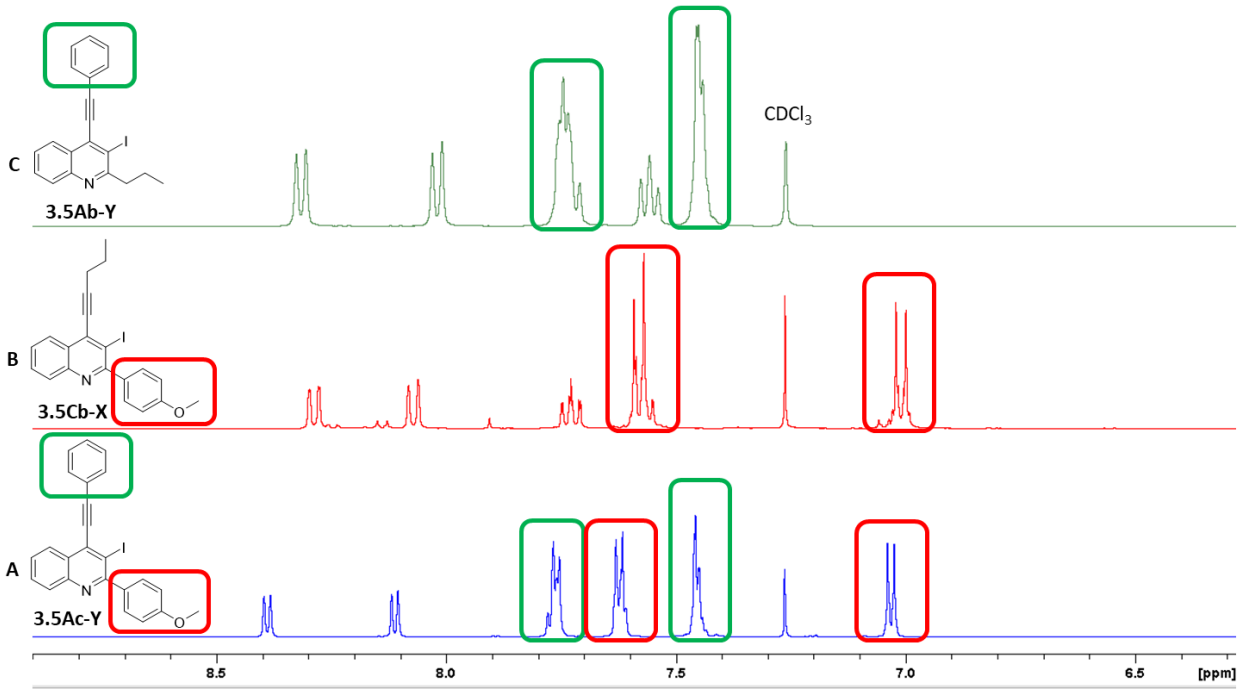
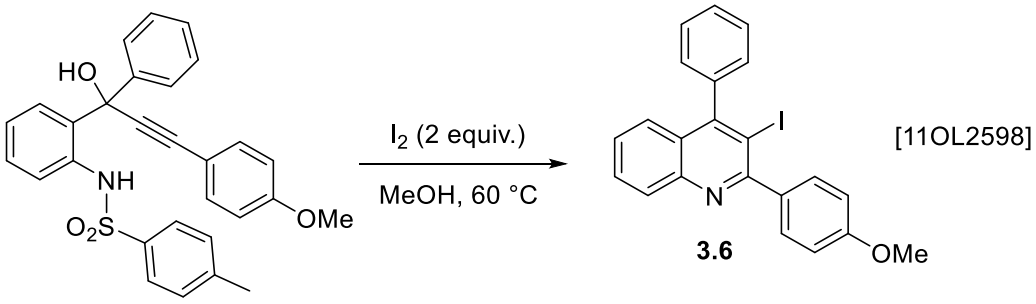


Figure 3.7 ^{1}H NMR spectra comparison of 3-iodoquinolines **3.5Ac-Y** with **3.5Cb-X** and **3.5Ab-Y** in $CDCl_3$

Ali *et al.* reported the preparation of 3-iodo-2-(4-methoxyphenyl)-4-phenylquinoline **3.6** (Scheme 3.21) [11OL2598]. The ^{1}H NMR absorptions for the 2-(4-methoxyphenyl) unit (δ_H 7.60 ppm and 7.01 ppm) are nearly identical to those of **3.5Ac-Y** (δ_H 7.60 ppm and 7.02 ppm). Thus, this data further corroborates the assignment of the quinoline structure as **3.5Ac-Y.**



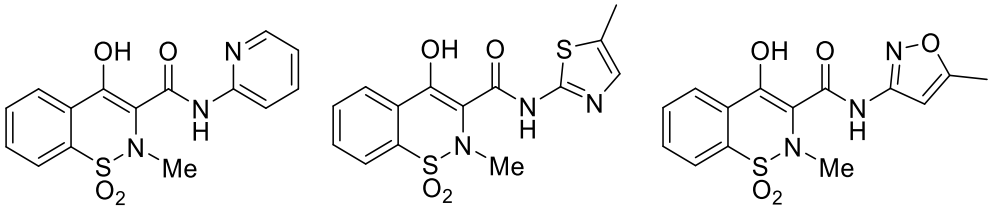
Scheme 3.21

In summary, synthesis of the 3-iodoquinolines **3.5** from the unsymmetrical dialkynols **2.19** proved to be less successful than those from their symmetrical counterparts **2.5 – 2.8** that give the 4-alkynyl-3-iodoquinolines **3.2**. Some examples of quinolines **3.5** provided very low

yields or an intractable mixture of products. Clearly future optimisation of the reaction is required.

3.2 Silver(I) Mediated Cyclisations of [3-2-(Sulfamoyl)phenyl]penta-1,4-diyn-3-ols to 1,2-Benzothiazine 1,1-dioxides and Derivatives

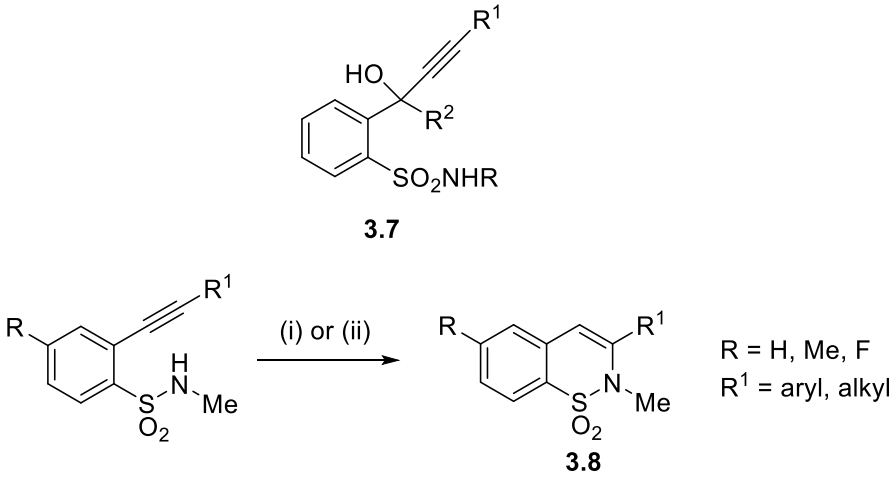
Since the 1960s there has been sustained interest in 1,2-benzothiazines and especially their 1,1-dioxides, following the discovery of the non-steroidal anti-inflammatory oxicams, of which three representatives are shown below.



Piroxicam Meloxicam Isoxicam

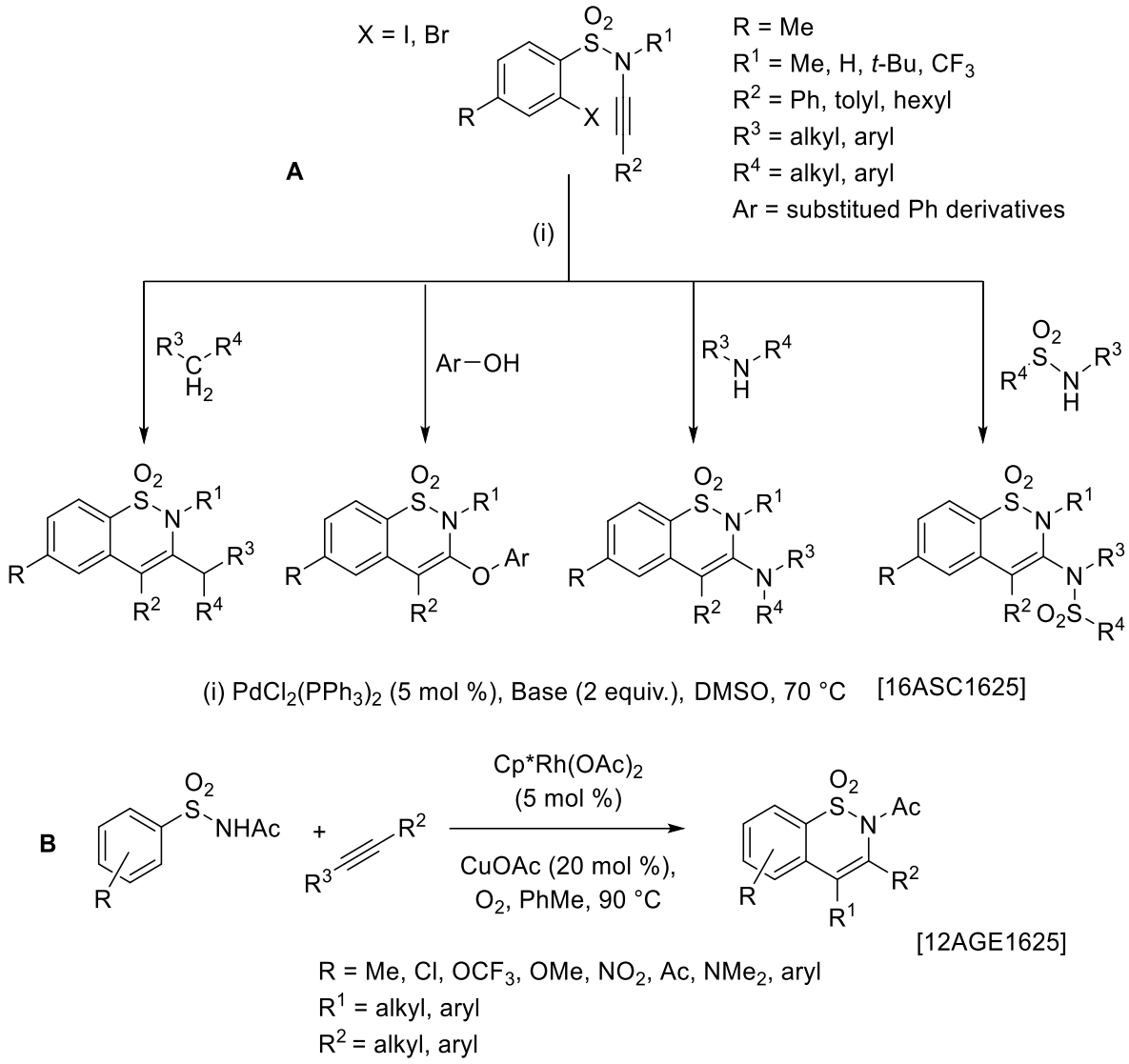
Traditional routes to 1,2-benzothiazine 1,1-dioxides involve the intramolecular Claisen condensation of sulfonamides derived from methyl 2-(chlorosulfonyl)benzoate and α-amino carbonyl compounds. The base-promoted ring expansion of *N*-(acylmethyl) saccharins provides access to 3-acyl-4-hydroxy-1,2-benzothiazine 1,1-dioxides. These and related approaches have been reviewed [81AHC(28)73, 20MRO148]. Developments in the chemistry and synthetic routes to 1,2-benzothiazines have been reviewed more recently [18SC3033]. Some of the recent syntheses of the ring system are outlined in Section 1.5.4 and below. This section describes a novel means to construct the 1,2-benzothiazine 1,1-dioxide nucleus.

As discussed in Section 2.2 there are few aryl (di)alkynols in which the aryl ring is substituted with a primary, secondary or tertiary sulfamoyl group i.e. $-SO_2NH_2$, $-SO_2NHR$ or $-SO_2NR_2$ respectively. Indeed, the only examples are arylacetylenes possessing an *ortho*-sulfamoyl group, whilst compounds containing a 1-(2-sulfamolyphenyl)prop-2-yn-1-ol unit e.g. **3.7** have not been reported previously (cf. Section 2.2). Silver(I)-mediated cyclisations of (2-sulfamoylphenyl)acetylenes (2-alkynylbenzenesulfonamides) have been shown to afford 1,2-benzothiazine 1,1-dioxides **3.8** *via* a 6-*endo*-*dig* pathway (Scheme 3.22) [07JOC8547, 12TL6577].



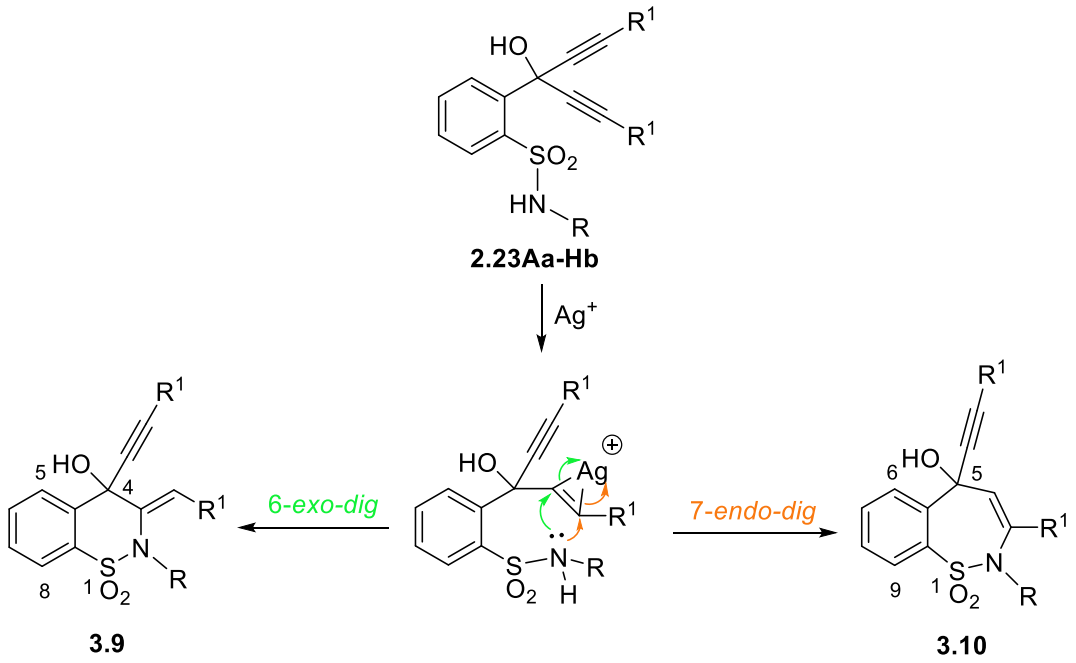
Scheme 3.22

Other more expensive metal catalysts have been utilised for the formation of 1,2-benzothiazine 1,1-dioxides and complexes of palladium(0) and rhodium(III) have proved particularly useful [18SC3033]. Reddy and co-workers produced a range of sultams (**A**, Scheme 3.23) utilising a Pd(0) catalyst generated *in situ* from $[PdCl_2(PPh_3)_2]$, to activate the triple bond of *N*-(phenylsulfonyl)propargylamines to attack from a range of nucleophiles [16ASC1625]. Pham, Ye and Cramer synthesised a range of 1,2-benzothiazines (**B**, Scheme 3.23) from a Rh(III)-mediated oxidative C-H activation-alkynylation reaction of *N*-acetylbenzenesulfonamides. It was found that low or stoichiometric loadings of copper(I) were unfavourable and that to minimise acetyl group cleavage, molecular oxygen was required as a terminal oxidant [12AGE10610].



Scheme 3.23

The present project has demonstrated that silver(I) salts are effective for the cyclisation of the tosylamidophenyl dialkynols **2.5** to afford indoles **2.32** and indolines **2.33** (Section 2.4) *via* a 5-*exo*-*dig* pathway. Clearly the isomeric sulfamoylphenyldialkynols (reversed sulfonamides) **2.23Aa – Hb** could not cyclise in the same manner and upon π-complexation with Ag(I) would be activated to ring closure *via* either 6-*exo*-*dig* or 7-*endo*-*dig* pathways (Scheme 3.24). Both pathways are favoured under Baldwin's rules [76CC734, 16CMS487]. The cyclisations potentially constitute a novel means to construct the 1,2-benzothiazine and/or 1,2-benzothiazepine ring systems.



Scheme 3.24

Initially the dialkynol **2.23Aa** was treated with AgOAc (5 mol %) in MeCN at reflux overnight. Purification of the reaction mixture by flash chromatography (10% EtOAc – hexane) provided a complex minor component in the initial fractions. However, the major final fraction exhibited a very different ^{1}H NMR spectrum to that of the starting material (blue spectrum, Figure 3.8). The benzo ring signals are shifted upfield (red spectrum, Figure 3.8) compared with that of the starting material, furthermore the N-*Me* group signal is shifted downfield and appears as a singlet, consistent with formation of a cyclisation product (Figure 3.8). Coupling of the N*H* proton with the methyl group (J_{NHMe} = 5.3 Hz) is a distinctive feature of the ^{1}H NMR spectrum of the starting material **2.23Aa** (blue spectrum, Figure 3.8).

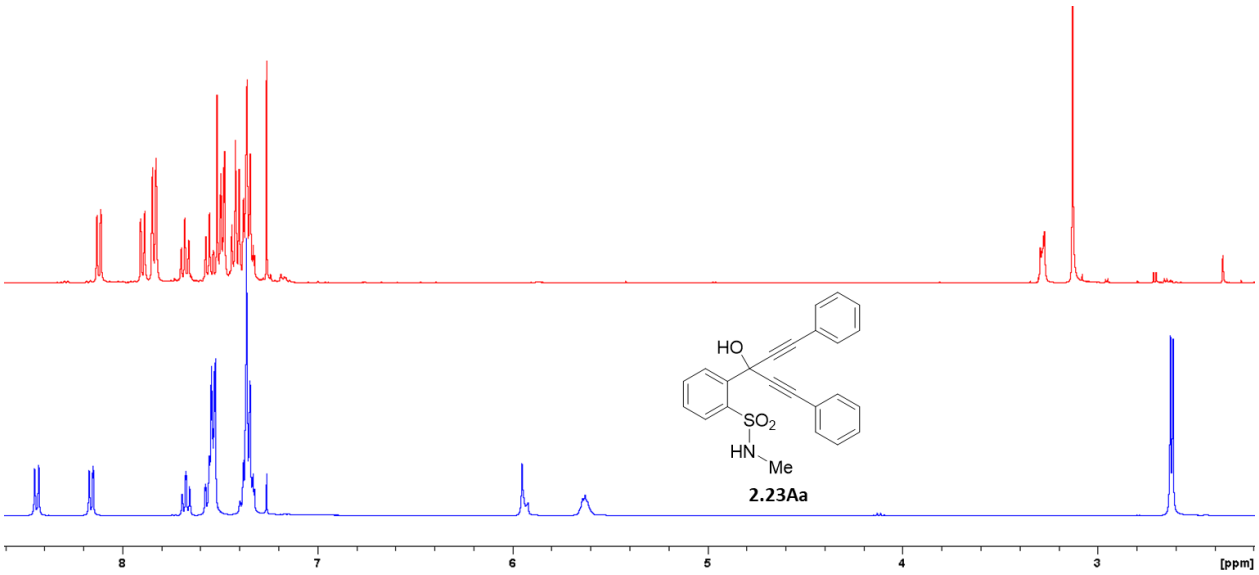
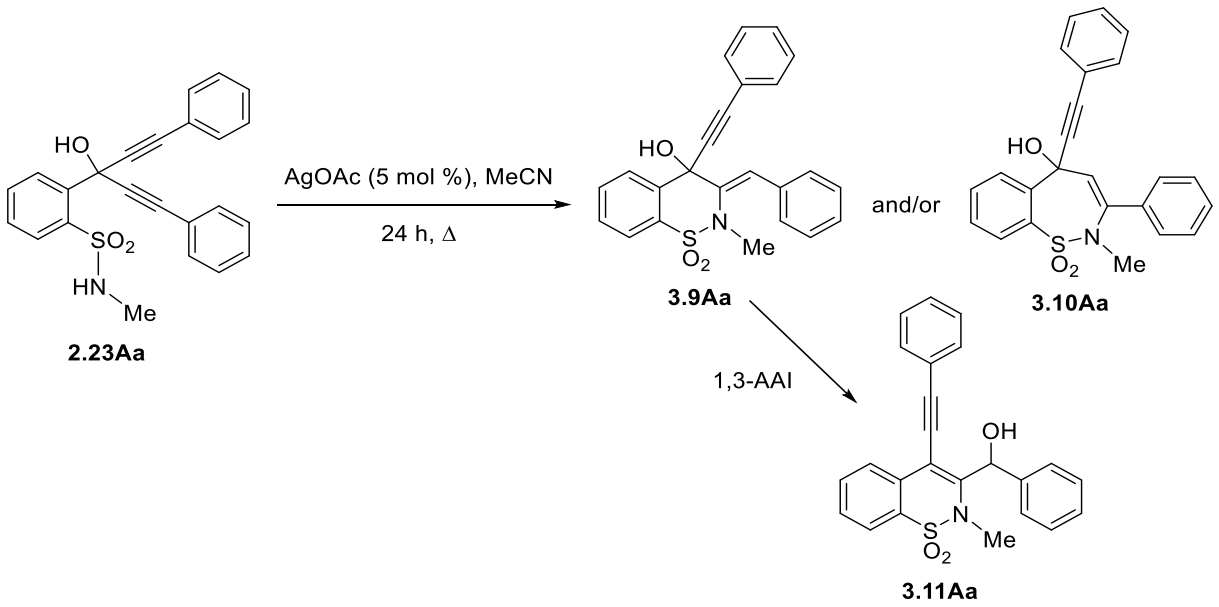


Figure 3.8 400 MHz ^{1}H NMR spectra comparison of **2.23Aa** to unknown fraction in $CDCl_3$

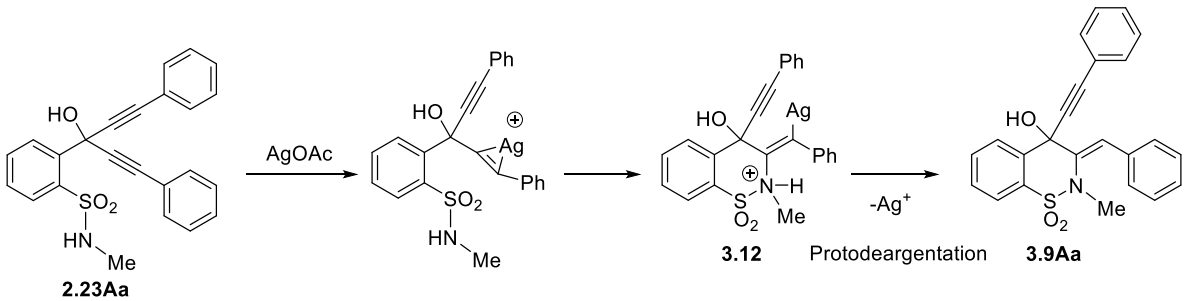
There are three potential cyclisation products from the cyclisation of dialkynol **2.23Aa** (Scheme 3.25). Coordination of Ag(I) to the alkyne activates it to nucleophilic attack from the sulfonamide nitrogen; the cyclisation pathway could then proceed *via* 6-*exo* or 7-*endo*-dig pathways to give six membered (**3.9Aa**) or seven membered (**3.10Aa**) rings respectively (Scheme 3.25). Furthermore, the benzylic enynol **3.9Aa** could also undergo a 1,3-allylic alcohol isomerization (1,3-AAI) [07TL8505] to give the isomeric 1,2-benzothiazine system **3.11Aa** (Scheme 3.25).



Scheme 3.25

If the reaction had furnished **3.11Aa** it would be expected that two doublets with a *geminal* coupling would be present in the ^{1}H spectrum (as there was for indole **3.32a**), corresponding to the alcohol and the benzylic C*H* protons. However, the absence of these signals discount structure **3.11Aa**. Moreover, it was considered less likely that the major product was the seven-membered 1,2-benzothiazepine ring **3.10Aa** because of the less favoured conformation the substituents must adopt for the cyclisation to proceed.

Of the possible structures, the 1,2-benzothiazine 1,1-dioxide **3.9Aa**, resulting from a 6-*exo*-*dig* cyclisation, would appear to be the most probable. It was considered likely that the product will process (*Z*)-stereochemistry as interactions of the benzylidene moiety and the benzothiazine C-4 substituents in the intermediate silver(I) species **3.12** will be minimised. Furthermore, the 6-*exo*-*dig* cyclisation will proceed *via* an anti-addition of the sulfonamide function to the metallocyclopropene intermediate as shown below in Scheme 3.26.



Scheme 3.26

The constitution of 1,2-benzothiazine 1,1-dioxide **3.9Aa** was established by examination of the NOESY spectrum (Figure 3.9), which revealed a through-space interaction between the benzylidene *CH* signal (δ_H 7.49 ppm) and the *OH* signal (δ_H 3.42 ppm). The latter signal also exhibited a correlation with that of the apparent doublet at δ_H 8.10 ppm, thus providing confirmation that the most deshielded signal corresponds to the 5-*H* proton (cf. Section 2.2, Figure 2.2). Further evidence in support of the (*Z*)-stereochemistry of **3.9Aa** was provided by the cross-peak (Figure 3.9) corresponding to an interaction between the *ortho-Ph* protons (δ_H 7.47 ppm) of the benzylidene unit and the *Me* protons (δ_H 3.12 ppm).

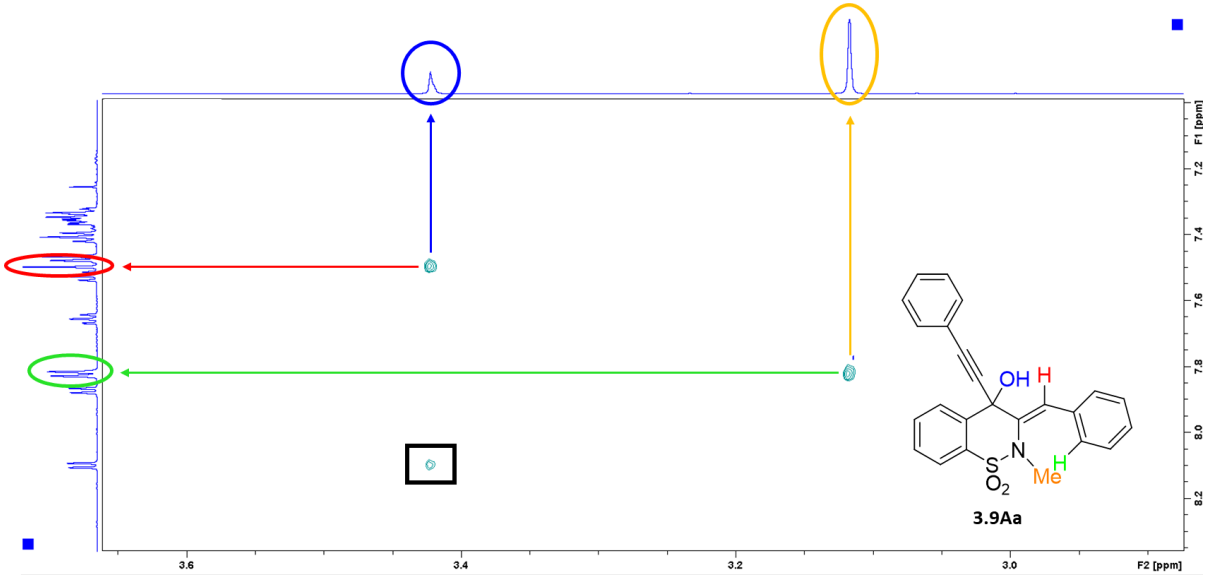
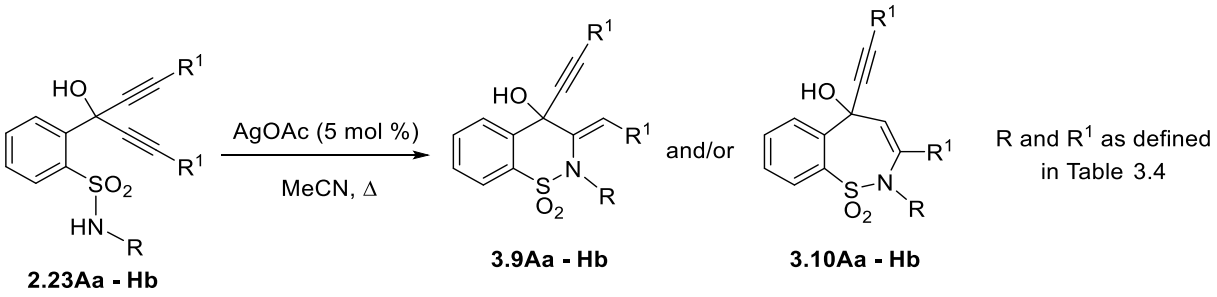


Figure 3.9 NOESY spectrum of **3.9Aa**

Both 1,2-benzothiazine 1,1-dioxide **3.9Aa** and 1,2-benzothiazepine 1,1-dioxide **3.10Aa** structures are novel, and additional derivatives were required not only to confirm the structure of **3.9Aa** but also to investigate the scope and limitations of these cyclisation reactions. Consequently, the reactivity of a range of reversed sulfonamides **2.23Aa – Hb** towards AgOAc in MeCN was examined, Scheme 3.27. The results of these cyclisations are collated in Table 3.4.



2.23Aa - Hb **3.9Aa - Hb** **3.10Aa - Hb**

Scheme 3.27

Entry	R	R^1	Dialkynol	Time (h)	Product	1,2-Benzothiazine Yield (%)	Product	1,2-Benzothiazepine Yield (%)
1	Me	Ph	**2.23Aa**	24	**3.9Aa**	48	**3.10Aa**	0
2[ab]	Me	C_3H_7	**2.23Ab**	20	**3.9Ab**	12[b]	**3.10Ab**	7
3	Tolyl	Ph	**2.23Ba**	3	**3.9Ba**	78	**3.10Ba**	0
4	Tolyl	C_3H_7	**2.23Bb**	1	**3.9Bb**	82	**3.10Bb**	0
5	Tolyl	4-$MeOC_6H_4$	**2.23Bc**	23	**3.9Bc**	62	**3.10Bc**	0
6[c]	Tolyl	TMS	**2.23Be**	2	**3.9Be**	61	**3.10Be**	0
7	Tolyl	CH_2OMe	**2.23Bf**	20	**3.9Bf**	86	**3.10Bf**	0
8	3-MeC_6H_4	Ph	**2.23Ca**	4	**3.9Ca**	72	**3.10Ca**	0
9	3-MeC_6H_4	C_3H_7	**2.23Cb**	1.5	**3.9Cb**	59	**3.10Cb**	0
10	2-$MeOC_6H_4$	Ph	**2.23Da**	2	**3.9Da**	86	**3.10Da**	0
11	2-$MeOC_6H_4$	C_3H_7	**2.23Db**	2	**3.9Db**	61	**3.10Db**	0
12	3-$MeOC_6H_4$	Ph	**2.23Ea**	3	**3.9Ea**	96	**3.10Ea**	0
13	3-$MeOC_6H_4$	C_3H_7	**2.23Eb**	3	**3.9Eb**	80	**3.10Eb**	0
14	3-thienyl	C_3H_7	**2.23Gb**	3.7	**3.9Gb**	70	**3.10Gb**	11
15	2-naphthyl	Ph	**2.23Ha**	3	**3.9Ha**	75	**3.10Ha**	0
16	2-naphthyl	C_3H_7	**2.23Hb**	3	**3.9Hb**	84	**3.10Hb**	0

Table 3.4 Yields from the AgOAc cyclisation of reversed sulfonamides **2.23Aa – Hb.** a = 3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2*H*-1,2-benzothiazine 1,1-dioxide **3.11Ab** also obtained from this reaction. b = yield from ^{1}H NMR spectrum c = 4-Hydroxy-3-methylene-2-(*p*-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide **3.9Be'** also obtained from the reaction

The reaction of 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide **2.23Ab** AgOAc in MeCN (entry 2, Table 3.4) provided a mixture of compounds that could only be separated with difficulty by extensive flash column chromatography. However, it proved possible to identify three novel compounds (Scheme 3.28). The major fraction from flash column chromatography, was identified as an inseparable mixture of 1,2-benzothiazine 1,1-dioxide **3.9Ab** and starting material **2.23Ab** (in several solvents). The yield quoted (12%, Table 3.4) is from integration ratios in the ^{1}H NMR spectrum. (*Z*)-3-Butenylidene-1,2-benzothiazin-4-ol **3.9Ab** (Scheme 3.28) was identified on the basis of its ^{1}H NMR spectrum which exhibited a triplet at δ_H 6.64 ppm (J = 7.3 Hz). The constitution of this material was also confirmed by LC-MS with a molecular ion at *m/z* $[M+H]^+$ = 333.1391 corresponding to $C_{18}H_{22}NO_3S$.

A faster running (less polar) component was isolated and identified as the 7-*endo-dig* product the 1,2-benzothiazepine 1,1-dioxide **3.10Ab** (7%, Scheme 3.28). The ^{1}H NMR spectrum exhibited two singlets at δ_H 5.77 and 5.34 ppm corresponding to the 4-*H* and O*H* protons respectively (Figure 3.10). The absence of allylic coupling between the C-3 propyl group and the 4-*H* is noteworthy (Figure 3.10). HRMS also provided additional support for **3.10Ab** and displayed $[M+H]^+$ at *m/z* 334.1463 corresponding to $C_{18}H_{23}NO_3S$.

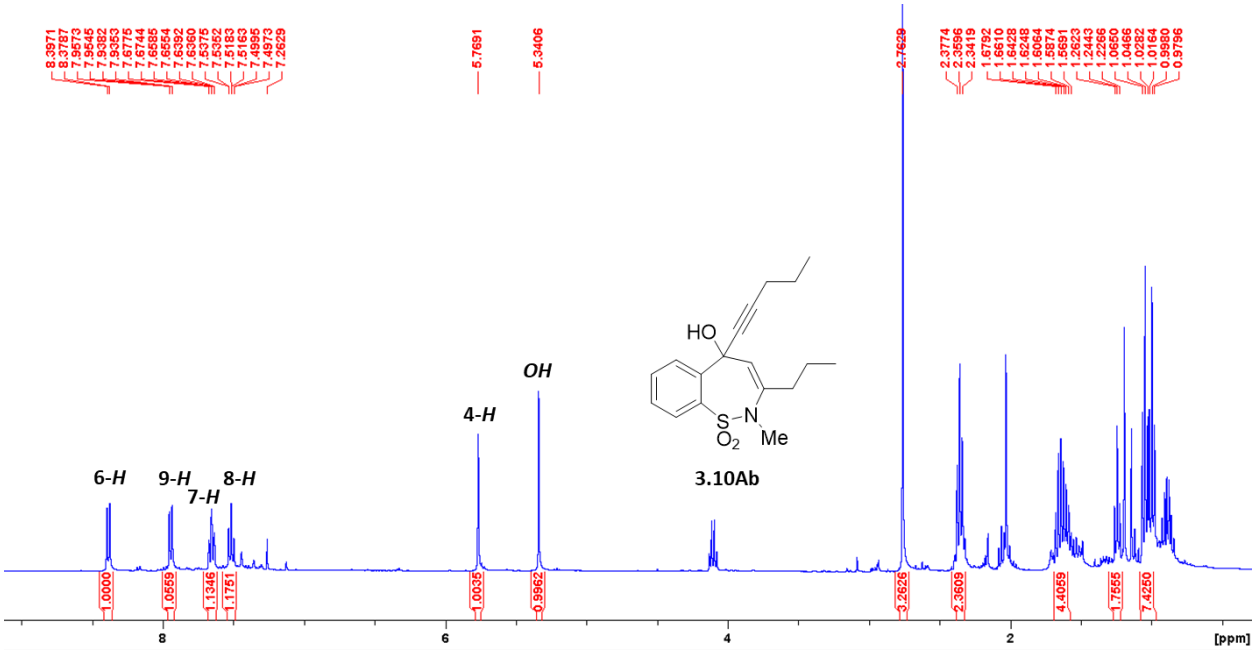
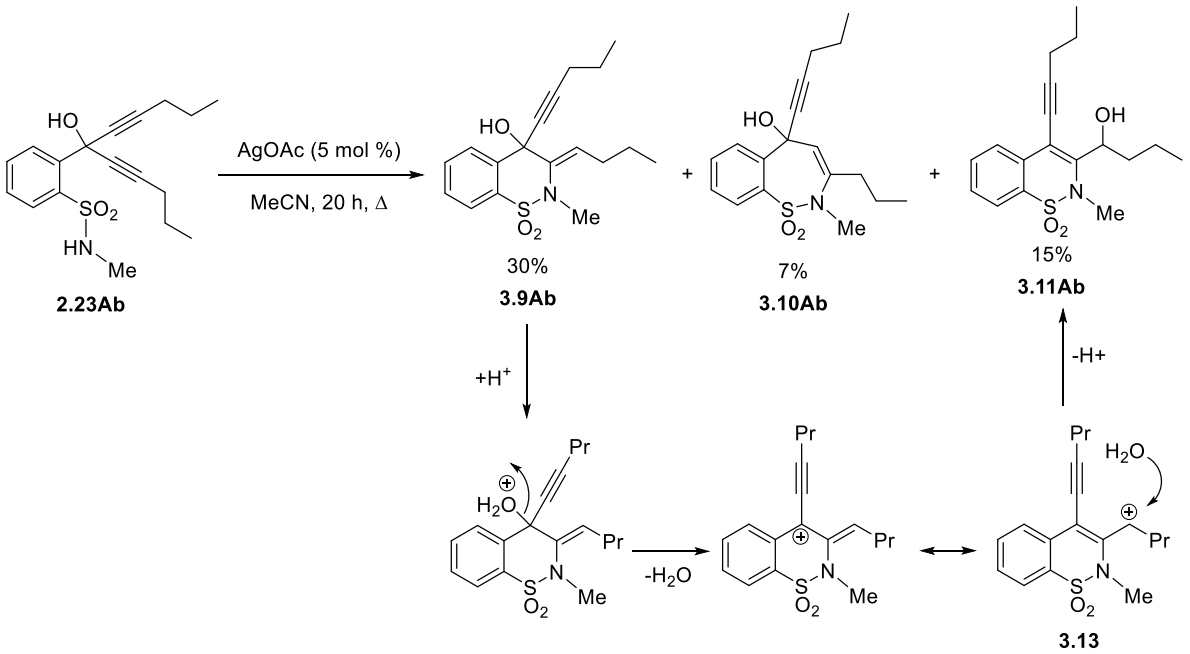


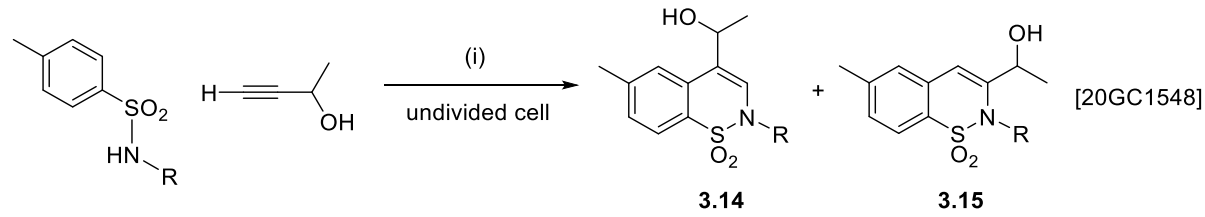
Figure 3.10 400 MHz ^{1}H NMR spectrum of 1,2-benzothiazepine 1,1-dioxide **3.10Ab** in $CDCl_3$

Another non-polar orange oil was also obtained from attempted purification of the reaction mixture (entry 2, Table 3.4) and identified as 3-(1-hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2*H*-1,2-benzothiazine 1,1-dioxide **3.11Ab** (15% yield, Scheme 3.28). This compound is thought to be formed during repeated chromatographic purification during which the 1,2-benzothiazin-4-ol **3.9Ab** is protonated by the acidic silica gel. Subsequent dehydration will generate the highly delocalised carbocation **3.13** which is susceptible to nucleophilic attack (S_N1) from water to afford **3.11Ab** (Scheme 3.28). The latter was characterised by its ^{1}H NMR spectrum which exhibited a multiplet for the side-chain methine proton centred at δ_H 5.18 ppm. The adjacent O*H* proton appeared as a doublet ($J_{CH\text{-}OH}$ = 5.2 Hz) at δ_H 2.59 ppm. Characteristic signals for the alkyne carbons were observed at δ_C 74.18 and 100.61 ppm.



Scheme 3.28

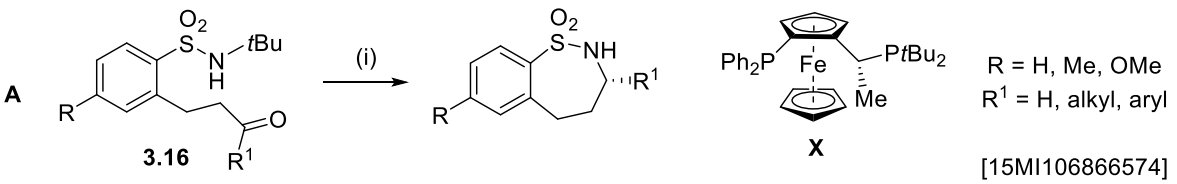
Lei and co-workers synthesised the (1-hydroxyethyl)-1,2-benzothiazine 1,1-dioxides **3.14** and **3.15**, by anodic oxidation of an *N*-heteroaryl sulfonamide and but-3-yn-2-ol in an undivided cell (Scheme 3.29). However, NMR data was only reported for the major isomer **3.14** [20GC1548]. There are no other similar model compounds to 3-hydroxy-1,2-benzothiazine 1,1-dioxide (**3.11Ab**) in the literature to date.



Scheme 3.29

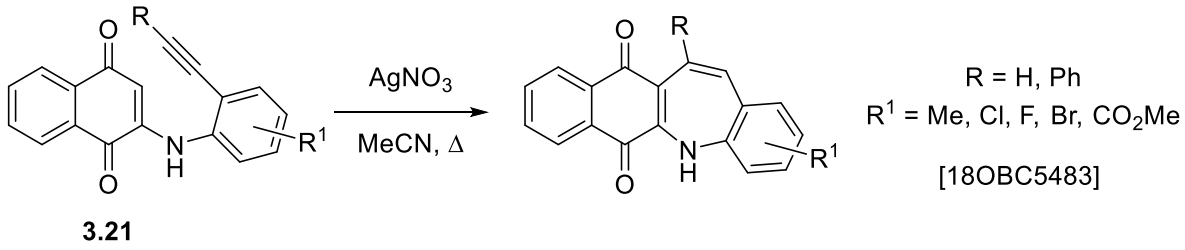
1,2-Benzothiazepines are relatively uncommon. Synthetic routes to this ring system are highlighted in Scheme 3.26 and often involve numerous steps or employ specialist photochemical equipment [80CJC369, 08SC3662, 11JME716, 13JCD4410, 17OCF14, 17OL6020, 19JOC3871]. Sulfonamide **3.16** (**A**, Scheme 3.30) was reductively cyclodehydrated to 1,2-benzothiazepines with high *ee* (91 – 99%) [15MI106866574]. 2-Azidothiochromone 1,1-dioxides upon irradiation in acetophenone undergoes a ring

expansion affording **3.17** in an 81% yield (**B**, Scheme 3.30) [80CJC369]. 1,2-Benzothiazin-3-ones undergo a ring expansion in the presence of a strong base (**C**, Scheme 3.30) [08SC3662]. Ganguly and co-workers found that the readily available *N*-allylsulfonamides **3.18** undergo a radical chain cyclisation to saturated 1,2-benzothiazepine-1,1-diones (**D**, Scheme 3.30) [11JME7176]. The palladium(II)-catalysed reaction of 2-alkynylbenzensulfonamides and 2-alkynylvinyl bromide were employed to synthesise 6*H*-benzo[*f*]cyclopenta[*d*][1,2]thiazepine 5,5-dioxides (**E**, Scheme 3.30) in high yields (56 – 99%) [13JCD4410]. Wen used a rhodium(III) complex to catalyse the C-H functionalisation of sulfoximines with enones to afford 1,2-benzothiazepine 1-oxides **3.19** (**F**, Scheme 3.30) [17OL6020]. Figueroa *et al.* obtained the 1,2-benzothiazepin-5-one 1,1-dioxide **3.20** from a photochemically induced ring expansion of sodium saccharin with phenylacetylene (**G**, Scheme 3.30) [19JOC3871].


A
(i)
3.16
X
R = H, Me, OMe
R1 = H, alkyl, aryl
[15MI106866574]
(i) X, Pd(OCOCF3)2, (R,Sp)-JosiPhos, TsOH.H2O, H2, TFE, 80 °C
B
acetophenone
λirr > 300 nm
[80CJC369]
3.17
C
NaOC2H5
[08SC3662]
D
AIBN, TBTH,
PhMe, Δ
3.18
R = H, CF3
R1 = H, F, CF3, OMe
R2 = H, Me
TBTH = tributyltin hydride
[11JME7176]
E
(i)
R = H, Me, OMe, Cl
R1 = alkyl, aryl
R2 = Me, Bn
R3 = Et, n-Pr
R4 = Ph, tolyl, 4-ClC6H4, 4-MeOC6H4
(i) Pd(OAc)2 (5 mol %), DPPP (5 mol %), 1,4-dioxane, K2CO3, Δ
[13JCD4410]
F
(i)
R = H, Me, OMe, F, Cl, CO2Me
R1 = Me, Et, Ph, Bn, C3H5
R2 = aryl, alkyl
3.19
[17OL6020]
(i) = [Cp*RhCl2]2 (2.5 mol %), AgAbF6 (10 mol %), 1-AdCO2H (3 equiv.), PhMe,100 °C
G
(i) hν = 300 nm, MeOH, NaOH 1M
(ii) dil. HCl or DMF, MeI
R = H when HCl used
R = Me when MeI used
[19JOC3871]
3.20

Scheme 3.30

Although 7-*endo-dig* cyclisations are known, they are still relatively scarce. A SciFinder search uncovered 65 references. An example of a 7-*endo-dig* cyclisation pertinent to the present project is illustrated in Scheme 3.31. The Ag(I)-catalysed cyclisation of the 2-(2-alkynylphenyl)amino-1,4-naphthoquinones **3.21** to benzo[*b*]naptho[2,3-*f*]azepine-6,11-diones proceeds in excellent yields (69 – 99%) [18OBC5483].

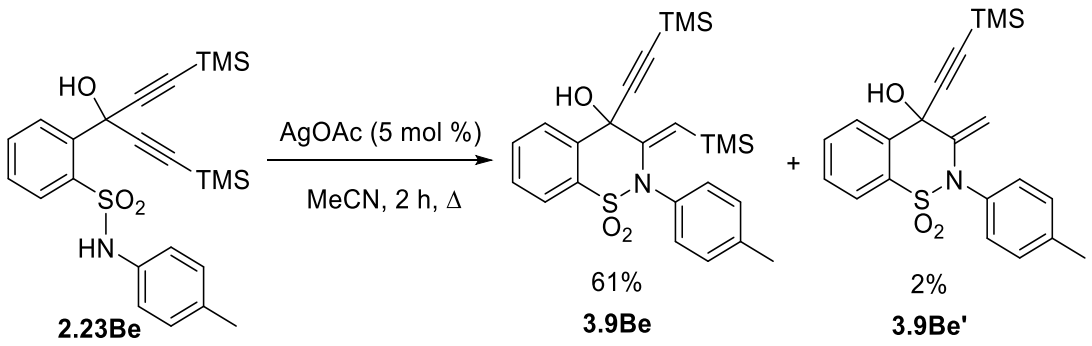


3.21

Scheme 3.31

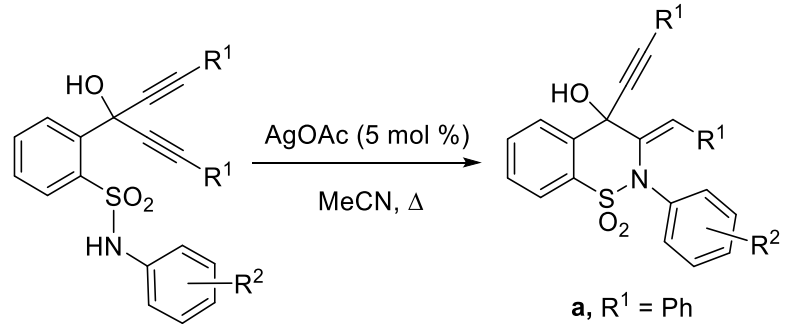
The AgOAc-mediated ring closure of the 3-(*N*-methylsulfamoylphenyl)pentadiynols **2.23Aa – b** provided an entry to novel 1,2-benzothiazine 1,1-dioxides albeit in fair yields (entries 1 and 2, Table 3.4). It was of interest to explore the scope of the influence of the alkyne groups upon the outcome of the reaction. To this end, the Ag-mediated cyclisation was extended to the range of 3-[2-(*N*-tolylsulfamoyl)phenyl]penta-1,4-diyn-3-ol derivatives. Thus, the dialkynols **2.23Ba – f** cyclised efficiently to afford the corresponding 2-(4-methylphenyl)-1,2-benzothiazine 1,1-dioxides **3.9Ba – f** in yields ranging from 61 – 82% (entries 3 – 7, Table 3.4). All of the products were obtained as yellow or orange oils after flash column chromatography and the cyclisation was successful with alkynes possessing either alkyl or aryl terminal groups.

In the case of the sulfamoyl dialkynol **2.23Be** the cyclisation proceeded rapidly (2 h) to afford **3.9Be** in 61% yield (entry 6, Table 3.4). In addition, a small amount of a compound identified as the desilylation product as **3.9Be'** (Scheme 3.32) was also obtained in 2% yield. The structure of the latter was confirmed by the ^{1}H NMR spectrum, which exhibited two doublets at δ_H 5.82 and 4.76 ppm (^2J = 1.8 Hz) corresponding to the alkenic protons. The constitution of **3.9Be'** was also confirmed by HRMS with which exhibited a molecular ion at *m/z* $[M+H]^+$ = 398.1251 corresponding to $C_{21}H_{23}NO_3SSi$.



Scheme 3.32

The *N*-aryl group in **2.23** was also varied to give three additional compound series of 1,2-benzothiazine 1,1-dioxides **3.9C – E** (entries 8 – 13, Table 3.4) (Scheme 3.33), of which the latter were obtained in generally high yields (59 – 96%). A near quantitative yield was obtained of **3.9Ea.** None of these cyclisations were accompanied by a 1,2-benzothiazepine 1,1-dioxide.



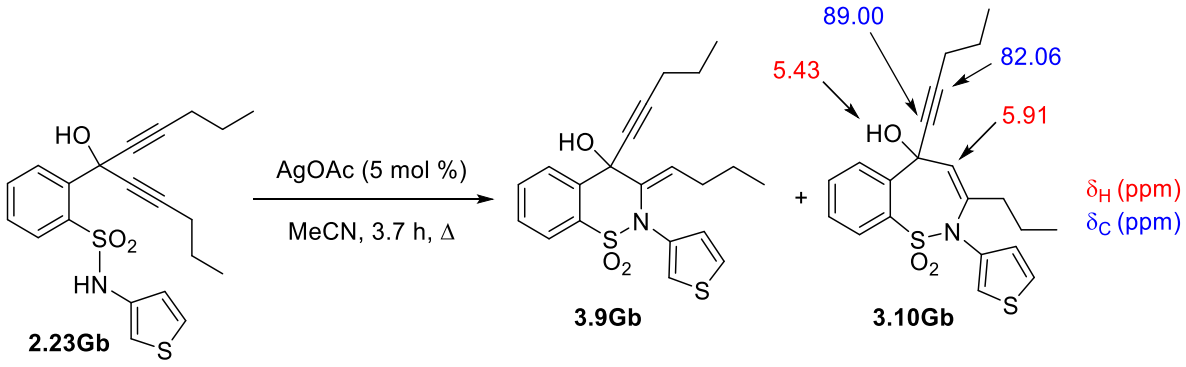
a, R^1 = Ph
b, R^1 = C_3H_7
2.23C, R^2 = 3-Me
2.23D, R^2 = 2-OMe
2.23E, R^2 = 3-OMe

a, R^1 = Ph
b, R^1 = C_3H_7
3.9C, R^2 = 3-Me
3.9D, R^2 = 2-OMe
3.9E, R^2 = 3-OMe

Scheme 3.33

Replacement of the *N*-aryl substituent in dialkynols **2.23B – E** with a 3-thienyl unit provided the *N*-heteroarylsulfonamide **2.23Gb.** In this case, silver-mediated cyclisation proceeded readily to give the 2-(3-thienyl)-1,2-benzothiazine 1,1-dioxide **3.9Gb** in 70% yield, together with a small amount of the 7-*endo-dig* cyclisation product **3.10Gb** (Scheme 3.34). The latter was characterised from its ^{1}H and ^{13}C NMR spectra, the former exhibited a singlet at δ_H 5.91 ppm for the 4-*H* proton together with an O*H* signal at δ_H 5.43 ppm. The presence of alkyne

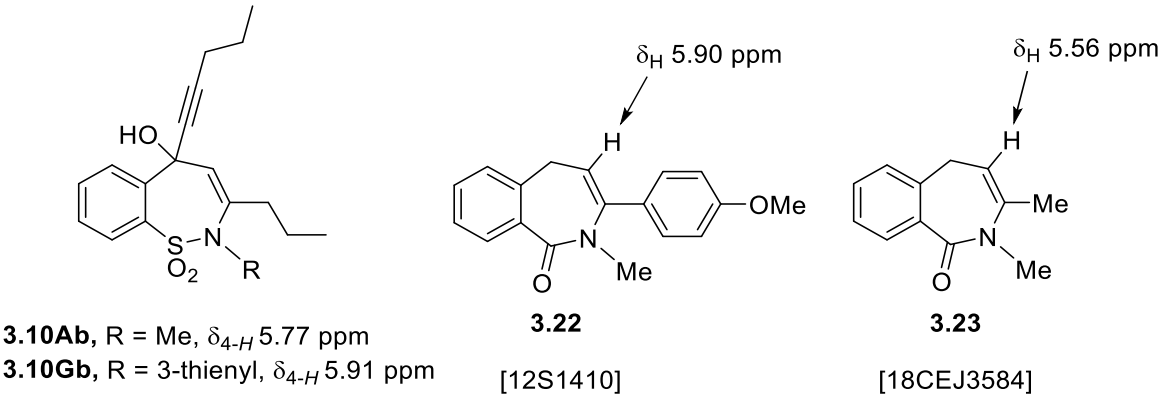
carbon signals at δ_C 89.00 and 82.06 ppm confirmed the presence of the pentynyl group, whilst the quaternary 5-C signal resonated at δ_C 72.89 ppm.



Scheme 3.34

The 2-methyl- and 2-(3-thienyl)-1,2-benzothiazepine 1,1-dioxides **3.10Ab** and **3.10Gb** isolated from **2.23Ab** and **2.23Gb** respectively (entries 2 and 14, Table 3.4) contained impurities, further attempts to purify these compounds began to result in degradation (^{1}H NMR). The indication seemed to be that both the 1,2-benzothiazepines were unstable in ambient conditions (air and light). It is noteworthy that 1,2-benzothiazepine formation (i.e. 7-*endo-dig* cyclisation) was only observed from the undecadiynols **2.23Ab** and **2.23Gb**, a feature that merits further investigation.

Within the literature there are no 1,2-benzothiazepine 1,1-dioxides analogous to **3.10Ab** and **3.10Gb.** However, the chemical shift of the 4-*H* protons in these examples are remarkably close to those in the 2-benzazepin-1-ones **3.22** and **3.23** that contain an electronically similar enamide moiety Scheme 3.35 [12S1410, 18CEJ3584].

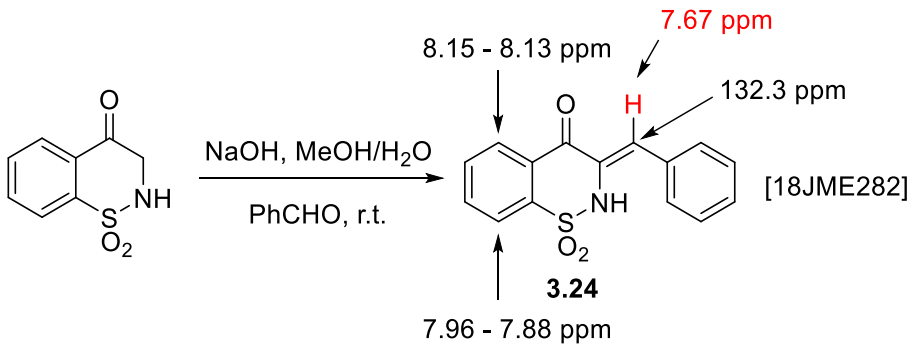


Scheme 3.35

Cyclisations of *N*-(2-naphthyl)sulfonamide **2.23H** (entries 15 and 16, Table 3.4) proceeded straightforwardly to afford the 2-(2-naphthyl)-1,2-benzothiazine 1,1-dioxides **3.9Ha – b** in high yields.

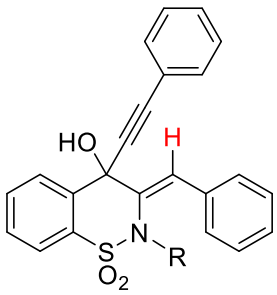
Characterisation data for the compounds prepared merit some consideration. The benzylidene (methine) proton (C***H***) of benzothiazines **3.9Aa – Ha** and **3.9Bc** (Table 3.5), are in some cases shifted downfield by as much as 1 ppm in comparison to the 3-alkylidene-1,2-benzothiazines **3.9Ab** – **Hb** and **3.9Be – f** (Table 3.6). There does not appear to be any examples of 3-alkylidene-1,2-benzothiazin-4-ols or -4-ones in the literature for comparison with the data in Table 3.6. However, in the series **3.9Ab** – **3.9Hb** and **3.9Be – f**, shielding of the alkenic hydrogen stems from a combination of the inductive effect of the alkyl group and the absence of a *geminal* anisotropic group.

Whilst the NOESY spectrum for 1,2-benzothiazine 1,1-dioxide **3.9Aa** (Figure 3.9) established a (*Z*)-configuration it is worth noting that the chemical shift of the benzylidene proton (δ_H 7.49 ppm, δ_C 131.06 ppm) is also in accord with these of the (*Z*)-3-benzylidene-2-methyl-2*H*-1,2-benzothiazine-4-(3*H*)-one 1,1-dioxide derivative **3.24** obtained by Asharaf and co-workers. The latter (**3.24**) was obtained from a ketone and arylaldehyde in a base-catalysed aldol condensation (Scheme 3.36) [18JME282]. It was observed that electron donating substituents in the benzylidene group resulted in shielding of the methine proton signal, whereas the latter was deshielded when an electron withdrawing substituent was present. However, the chemical shift differences between the derivatives of **3.24** were small (δ_H 7.77 – 7.62 ppm, $\Delta\delta_H$ 0.15 ppm). A similar small difference was observed here between **3.9Ba** (δ_H 8.24 ppm) and **3.9Bc** (δ_H 8.22 ppm).

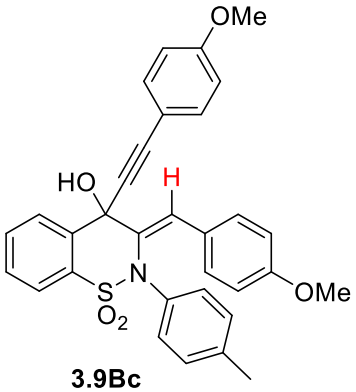


Scheme 3.36

The coupling constants (Table 3.6) of the methine proton and the C***H*₂** in the 3-alkylidene series **3.9Ab – Hb** and **3.9Be – f** along with the similarity of the ^{13}C shift of the methylidene carbon in both the 3-arylidene- and 3-alkylidene-1,2-benzothiazines (Tables 3.5 and 3.6 respectively) is noteworthy; on the basis of this data and the probable reaction mechanism (Scheme 3.37) (*Z*)-stereochemistry is also assigned to the 3-alkylidene-1,2-benzothiazines **3.9Ab – Hb** and **3.9Be – f**.



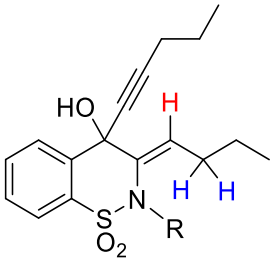
3.9Aa, R = Me
3.9Ba, R = tolyl
3.9Ca, R = 3-MeC_6H_4
3.9Da, R = 2-$MeOC_6H_4$
3.9Ea, R = 3-$MeOC_6H_4$
3.9Ha, R = 2-naphthyl



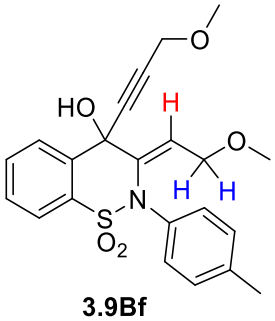
3.9Bc

Entry	R	1,2-Benzothiazine 1,1-dioxide	5-*H* (ppm)	8-*H* (ppm)	C*H*= (ppm)	δ_C C*H*= (ppm)
1	Me	**3.9Aa**	8.10	7.87	7.49	131.06
2	Tolyl	**3.9Ba**	8.24	7.79	7.57	131.86
3	Tolyl	**3.9Bc**	8.22	7.79	7.51	131.48
4	3-MeC_6H_4	**3.9Ca**	8.26	7.84	7.59	131.89
5	2-$MeOC_6H_4$	**3.9Da**	8.30	7.84	7.64	130.22
6	3-$MeOC_6H_4$	**3.9Ea**	8.26	7.84	7.61	132.26
7	2-naphthyl	**3.Ha**	8.23	7.89	–[a]	–[a]

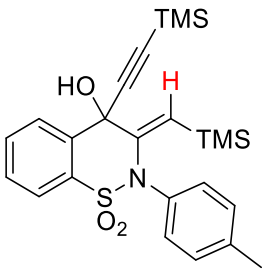
Table 3.5 ^1H and ^{13}C NMR shifts for aryl substituted 1,2-benzothiazine 1,1-dioxides **3.9Aa – Ha** and **3.9Bc.** a = overlapping with other signals



3.9Ab, R = Me
3.9Bb, R = tolyl
3.9Cb, R = 3-MeC$_6$H$_4$
3.9Db, R = 2-MeOC$_6$H$_4$
3.9Eb, R = 3-MeOC$_6$H$_4$
3.9Gb, R = 3-thienyl
3.9Hb, R = 2-naphthyl



3.9Bf



3.9Be

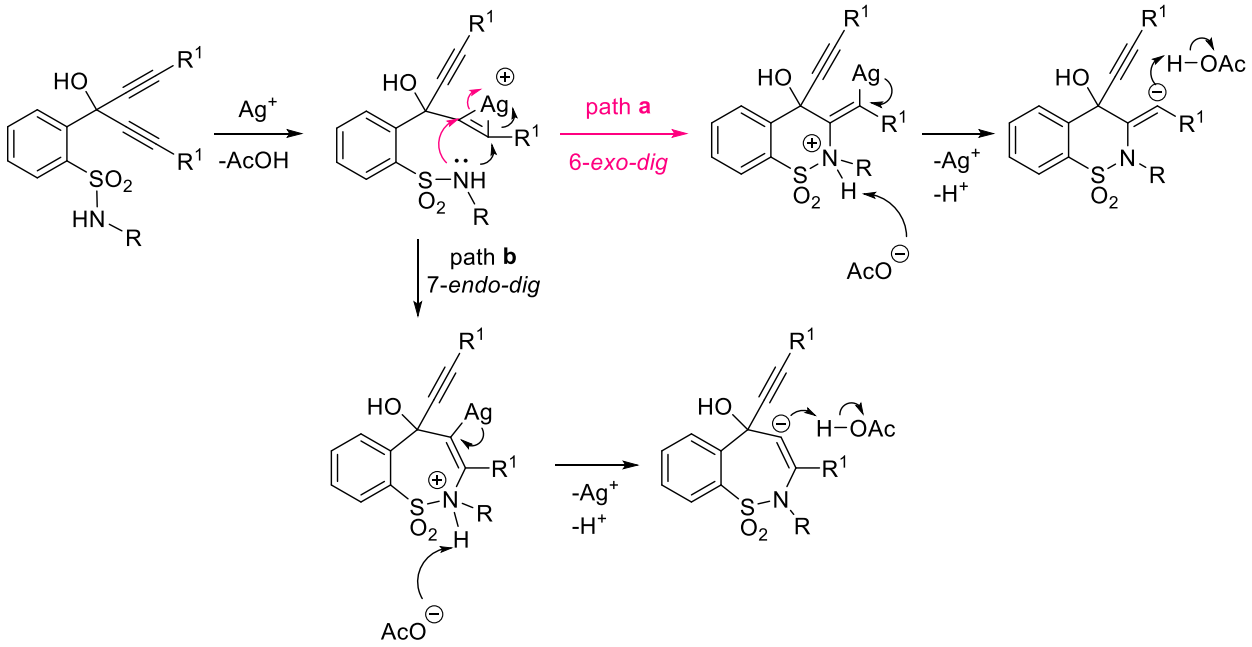
Entry	R	1,2-Benzothiazine 1,1-dioxide	5-*H* (ppm)	8-*H* (ppm)	C*H*= (ppm)	$J_{H\text{-}CH_2R}$ (Hz)	δ_C C*H*= (ppm)
1	Me	**3.9Ab**	7.94	7.77	6.64	7.3	136.24
2	Tolyl	**3.9Bb**	8.13	7.77	6.62	7.3	134.96
3	Tolyl	**3.9Be**	8.16	7.73	6.91	–	134.70
4	Tolyl	**3.9Bf**	8.14	7.79	6.67	5.6	131.38
5	3-MeC$_6$H$_4$	**3.9Cb**	8.11	7.79	6.62	7.3	135.06
6	2-MeOC$_6$H$_4$	**3.9Db**	8.15	7.77	6.62	7.4	133.74
7	3-MeOC$_6$H$_4$	**3.9Eb**	8.11	7.78	6.64	7.3	135.52
8	3-thienyl	**3.9Gb**	8.07	7.80	6.67	7.3	135.81
9	2-naphthyl	**3.9Hb**	8.15	7.84	6.68	7.2	135.35

Table 3.6 ^{1}H and ^{13}C NMR shifts for alkyl substituted 1,2-benzothiazine 1,1-dioxide **3.9Ab** – **3.9Hb** and **3.9Be – f**

The 6-*exo-dig* and 7-*endo-dig* cyclisation pathways are depicted in Scheme 3.37. At present it is unclear why there was competition from the latter pathway with two of the dialkynol substrates. Further investigation of this aspect is clearly merited. The cyclisation of the sulfamoyl dialkynols **2.23Aa – Hb** under Ag(I) catalysis represents a new route to 1,2-benzothiazine 1,1-dioxides.

The proposed mechanism for the synthesis of 1,2-benzothiazine 1,1-dioxides **3.9Aa – Hb** and 1,2-benzothiazepine 1,1-dioxides **3.10Ab** and **3.10Gb,** *via* path **a** and path **b**

respectively. Both routes are envisaged to start from silver coordination to the triple bond by π-complexation [15CSR8124, 19MI1] which activates the triple bond to attack from the nucleophilic sulfonamide nitrogen. Cyclisation can occur *via* path **a** (6-*exo-dig*) or **b** (7-*endo-dig*), followed by protodeargentation and proton removal from the quaternary nitrogen (by most likely an acetate anion), affording the relevant products (Scheme 3.37).



Scheme 3.37

Chapter 4

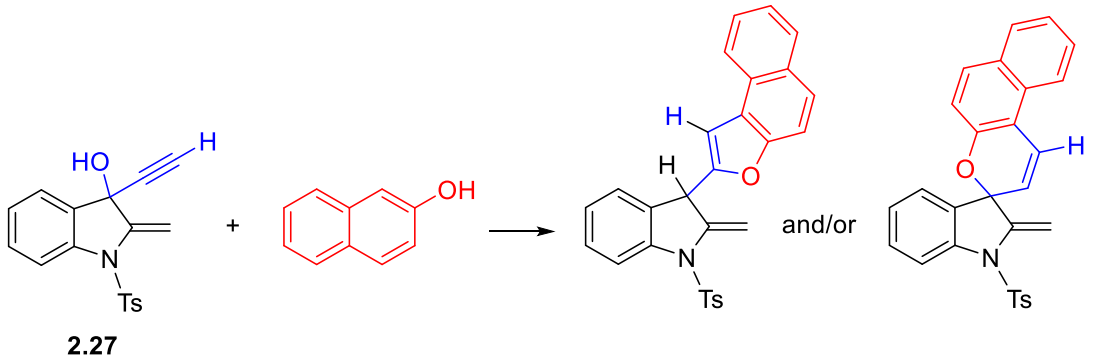
Ring Functionalisations and Annulations

Chapter 4 Ring Functionalisations and Annulations

4.1 Functionalisation of the 3-Alkynylindol-3-ol Ring System

With the aim of exploiting the multifunctional nature of the ring systems prepared during the course of this project (Sections 2.0 and 3.0), the 3-alkynyl-2-methyleneindol-3-ols (**2.27**, **2.30A-C** and **2.33a**) and the 4-alkynyl-3-iodoquinoline **3.2a – c** were subjected to a selection of reactions which will be discussed in this chapter. Initially chosen because it has multiple motifs which can be easily manipulated, was the 2-methyleneindoline **2.27**.

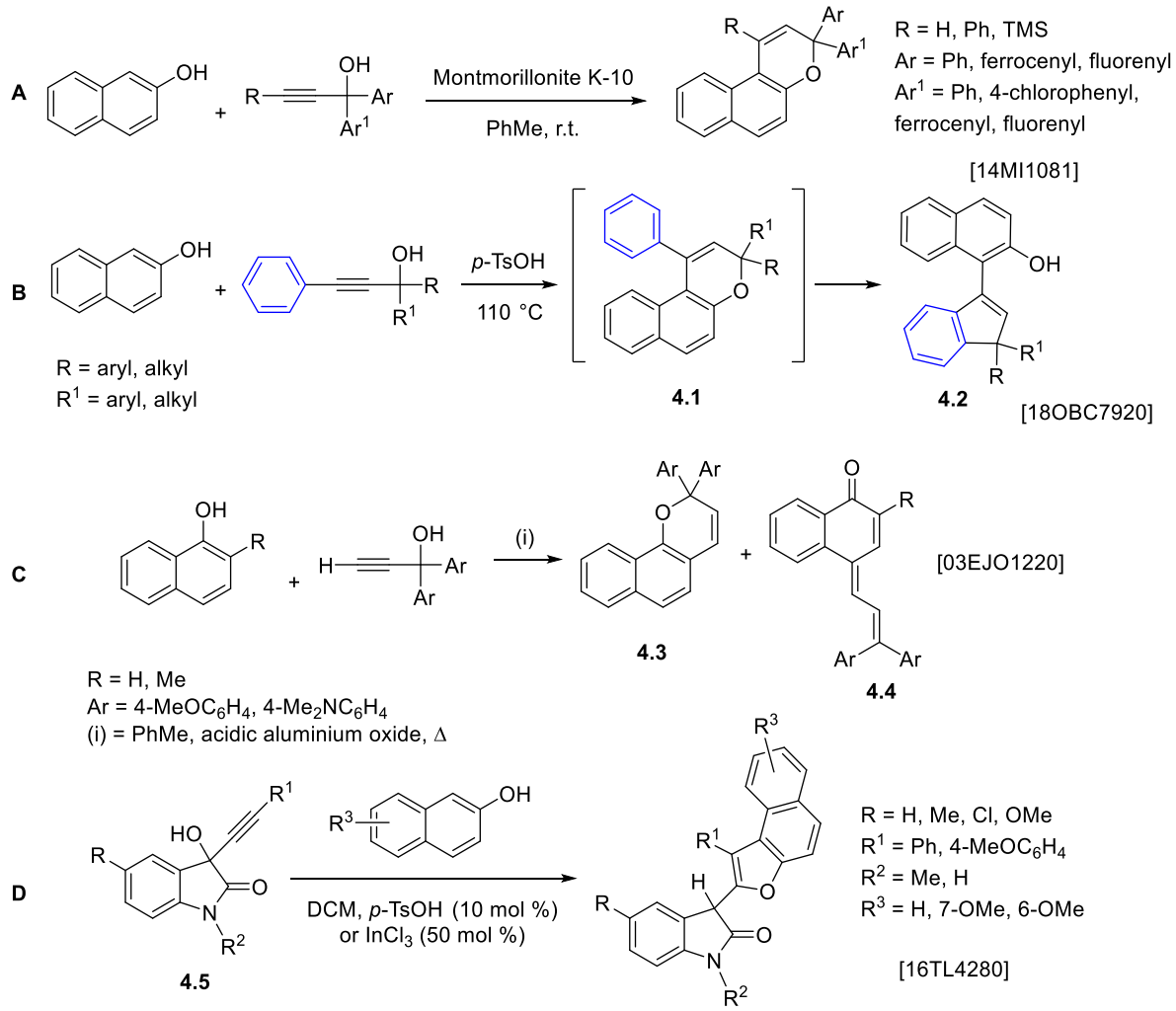
One way in which **2.27** can potentially be elaborated utilises the embedded alkynol function in a cyclocondensation reaction with 2-naphthol as shown below (Scheme 4.1).



Scheme 4.1

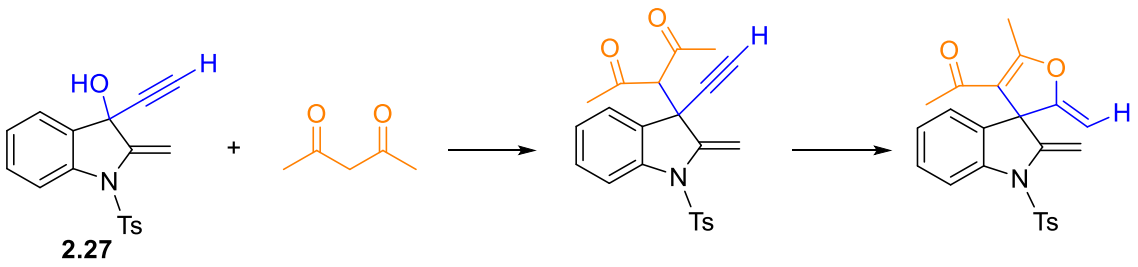
Montmorillonite has been utilised to catalyse the formation of naphthopyran derivatives in high yields (66 – 98%) from the cyclocondensation of 1,1-diaryl-2-propyn-1-ols and 2-naphthol (**A**, Scheme 4.2) [14MI1081]. Montmorillonite K-10 is an inexpensive, green, heterogenous clay catalyst, which over the past 30 years has found numerous uses in the catalysis of many reaction types [19EROS1]. It can also be used as a support for a variety of metal salts [18MI1249]. Yaragorla and Khan found that when alkynols and 2-naphthol were heated with *p*-TsOH (neat), the naphthopyran **4.1** could be isolated; the reaction could also be driven to the rearrangement product **4.2** in fair to excellent yields (58 – 98%) (**B**, Scheme 4.2) [18OBC7920]. Naphtho[1,2-*b*]pyrans have been synthesised from the acid catalysed reaction of propyn-1-ols and 1-naphthols to give **4.3** (**C**, Scheme 4.2). The (*E*)-4-[3,3-bis(aryl)allylidene]naphthalen-1(4*H*)-ones **4.4** were also isolated as intense red dyes, their formation was rationalised by S_EAr of 1-naphthol by a propargylic-allenic cation to give a 4-

allenylnaphthol derivative, which undergoes a subsequent [1,7]-*H* shift [03EJO1220]. Kim and co-workers utilised 3-alkynyl-3-hydroxyindoline-2-ones **4.5** as a substrate in the Lewis acid-catalysed condensation with 2-naphthols (**D**, Scheme 4.2). 3-(Naphthofuranyl)-2-oxindoles were obtained in fair to good yields (45 – 78%) [16TL4280].



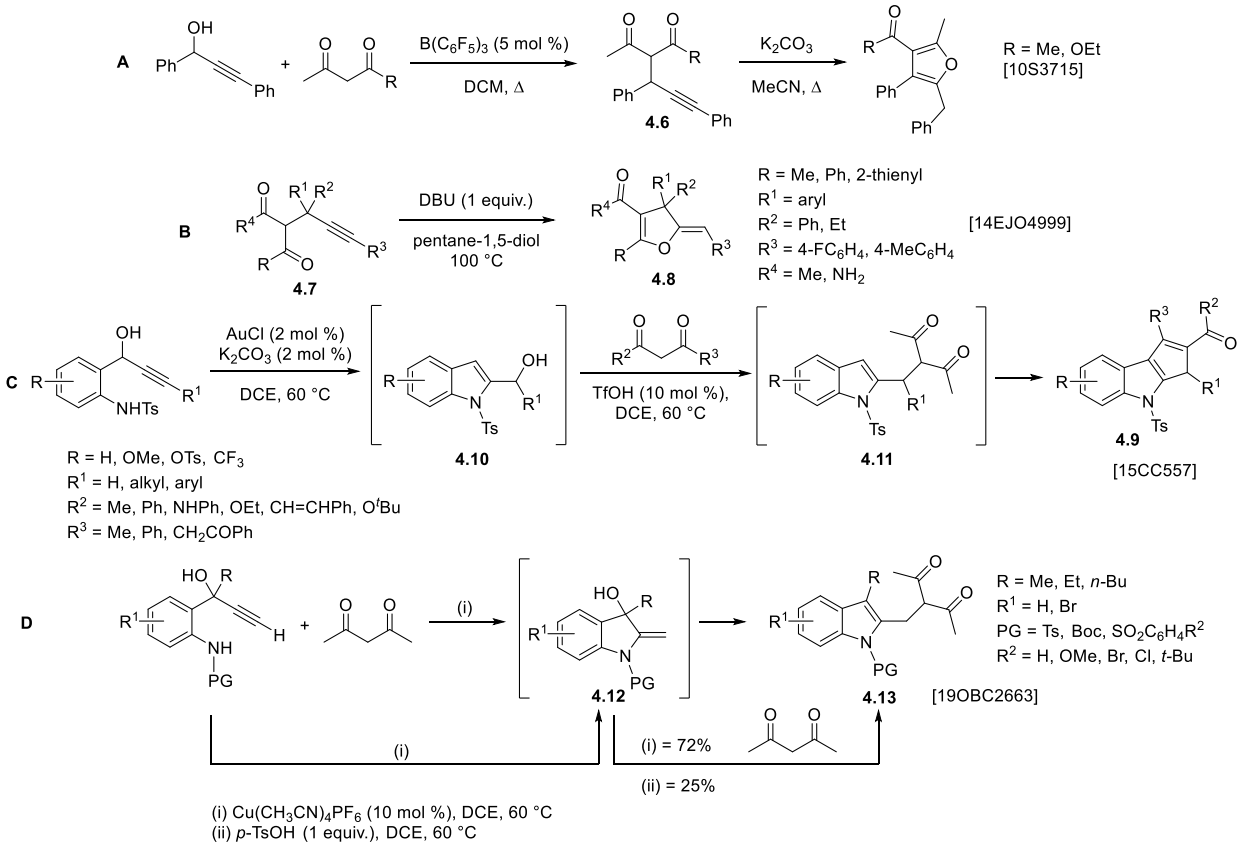
Scheme 4.2

Another way in which the novel 3-alkynylindol-3-ol ring system **2.27** could be exploited is *via* the dehydration and subsequent interception of the cation with a nucleophile (Scheme 4.3). The addition of a 1,3-dicarbonyl nucleophile to a propargylic cation (formed by dehydration), under metal catalysis or acidic (Brønsted and Lewis acid) conditions affords a functionalised alkyne that has been shown to cyclise under either basic or acidic conditions. Some examples are shown in Scheme 4.4 [10S3715, 14EJO4999, 15CC557, 19OBC7920].



Scheme 4.3

Thus, 1,3-diphenylprop-2-yn-1-ol underwent easy nucleophilic addition of a 1,3-dicarbonyl compound in the presence of a Lewis acid. The corresponding intermediate compound **4.6** undergoes base-catalysed cyclisation to substituted furans (**A**, Scheme 4.4) [10S3715]. 2-Propynyl-1,3-dicarbonyl compounds **4.7** undergo cyclisation in the presence of base to yield dihydrofuran derivatives **4.8** (**B**, Scheme 4.4) in excellent yields (76 – 93%) [14EJO4999]. Dhiman *et al.* found that 1,2,3-trisubstituted cyclopenta[*b*]indoles **4.9** could be obtained in a one-pot reaction from propargylic alcohols *via* an initial formation of indole **4.10** in the presence of a Au(I) catalyst with a basic co-catalyst. Subsequent addition of a 1,3-dicarbonyl compound to **4.10** in the presence of a Brønsted acid generates the indole dicarbonyl compound **4.11**. The latter underwent an intramolecular Friedel-Crafts type reaction to give the tricyclic heterocycle **4.9** (**C**, Scheme 4.4). Both intermediates were isolated to provide evidence for the reaction mechanism [15CC557]. A Cu(I) catalysed tandem cyclisation and addition reaction was observed when 1-(2-amidophenyl)propynol derivatives were treated with a range of 1,3-dicarbonyl nucleophiles (**D**, Scheme 4.4). The corresponding indoline intermediate **4.12** could also be isolated in the absence of a nucleophile in 92% yield (when PG = Ts, R = Me and R^1 = H). Addition of the nucleophile to the pre-formed indoline, also proceeded smoothly with the Cu(I) catalyst. Nucleophilic addition to indoline **4.12** was also successful when *p*-TsOH (1 equiv.) was used as the catalyst but gave much lower yields of the indole **4.13** (when PG = Ts, R = Me and R^1 = H). However, *p*-TsOH alone did not initiate the same tandem cyclisation and addition pathway as the Cu(I) catalyst [19OBC2663].

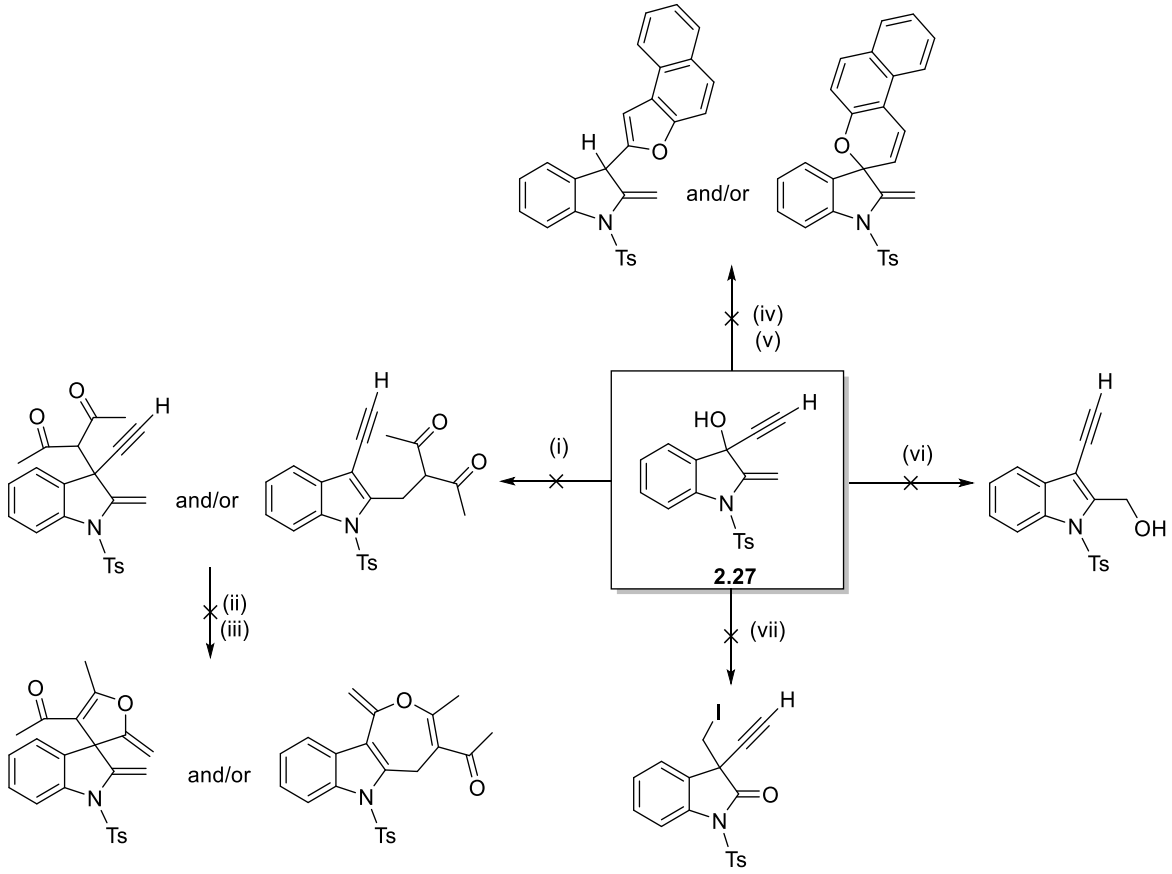


Scheme 4.4

Initially indoline **2.27** was subjected to a variety of reaction conditions, some of which were adapted, from literature examples (Scheme 4.5) [12JOC7166, 16TL4280, 17TL21, 17TL4094]. These include; dehydration and interception with a nucleophile (i, Scheme 4.5), cyclocondensation with 2-naphthol (iv, v, Scheme 4.5), 1,3-AAI (vi, Scheme 4.5) and oxidative rearrangement (vii, Scheme 4.5). Surprisingly and disappointingly no tractable products could be isolated from any of these reactions, only very complex mixtures were obtained, suggesting that 3-ethynyl-2-methylene-1-tosylindol-3-ol **2.27** is highly reactive and undergoes multiple reactions and/or degradation. The ^{1}H NMR spectrum of the crude product from reaction (i) in Scheme 4.5 indicated that no starting material was present, but purification was not possible due to the complexity of the mixture (TLC). Thus, the mixture was carried forward into the next reaction and treated under basic conditions (ii, iii, Scheme 4.5). However, no characterisable products could be isolated from exposure to either K_2CO_3 in MeCN or to DBU in MeCN.

All efforts to effect a cyclocondensation with 2-naphthol were unsuccessful (iv and v, Scheme 4.5), as were attempts to induce 1,3-AAI to the isomeric 2-(hydroxymethyl)indole

(vi, Scheme 4.5). Although Chan reported that 3-phenyl-2-methylene-1-tosylindol-3-ol undergoes an iodination rearrangement to 3-(iodomethyl)-3-phenyl-1-tosyloxindole with NIS [12JOC7166] efforts to extend this reaction to **2.27** gave only an intractable mixture (vii, Scheme 4.5).



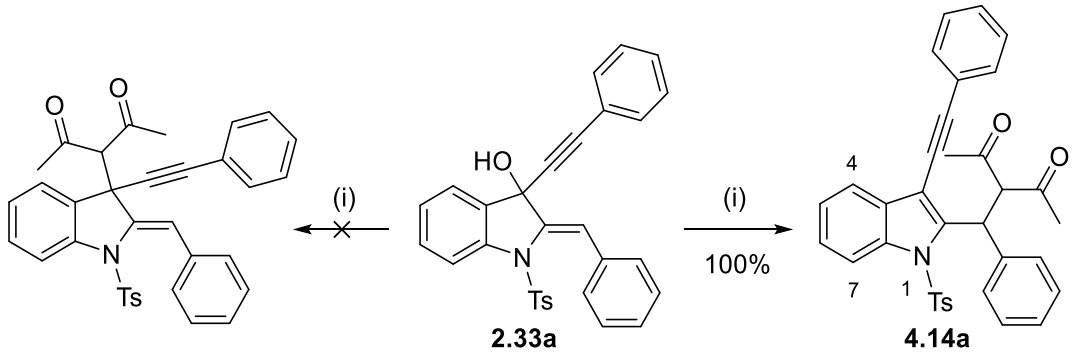
(i) Montmorillonite K-10 (100 % w/w), $MeCOCH_2COMe$ (3 equiv.), DCE, N_2, 24 h, Δ ; (ii) K_2CO_3 (1 equiv.), MeCN, 24 h, Δ; (iii) DBU (1 equiv.), MeCN, 24 h, Δ
(iv) 2-naphthol (1 equiv.), trimethylorthoformate (2 equiv.), *p*-TsOH catalytic amount, DCE, N_2, 24 h, Δ; (v) 2-naphthol (1 equiv.), montmorillonite K-10 (300 % w/w), DCE, N_2, 24 h, Δ; (vi) *p*-TsOH (1 equiv.), MeCN, r.t., 5 h; (vii) NIS (2 equiv.), MeCN, N_2, 24 h, Δ

Scheme 4.5

Due to the complexity of the mixtures obtained from the reactions of 3-ethynyl-2-methylene-1-tosylindolin-3-ol **2.27** shown in Scheme 4.5, no other reactions with this substrate were attempted.

In view of these disappointing results investigations were extended to the 2-benzylideneindoline **2.33a** with the rationale that the additional phenyl group would stabilise intermediates formed in the reactions. Thus **2.33a** and acetylacetone (in DCE) in the presence of an acid catalyst (Montmorillonite K-10) was refluxed for 2h; after filtration

though Celite, the ^{1}H NMR spectrum of the crude material showed the reaction had gone to completion (100% yield). After consideration of 1D NMR spectra (^{1}H and ^{13}C), the isolated product was not the expected indoline but the indole **4.14a** (Scheme 4.6).



(i) Montmorillonite K-10 (100 % w/w), $MeCOCH_2COMe$ (3 equiv.), DCE, N_2, 2 h, Δ

Scheme 4.6

The ^{1}H NMR spectrum of 3-{phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methyl}pentane-2,4-dione **4.14a** is shown in Figure 4.1. Neither this nor the ^{13}C NMR spectrum exhibit any peaks corresponding to the enol tautomer, which is in line with similar compounds reported in the literature [07OL727, 19OBC2663]. Interestingly, the doublets corresponding to the *vicinal* sp^3 hydrogens absorb over a close range, δ_H 6.10 and 5.95 ppm (^{3}J = 12.06 Hz).

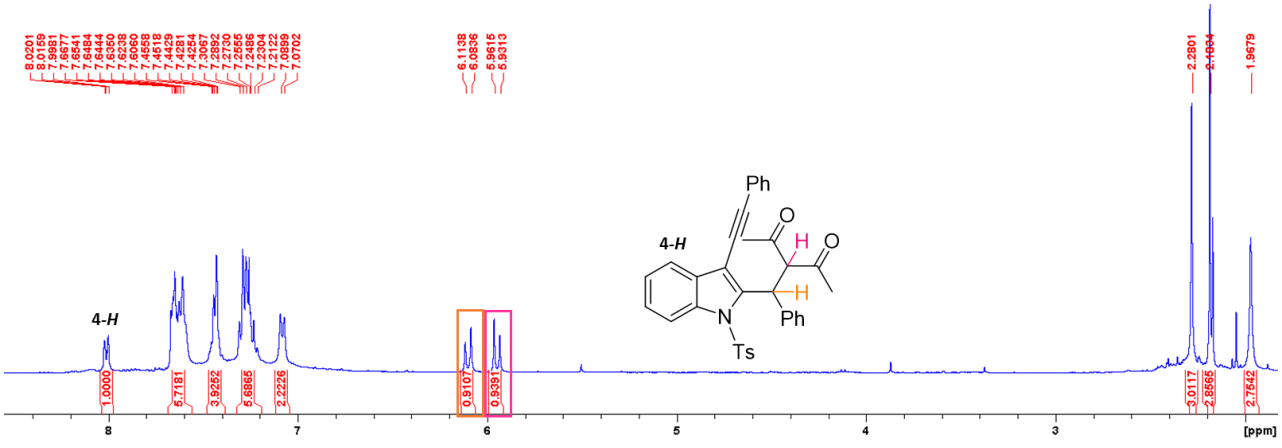


Figure 4.1 400 Mhz ^{1}H NMR spectrum of **4.14a** in $CDCl_3$

The proton signals for **4.14a** (Figure 4.1) were assigned from examination of the NOESY spectrum (Figure 4.2). The stronger though-space interaction between the doublet at δ_H 6.10 ppm and the phenyl protons established distinction between the *vicinal* protons. The doublet at δ_H 5.95 ppm displayed an interaction with the two methyl groups (δ_H 2.19 and

1.97 ppm) of the diketone unit. The high field aromatic proton doublet (δ_H 7.08 ppm), integrating for two protons, shows a correlation with the tosyl methyl group protons (δ_H 2.28 ppm). Comparison of the ^{1}H NMR shifts with those of some model compounds is instructive (Scheme 4.7).

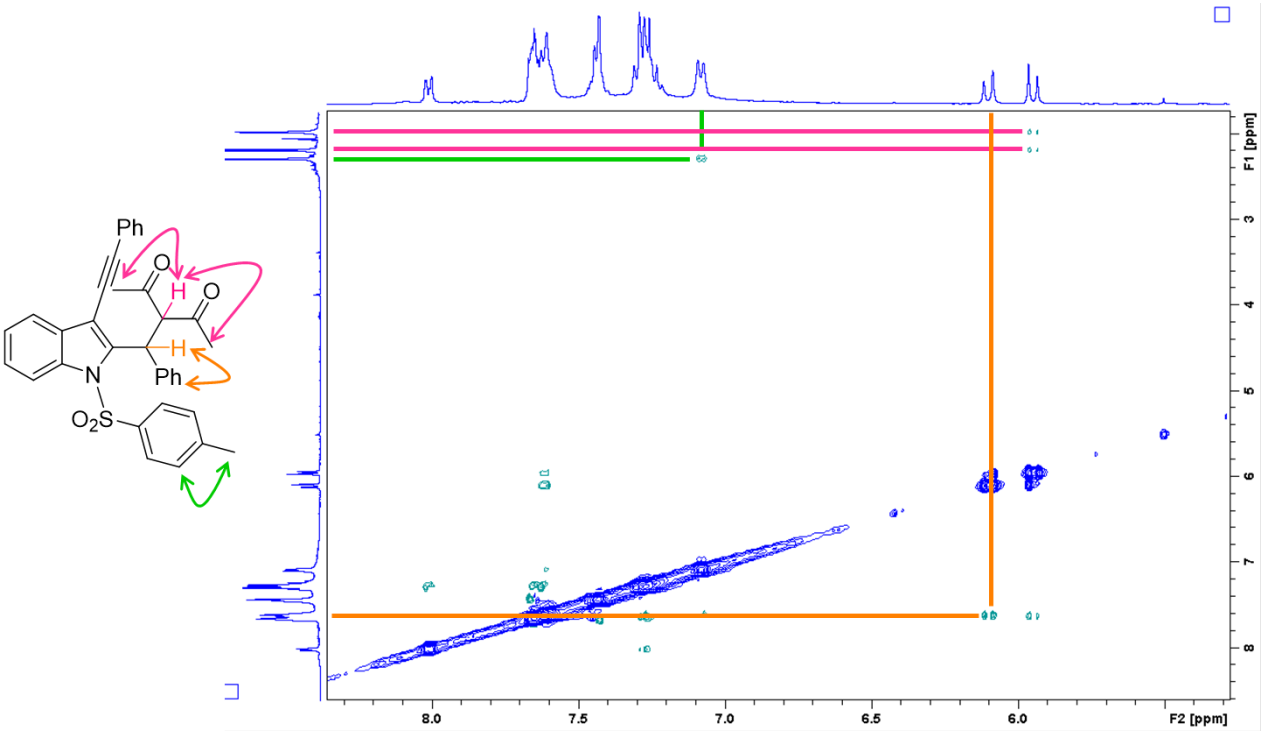
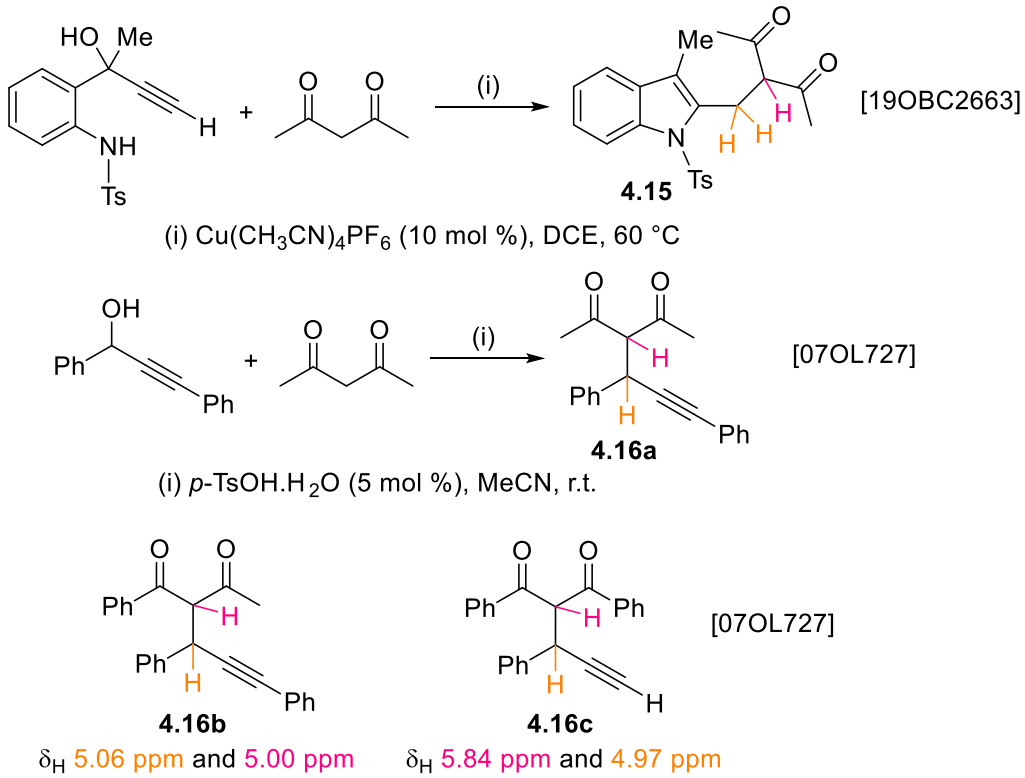


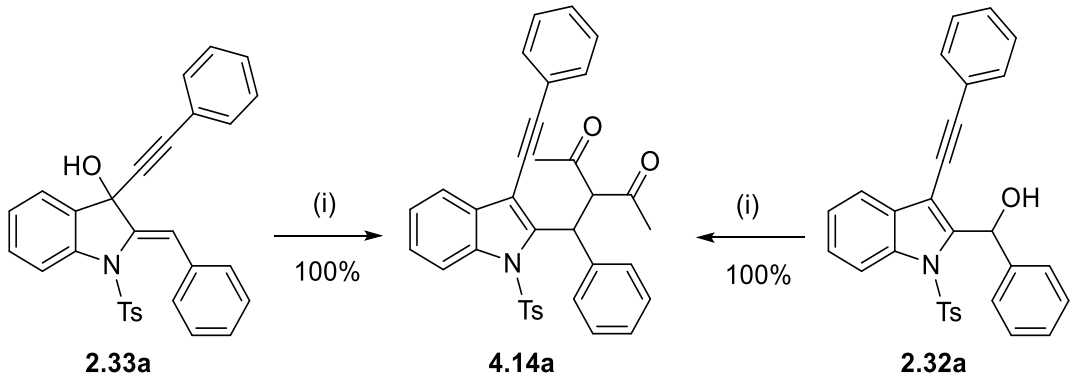
Figure 4.2 NOESY spectrum of **4.14a**

Song and co-workers reported the *vicinal* sp^3 hydrogens in indole **4.15** (Scheme 4.7) absorbed at δ_H 4.64 and 3.44 ppm [19OBC2663]. The 3-(1,3-diphenylprop-2-yn-1-yl)pentane-2,4-dione **4.16a** exhibits two doublets at δ_H 4.67 and 4.23 ppm with a coupling constant of ^3J = 10.9 Hz. The downfield shift of the methine proton signals seen in **4.14a** compared to the model compounds in Scheme 4.7, is presumably due to the combined influence of the adjacent alkyne moiety along with the anisotropic indole and phenyl groups deshielding the protons. The *vicinal* proton shifts in the 1,3-diketones **4.16a – c** exhibit increased deshielding with increased steric crowding (Scheme 4.7).



Scheme 4.7

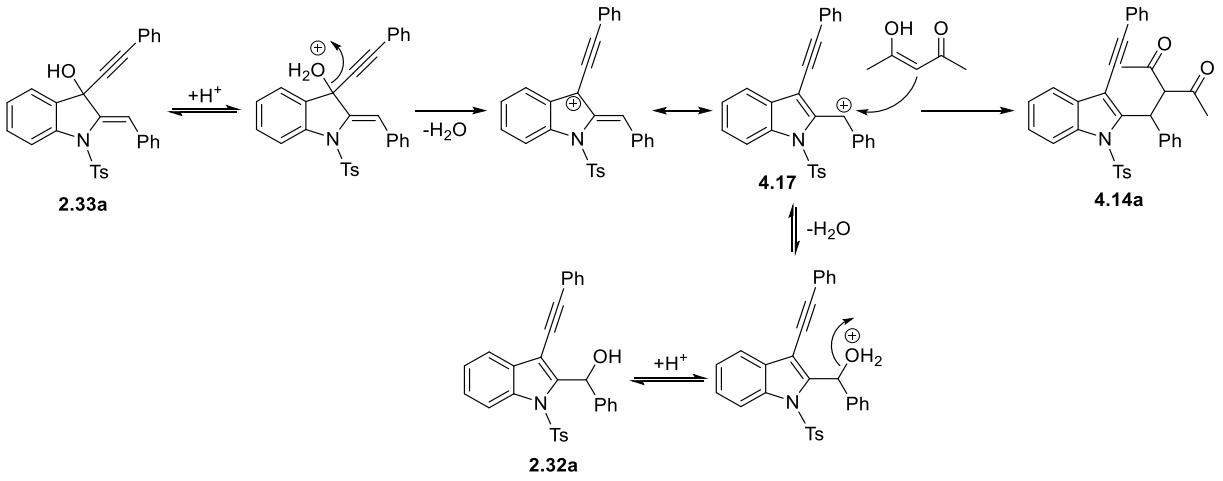
The indole **4.14a** can be envisaged as being generated from the nucleophilic addition of the enolic nucleophile to the benzylic cation derived from the 2-benzylideneindol-3-ol **2.33a** (Scheme 4.9). Consequently **4.14a** should also be accessible from the indolyl alcohol **2.32a**, under identical conditions. In order to verify this proposal, the latter was also treated with acetylacetone in DCE in the presence of K-10. Gratifyingly, under these conditions the 3-alkynylindole **4.14a** was also obtained in quantitative yield (Scheme 4.8).



(i) Montmorillonite K-10 (100 % w/w), $MeCOCH_2COMe$ (3 equiv.), DCE, N_2, 2 h, Δ

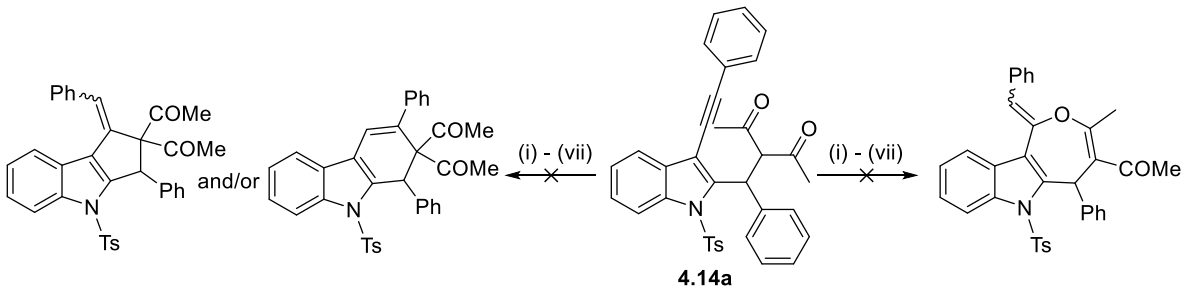
Scheme 4.8

The formation of the indole **4.14a** from indoline **2.33a** can be rationalised by the initial protonation and elimination of water (E_1) followed by generation of the benzylic cation **4.17** (Scheme 4.9). This cation (**4.17**) will also be formed from dehydration (E_1) of the indolyl alcohol **2.32a**, after protonation, the nucleophilic centre of the 1,3-diketone will then attack the cation leading to **4.14a** in which aromaticity is retained (Scheme 4.9).



Scheme 4.9

With 3-{phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methyl}pentane-2,4-dione **4.14a** to hand it was subjected to basic conditions (K_2CO_3, DBU and Cs_2CO_3). However, in each case only starting material was recovered from the reaction and none of the cyclisation products were observed (i – iii, Scheme 4.10). Consequently, it was envisaged the triple bond of **4.14a** may require additional activation to nucleophilic attack from the enol or enolic OH. Therefore, a variety of electrophilic activators – I^+, Ag(I) and In(III) – were employed along with K_2CO_3 in MeCN (iv – viii, Scheme 4.10). Again, only starting material was isolated from these reactions. More work is required to define the scope and limitations of this reaction, use of a wider range of solvents may increase the amount of enol tautomer [85JOC1216] and therefore the ability to react with the alkyne moiety.



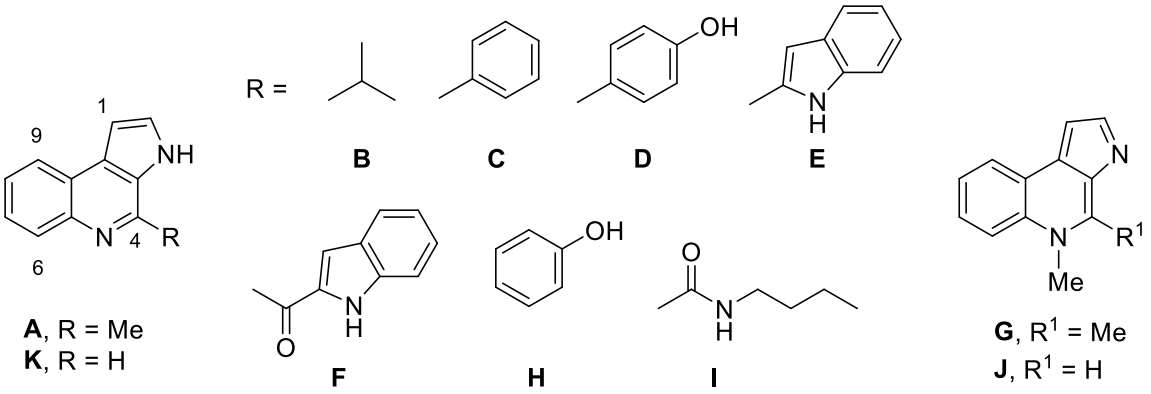
(i) K_2CO_3 (1 equiv.), MeCN, 24 h, Δ; (ii) DBU (1 equiv.), MeCN, 24 h, Δ; (iii) Cs_2CO_3 (1.1 equiv.), PhMe, 5 h, 90 °C; (iv) ICl (3 equiv.), K_2CO_3 (1 equiv.), MeCN, 24 h, Δ; (v) AgOAc (5 mol %), K_2CO_3 (1 equiv.), MeCN, 24 h, Δ; (vi) AgOTf (5 mol %), K_2CO_3 (1 equiv.), MeCN, 24 h, Δ; (vii) $In(OTf)_3$ (5 mol %), K_2CO_3 (1 equiv.), MeCN, 24 h, Δ

Scheme 4.10

All of the attempted base-catalysed intramolecular cyclisations of 3-{phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methyl}pentane-2,4-dione **4.14a** were unsuccessful (Scheme 4.10). No further indoles and/or indolines were investigated as substrates for intramolecular alkyne cyclisations.

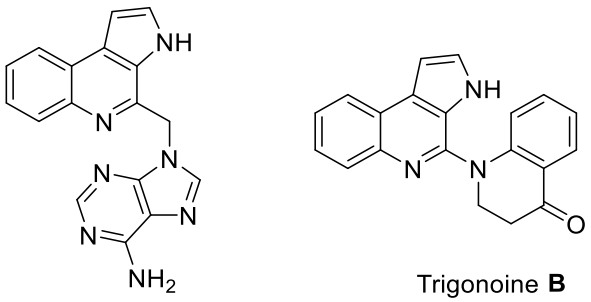
4.2 Annulations of 4-Alkynyl-3-iodoquinolines: Synthesis of Pyrrolo[2,3-*c*]quinolines

Pyrrolo[2,3-*c*]quinolines which can be obtained from marine bacteria (*Ohtaekwangia kribbensis, Mooreia alkaloidigena*, and *Catalinimonas alkaloidigena*), have attracted interest because of their varied biological activities [11TL3186]. Recently discovered Marinoquinolines A – K (Scheme 4.11) [11JNP603, 18JME5547] have been found to exhibit anti-bacterial and cytotoxic properties and a number also exhibit anti-malarial activity.



Scheme 4.11

Aplidiopsamine A and Trigonoine B are two more pyrrolo[2,3-*c*]quinoline structures. Aplidiopsamine A has been obtained from the Australian ascidian, *Aplidiopsis confluata* [10JOC8291]. Whilst Trigonoine B has been isolated from four plant species native to China *Trigonostemon thyrsoideus*, *Trigonostemon huangmosu*, *Trigonostemon lii*, and *Trigonostemon filipes* [11TL3186]. These compounds also exhibit interesting biological activities (Aplidiopsamine A anti-malarial and Trigonoine B weak anti-HIV activities).

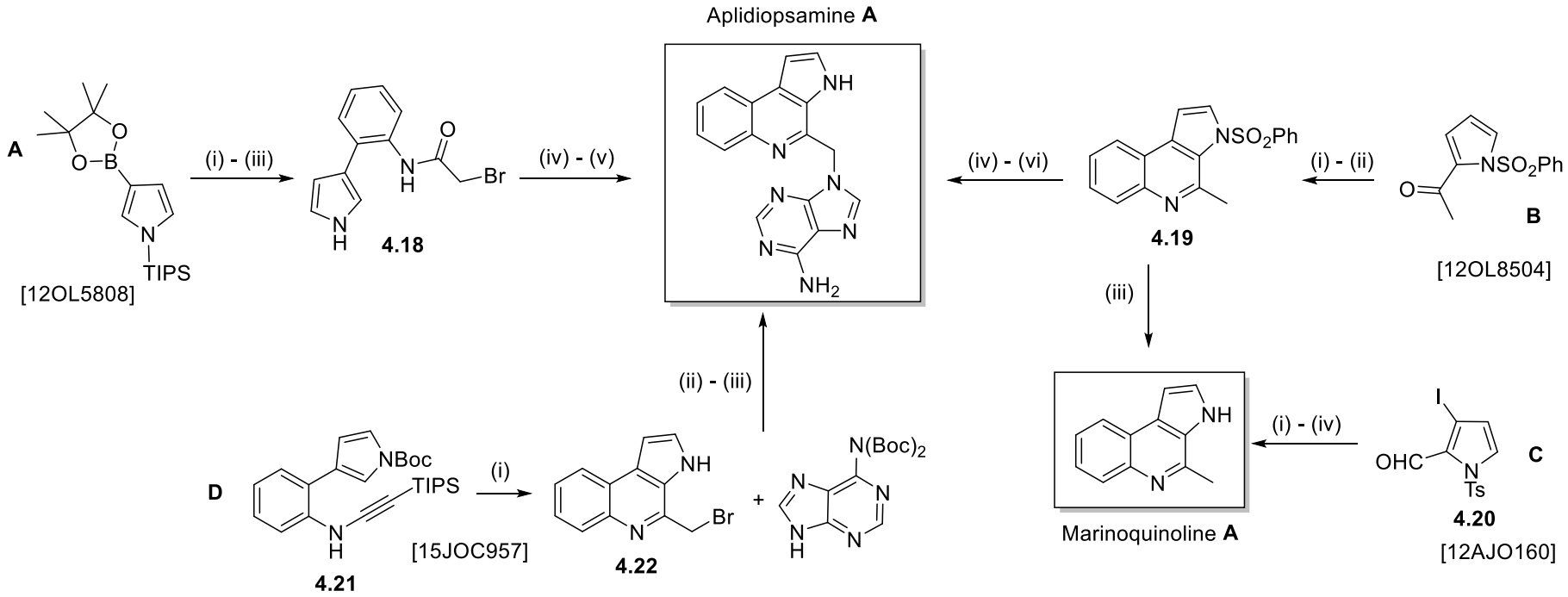


Aplidiopsamine **A** Trigonoine **B**

It is therefore surprising that relatively little attention has been paid to the total synthesis of these compounds. Only Aplidiopsamine A and Marinoquinolines (A to F and K) have been synthesised. The approaches are outlined in Scheme 4.12 [12AGE10610, 12OL5804, 12OL5808, 12TL1271, 12TL4836, 13SL461, 15JOC957, 18ACR1784, 18JME5547, 19MI35068, 20OL2215, 20JOC650].

Aplidiopsamine A was synthesised in a five-step sequence, 21% overall yield (**A**, Scheme 4.12). Halide displacement from the bromoacetamide intermediate **4.18** could also be employed with a variety of other nucleophiles to obtain, following cyclodehydration, other pyrrolo[2,3-*c*]quinoline derivatives [12OL5808]. Marinoquinoline A was synthesised in a high yield over three steps *via* Pd-mediated cyclisation of the imine from 2-acetyl-1-phenylsulfonylpyrrole and 2-iodoaniline. The protected pyrrolo[2,3-*c*]quinoline **4.19** obtained could be further elaborated to Aplidiopsamine A (**B**, Scheme 4.12) [12OL5804]. Willis *et al*. utilised an Ullman cross-coupling reaction of pyrrole-2-carbaldehyde **4.20** and 2-bromonitrobenzene. Subsequent treatment with MeLi was followed by oxidation of the secondary alcohol and reductive cyclisation with magnesium, afforded Marinoquinoline A in four steps in 85% overall yield (**C**, Scheme 4.12) [12AJO160]. Yamaoka and co-workers achieved the total syntheses of Marinoquinolines A and C and Aplidiopsamine A [15JOC957] by initially assembling the arene-ynamide **4.21** from a series of coupling reactions

[05OL3681]. The latter was then subjected to a Brønsted acid (Tf_2NH) mediated cyclisation affording pyrrolo[2,3-*c*]quinolines in high yields (73 – 90%). Interestingly, it was found that weaker acids lowered the product yield. For Aplidiopsamine A, arene-ynamide **4.21** could be transformed in a one-pot reaction to **4.22** from which halide displacement with adenine afforded Aplidiopsamine A in a final 90% yield (**D** Scheme 4.12). Yamaoka and co-workers extended this reaction to synthesise different (hetero)areno[2,3-*c*]quinolines [15JOC957]. Marinoquinolines A – C were synthesised from an initial Knoevenagel condensation, followed by the reduction of the nitro moiety and subsequent acylation of ethyl-2-aminocinnamate (**E**, Scheme 4.12). The α,β-unsaturated ester was then subjected to cyclocondensation with TosMIC to obtain pyrrole **4.23** which underwent a Morgan-Walls reaction to give Marinoquinolines A – C in excellent yields (85 – 92%) [12TL1271]. Schwalm and Correia synthesised Marinoquinolines A, B, C and E among other 3*H*-pyrrolo[2,3-*c*]quinolines, using different aldehydes to vary the substituent in the C-4 position, from the Pictet-Spengler reaction of 2-(1*H*-pyrrol-3-yl)aniline **4.24** with aldehydes followed by aromatization (**F**, Scheme 4.12) [12TL4836]. Most recently Banwell and co-workers synthesised the widest range of Marinoquinolines (A – F and K) *via* 3-tosyl-3*H*-pyrrolo[2,3-*c*]quinoline 5-oxide **4.25** using a range of conditions (**G**, Scheme 4.12). The *N*-oxide **4.25** was prepared by a Pd-catalysed Ullmann coupling of 3-iodo-1-tosylpyrrole-2-carbaldehyde with 2-bromonitrobenzene followed by reductive cyclisation [20JOC650].

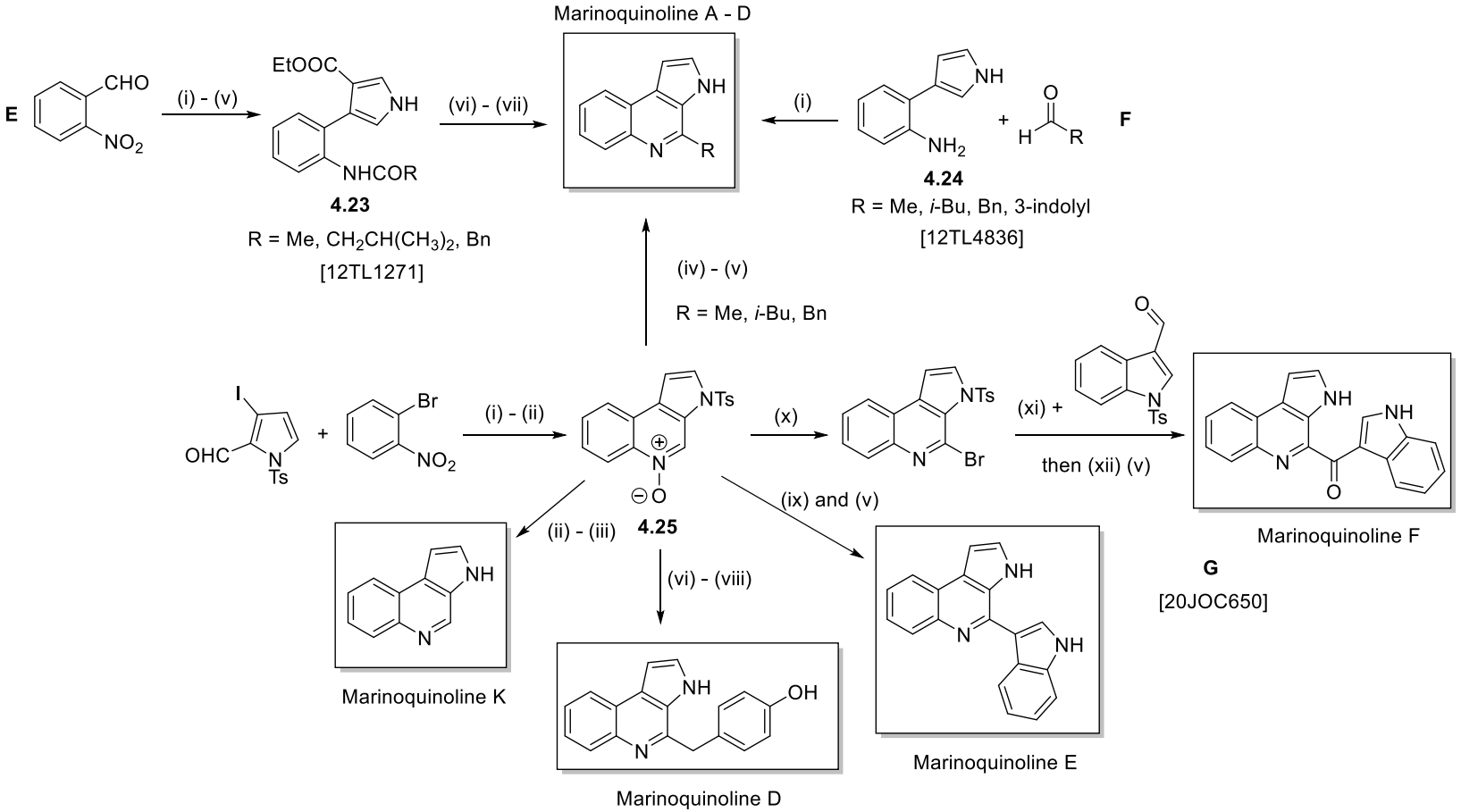


A = (i) $Pd(OAc)_2$ SPhos, K_3PO_4, *n*-BuOH, H_2O, 2-iodoaniline; (ii) NaOMe, MeOH; (iii) $BrCOCH_2Br$, Et_3N, DCM; (iv) adenine, NaH, DMF; (v) HCl, dioxanes, microwave 130 °C

B = (i) *p*-TsOH, PhMe, 2-iodoaniline, Δ; (ii) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, 1,4-dioxane, 120 °C; (iii) MeOH, K_2CO_3, Δ ; (iv) NBS, BPO, CCl_4; (v) K_2CO_3, 6-chloropurine, DMF, 50 °C; (vi) MeOH, NH_3, 150 °C

C = (i) 2-bromonitrobenzene, Cu(0)/Cu(I), $PdCl_2(dppf)_2$, DMSO; (ii) MeLi, THF, -78 °C; (iii) Dess-Martin periodinane, DCM, 0 °C; (iv) Mg, MeOH, r.t.

D = (i) TfOH, DCM, -78 °C, NBS; (ii) $CsCO_3$, MeCN, r.t.; (iii) TFA, DCM, r.t.



E = (i) $CH_2(COOH)_2$, piperidine, pyridine, 85 °C; (ii) EtBr, K_2CO_3, DMF, r.t. or EtOH c.H_2SO_4, Δ; (iii) Fe/NH_4Cl, EtOH:THF:H_2O = 6:2:1, 85 °C; (iv) ROCl, Et_3N, DCM, r.t.; (v) TosMIC, *t*-BuOK, DMSO, r.t.; (vi) $POCl_3$, MeCN, Δ; (vii) c.HCl, Δ

F = (i) = TFA, $MgSO_4$, DCM, 60 °C

G = (i) = Cu(I)/Cu(0), $PdCl_2(dppf)_2$, DMSO, 75 °C; (ii) H_2, Raney nickel, THF, r.t.; (iii) NaOMe, MeOH, r.t.; (iv) RMgBr, THF, 0 °C to r.t.; (v) NaOMe, MeOH, Δ; (vi) 4-$MeOC_6H_4CH_2MgBr$, THF, r.t.; (vii) H_2, 5% Pd on C, MeOH, r.t.; (viii) BBr_3, DCM, 0 °C to r.t.; (ix) Ts_2O, indole, THF, r.t.; (x) $POBr_3$, DCM, r.t.; (xi) *n*-BuLi, Et_2O, -78 °C; (xii) MnO_2, DCM, r.t.

Scheme 4.12

The earliest reported synthesis of 3*H*-pyrrolo[2,3-*c*]quinoline involved the high temperature cyclodehydration of 3-formamido-4-methylquinoline under vacuum in the presence of P_4O_{10} from which the reaction gave low yields [49MC607]. Later work investigated the indolisation of 3-hydrazino-2-phenylquinoline with butanone in conc. HCl [57JCS3722]. In 1976 Parrick and Wilcox reported the synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines *via* a Fischer indole synthesis by heating 3-hydrazino-2-methylquinoline **4.26** with either cyclohexanone or butanone in the presence of acetic acid. Routes to pyrrolo[2,3-*b*] and pyrrolo[3,2-*c*]quinolines were also proposed (**A**, Scheme 4.13) [76J(P1)2121]. A cascade reaction involving the copper(II)-mediated reductive amination of quinoline-3-boronic acid with di-*tert*-butyl azodicarboxylate afford 3-hydrazinequinoline *in situ*. When conducted in the presence of 2-phenylacetaldehyde the Fischer indolisation product, 1-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline was obtained in 61% yield (**B**, Scheme 4.13) [12TL564].

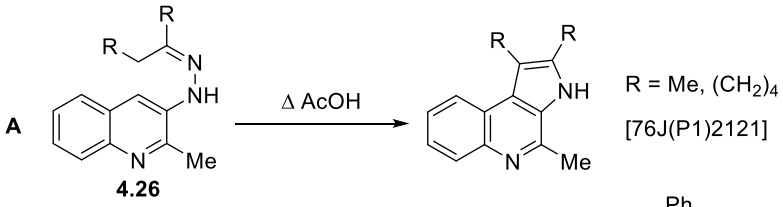
3-Substituted-3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones were obtained in moderate to excellent yields (45 – 99%) from a Pd(II)-catalysed domino amination-hydroamination sequence, starting from 3-bromo-4-trifloxyquinolin-2(1*H*)-ones **4.27** (**C**, Scheme 4.13) [14JOC9628]. Interestingly, in the case where R^1 = Me, R^2 = H, R^3 = Ph and R^4 = *c*-C_6H_{11} only the amination product, 3-(cyclohexylamino)-1-methyl-4-(phenylethynyl)quinolin-2(1*H*)-one, was isolated in 69% yield, the reasons for this were not explained. It was also found that 1-methyl-3-nitro-4-trifloxy-2-quinolone **4.28** readily undergoes Sonogashira coupling with aliphatic alkynes and selective metal-acid reduction provide access to the corresponding 4-alkynyl-3-amino-quinolones. The latter are smoothly hydroaminated upon treatment with $PdCl_2$ (10 mol %) in DMF to 2-alkyl-3*H*-pyrrolo[2,3-*c*]quinoline-4-(5*H*)-ones. However, access to the 2-aryl derivatives was only possible *via* initial formation of **4.29** and Sonogashira coupling with an aryl iodide (**D**, Scheme 4.13) [13OBC7334].

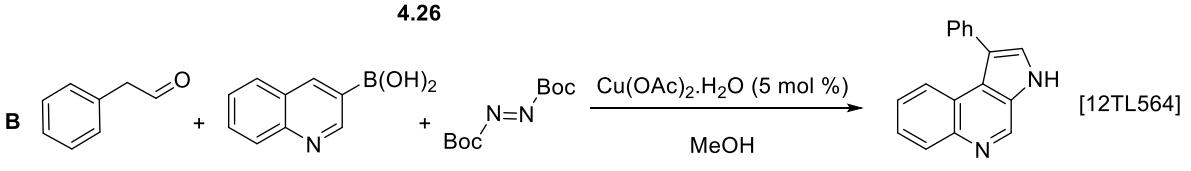
Other routes to pyrrolo[2,3-*c*]quinoline-4-(5*H*)-ones include nucleophilic addition of the TosMIC anion to 3-(acylmethylene)oxindoles (**E**, Scheme 4.13) [02T9179, 13T10836]. None of the routes outlined in **C**, **D** or **E** has been adapted for the synthesis of fully unsaturated pyrrolo[2,3-*c*]quinolines. In addition to the routes to the aromatic tricycles outlined in **A** and **B** Scheme 4.13 which are of limited scope other syntheses include: The Hemetsberger indole synthesis has been adapted to access pyrrolo[2,3-*c*]quinolines. Thus, condensation of 2-arylquinoline-4-carbaldehydes with ethyl azidoacetate proceeds readily at low temperature,

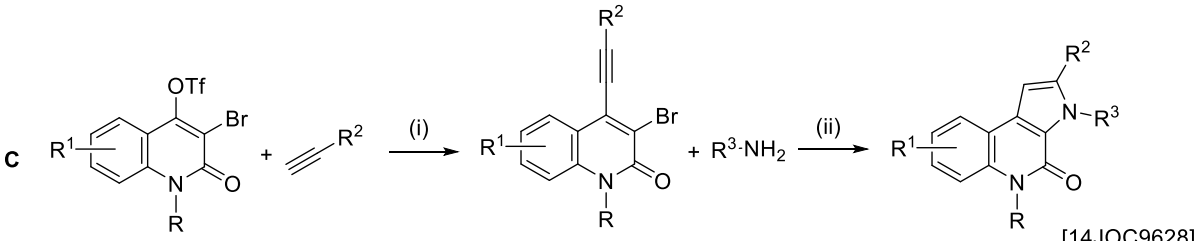
on warming to 0 °C expulsion of N_2 occurs with concomitant cyclisation to the tricycle (**F**, Scheme 4.13) [93S225].

The parent 3*H*-pyrrolo[2,3-*c*]quinoline system has been generated *via* a domino Pd-catalysed α-arylation-condensation reaction of 3-amino-4-bromoquinoline with acetaldehyde (**G**, Scheme 4.13) [09ARK(vi)174]. More recently the bicyclisation of 2-methyleneaminochalcones **4.30** and an imine in the presence of a base and oxidant (**H**, Scheme 4.13), affords the corresponding pyrrolo[2,3-*c*]quinolines in varying yields (35 – 84%) [17OL6712].

The Bartoli reaction is applicable to nitroquinolines and treatment of 2-chloro-3-nitroquinoline with 5 equiv. of vinylmagnesium bromide affords the 4-chloropyrroloquinolines in 49% yield (**I**, Scheme 3.14). Halide displacement by a variety of primary and secondary amines proceeds in high yields [18MI5386]. 2-Isocyanochalcones are 1,5-bielectrophiles and condensation with the anion of nitromethane generates a 3-nitro-1,4-dihydroquinoline. Reductive cyclisation of the latter also proceeds with dehydrogenation to the aromatic tricycle (**J**, Scheme 4.13) [18ASC1870]. Nucleophilic addition of enaminoesters to 2-azidochalcones under oxidative condations affords an intermediate pyrrole, from which a Staudinger-aza-Wittig reaction effects ring closure to afford a 1,2,3,4-tetrasubstituted-3*H*-pyrrolo[2,3-*c*]quinoline (**K**, Scheme 4.13) [19SL717].

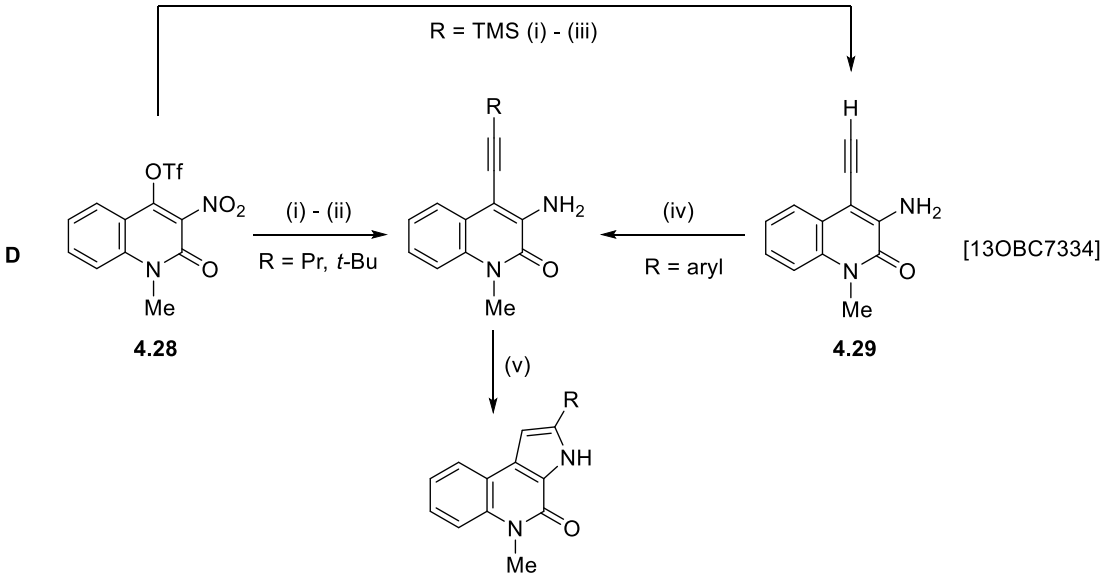






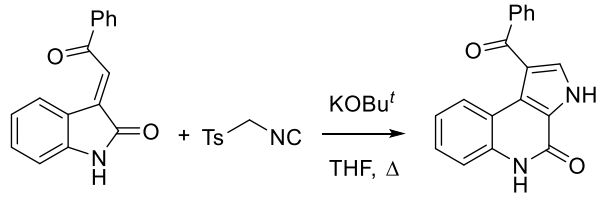
(i) $Pd(PPh_3)_2Cl_2$ (10 mol %), CuI (20 mol %), Et_3N (3.0 equiv.), DMF, r.t.
(ii) $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %), K_3PO_4 (3.0 equiv.), DMA, 130 °C

R = Me, Et, Ph
R^1 = H, Me
R^2 = Ph, 4-$MeOC_6H_4$, tolyl, 4-ClC_6H_4, 2-thienyl, *n*-Bu, *t*-Bu, *c*-Pr
R^3 = Ph, 4-$MeOC_6H_4$, tolyl, 2-ClC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, *c*-C_6H_{11}



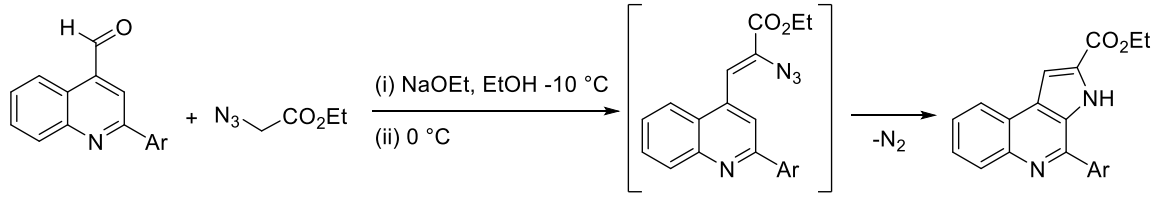
(i) R-acetylene, $Pd(PPh_3)_4$/CuI (10 mol %), K_2CO_3, THF, r.t.; (ii) Fe, DCM, HOAc, H_2O; (iii) K_2CO_3 (1.5 equiv.), MeOH, DCM; (iv) RI, $Pd(PPh_3)_4$/CuI (5 mol %), Et_3N, THF, r.t.; (v) $PdCl_2$ (10 mol %), DMF, Δ

E



[02T9179, 13T10836]

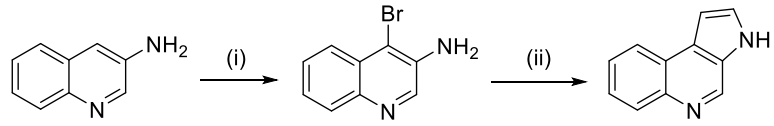
F



Ar = Ph, Tolyl, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-pyridyl, 4-$NO_2C_6H_4$

[93S225]

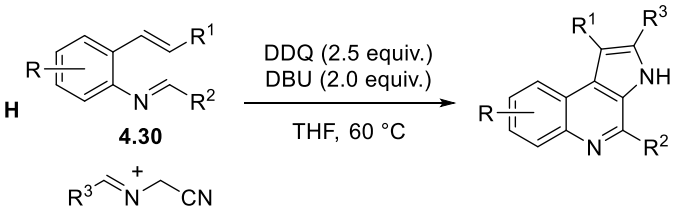
G



[09ARK(vi)174]

(i) NBS, NH_4OAc, MeCN, r.t.; (ii) CH_3CHO, $Pd(dba)_2$, X-Phos, DMF, 120 °C

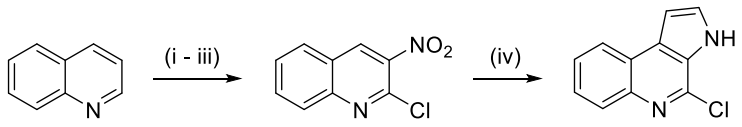
H



R = Cl, OMe
R^1 = COMe, COPh, CN, CO_2Me
R^2 = aryl, vinyl
R^3 = 4-ClC_6H_4,4-BrC_6H_4, 4-MeC_6H_4, 2-thienyl

[17OL6712]

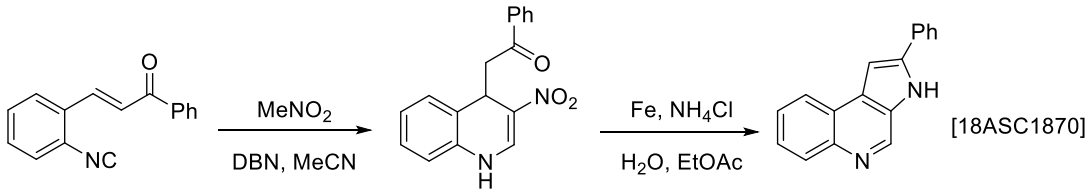
I



[18MI5386]

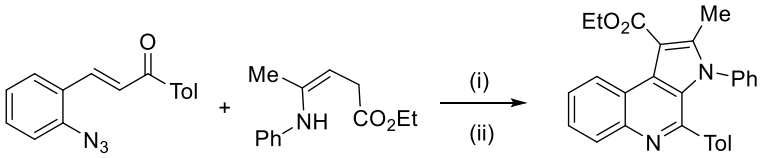
(i) *m*-CPBA, DCM, 0 °C to r.t.; (ii) *t*-BuONO, MeCN, Δ; (iii) $POCl_3$, Δ; (vi) CH_2=$CHMgBr$ (5 equiv.), THF, -78 °C to r.t.

J



[18ASC1870]

K

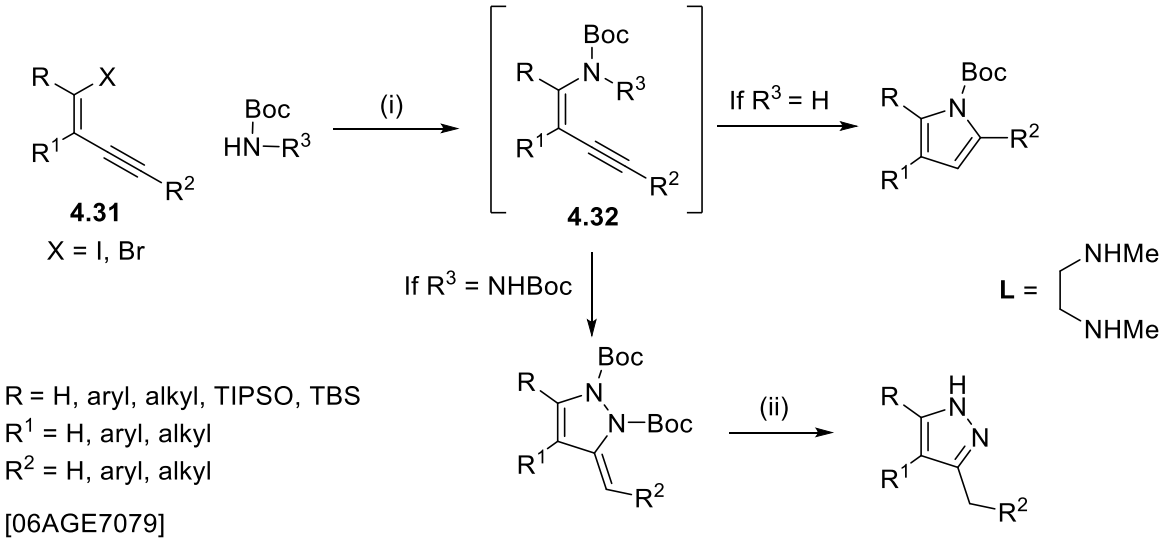


[19SL717]

(i) I_2, K_2CO_3, DCE, Δ; (ii) Ph_3P, PhMe, Δ

Scheme 4.13

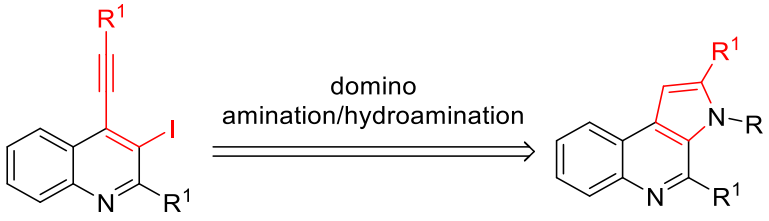
Buchwald *et al.* reported a copper-promoted domino amidation-hydroamidation sequence Scheme 4.14, to synthesise a range of pyrroles and pyrazoles. Copper(I) iodide was used as a pre-catalyst in place of a palladium species. Initial copper(I)-mediated amidation of an haloenyne **4.31** was followed by an intramolecular hydroamidation of the alkyne **4.32** affording both pyrroles and indoles in good yields (52 – 91%). Pyrazoles result from the use of *tert*-butyl carbazate (Boc-$NHNH_2$) [06AGE7079].



(i) CuI (5 mol %), **L** (20 mol %), Cs_2CO_3 (1.5 equiv), THF, 80 °C; (ii) TFA, DCM, r.t.

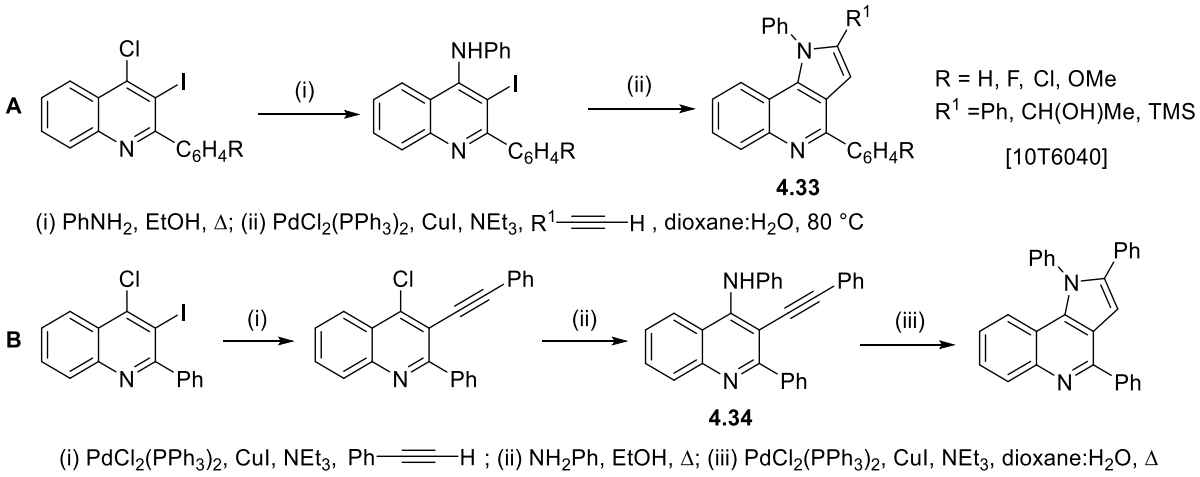
Scheme 4.14

There are many other examples in the literature of this domino amination-hydroamination reaction [05T11311, 09ASC1064, 11CC6936, 12JOC8191, 15TL86, 17TL3407]. The metal-initiated amination of alkenes and alkynes has been reviewed [98CRV675] as well as the metal-mediated hydroamination of alkenes and alkynes [19MI1b]. 4-Alkynyl-3-iodoquinolines **3.2** have the same structural fragment (shown in red, Scheme 4.15) as the examples in Scheme 4.13 and 4.14. Thus, employing a domino amination-hydroamination reaction on these substrates could furnish pyrrolo[2,3-*c*]quinolines, thereby providing a possible new route to Marinoquinolines (Scheme 4.11) and derivatives. This approach would also provide pyrrolo[2,3-*c*]quinolines with substituents in both the 2- and the 4-position of the ring system, to date there are only three examples of pyrrolo[2,3-*c*]quinolines substituted at both these positions (**A, F** and **H**, Scheme 4.13).



Scheme 4.15

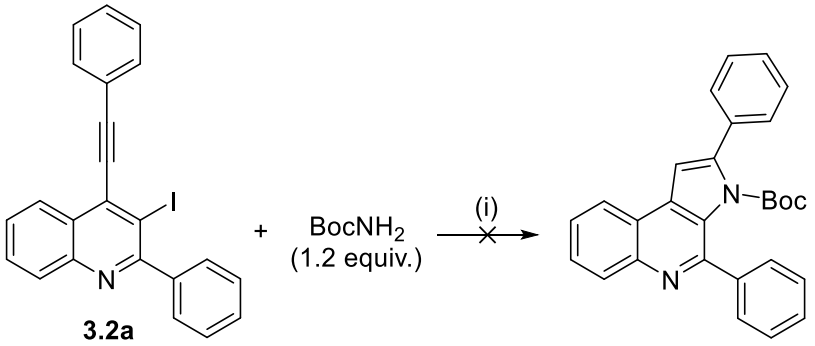
The isomeric 1*H*-pyrrolo[3,2-*c*]quinoline **4.33** (**A**, Scheme 4.16) has been synthesised in a similar manner to that proposed in Scheme 4.15 (i.e. the amination of a haloquinoline and the intramolecular hydroamination of an adjacent alkyne). The requisite 3-alkynylquinoline was synthesised by initial S_NAr displacement of chloride with $PhNH_2$ followed by a Sonogashira coupling of phenylacetylene with the 4-anilino-3-iodoquinoline. Under these conditions a domino hydroamination also occurred to afford **4.33**. The reaction was undertaken in a reversed manner (**B**, Scheme 4.16) to confirm the intermediacy of the 3-alkynyl-4-aminoquinoline **4.34** in the reaction [10T6040].



Scheme 4.16

In the light of the foregoing studies, initial experiments to access the pyrrolo[2,3-*c*]quinolines system utilised conditions reported by Buchwald (Scheme 4.14) and were first applied to 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a**. The latter was treated with *tert*-butyl carbamate in the presence of CuI (5 mol %), DMEDA (20 mol %) and Cs_2CO_3 in THF (Scheme 4.17). The mixture was stirred at 75 °C for 24 h, after this time the solution was evaporated to give a brown solid, that was purified by column chromatography (10% EtOAc – hexane). Unfortunately, the product and starting material co-eluted. Multiple attempts to

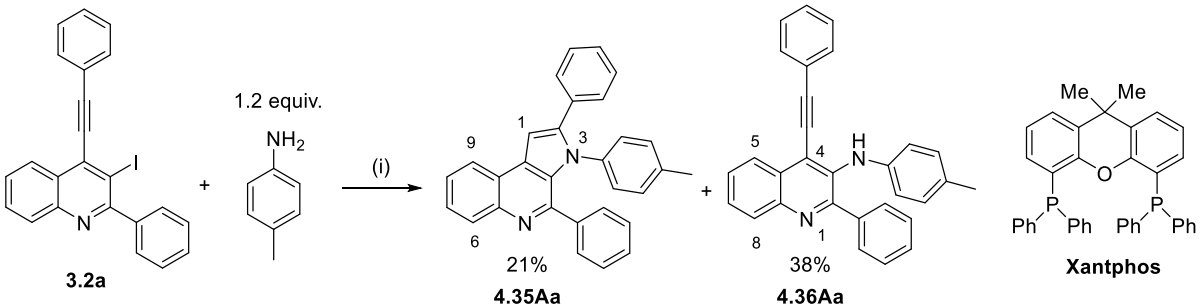
purify the mixture were unsuccessful, including the use of preparative TLC; signs of additional products resulting from degradation of the mixture became evident (^{1}H NMR).



(i) CuI (5 mol %), Cs_2CO_3 (2 equiv.), DMEDA (20 mol %), THF, N_2, Δ, 24 h

Scheme 4.17

Consequently, an alternative set of conditions to effect the Buchwald-Hartwig amination were employed, a modified method based on that from Wang *et al.* (Scheme 4.13) [14JOC9628] was adopted. Under these conditions we were delighted to observe that the domino amination-hydroamination of **3.2a** afforded 2,4-diphenyl-3-(*p*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinoline **4.35Aa** in a fair yield (21%), along with an orange solid subsequently identified as the amination product **4.36Aa**; both of these compounds are novel (Scheme 4.18).



(i) $Pd(OAc)_2$ (8 mol %), Xantphos (10 mol %), K_2CO_3 (3 equiv.), DMA (0.04 g/mL), 80 °C

Scheme 4.18

A distinct singlet for the pyrrole proton (1-*H*) is present at δ_H 7.33 ppm in the ^{1}H NMR spectrum of **4.35Aa** (Figure 4.3) with a corresponding ^{13}C resonance at δ_C 102.23 ppm. The 2,4-diphenyl-3-(*p*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinoline structure was also confirmed by HRMS which exhibited a molecular ion at *m/z* $[M+H]^+$ = 411.1859 corresponding to $C_{30}H_{22}N_2$. The aromatic protons for **4.35Aa** (Figure 4.3) were assigned with the aid of 2D NMR spectra (HSQC, HMBC and NOESY). The NOESY spectrum shows a through-space interaction

between the 1-*H* and 9-*H* protons and thus established that the latter resonates at δ_H 8.32 (Figure 4.4). Furthermore, the phenyl rings can be distinguished by the HMBC NMR spectrum, which shows an interaction between the phenyl **c**-ring *ortho* protons (4-postion) and the 4-C carbon (Figure 4.4). Moreover, and interaction between 1-*H* proton and the phenyl **a**-ring protons (2-position) with the quaternary 2-C carbon HMBC spectrum (Figure 4.4) leads to the assignments shown in Figure 4.3.

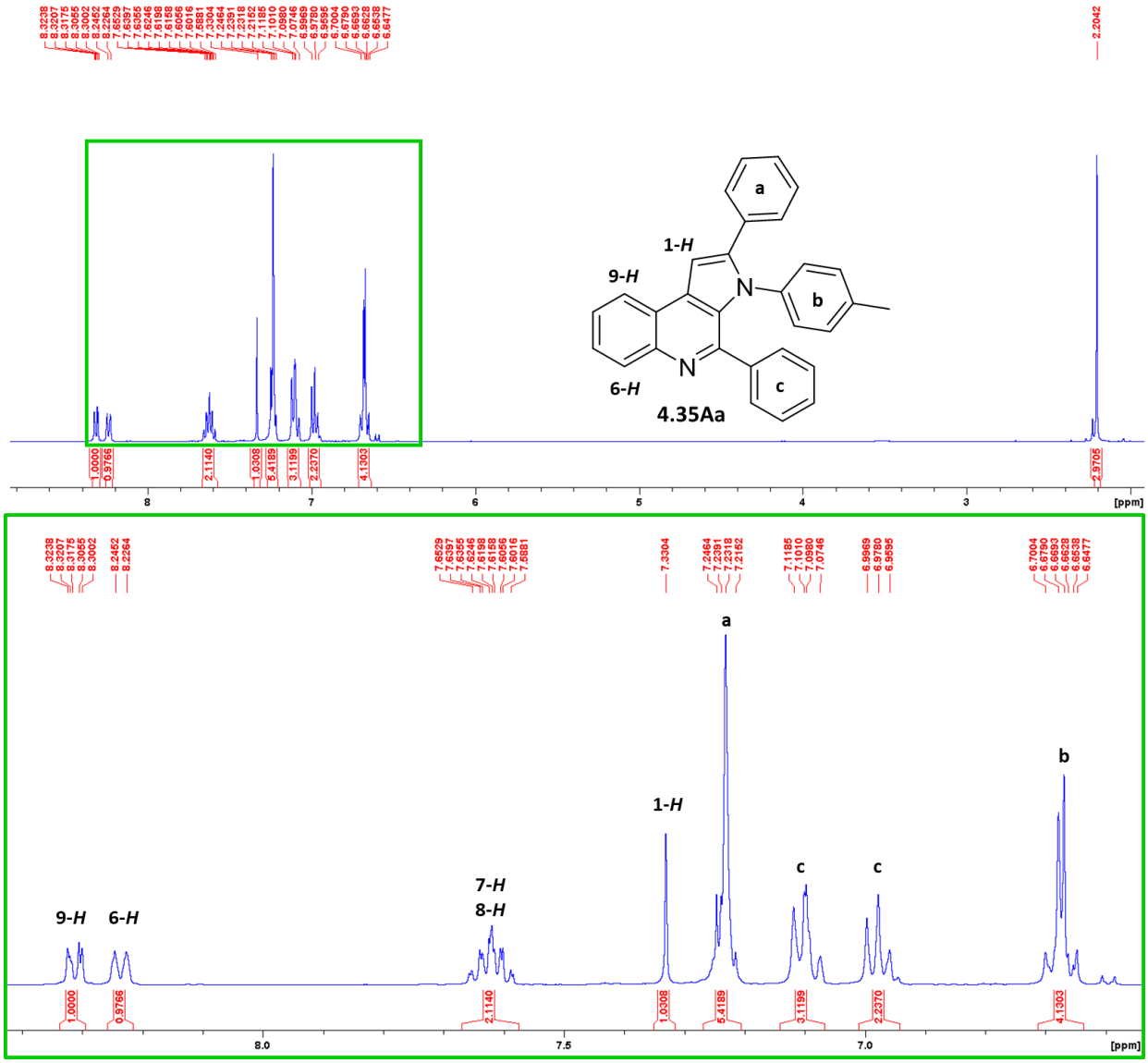


Figure 4.3 400 MHz ^{1}H NMR spectrum of **4.35Aa** in $CDCl_3$

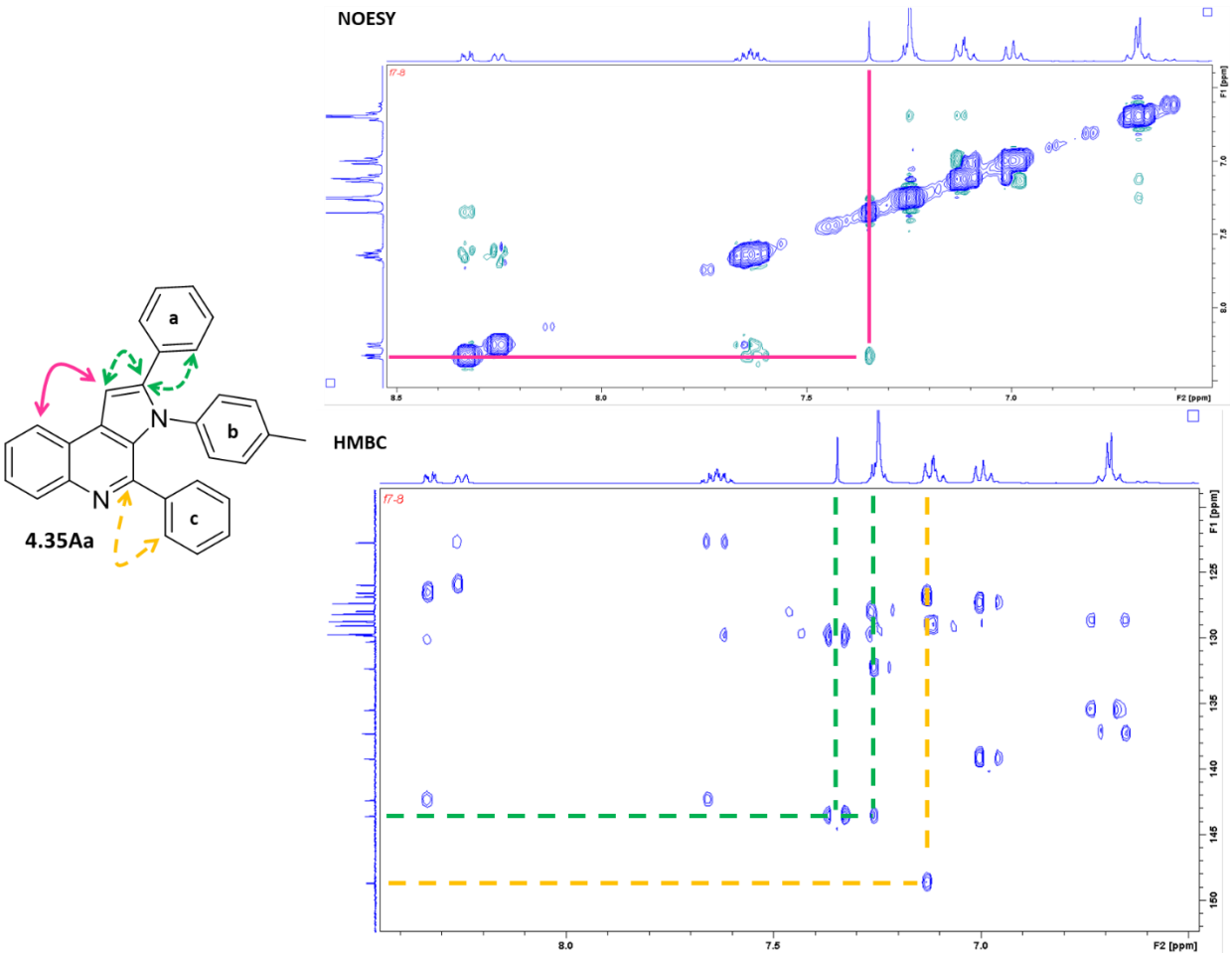


Figure 4.4 NOESY and HMBC spectra of **4.35Aa**

The structure of the 3-aminoquinoline **4.36Aa** was confirmed by its ^{1}H NMR and ^{13}C NMR spectra. The former exhibited the presence of a broad singlet at δ_H 6.03 ppm for the amine proton (Figure 4.5), additionally two quaternary carbon resonances at δ_C 106.29 and 83.99 ppm indicated the presence of acetylenic carbons. The assignments of protons in Figure 4.5 were confirmed by 2D NMR experiments (COSY, HSQC, HMBC and NOESY). A through-space interaction (NOESY) is observed (Figure 4.6) between the N*H* proton and the protons *ortho* to the N*H* in the tolyl ring. In addition, there is an interaction between the N*H* and phenyl **c**-ring *ortho* protons which absorb at δ_H 7.76 ppm (Figure 4.6). From these observations, the NOESY and the COSY spectra can be fully interpreted to assign all of the other phenyl ring protons, as shown in Figure 4.6.

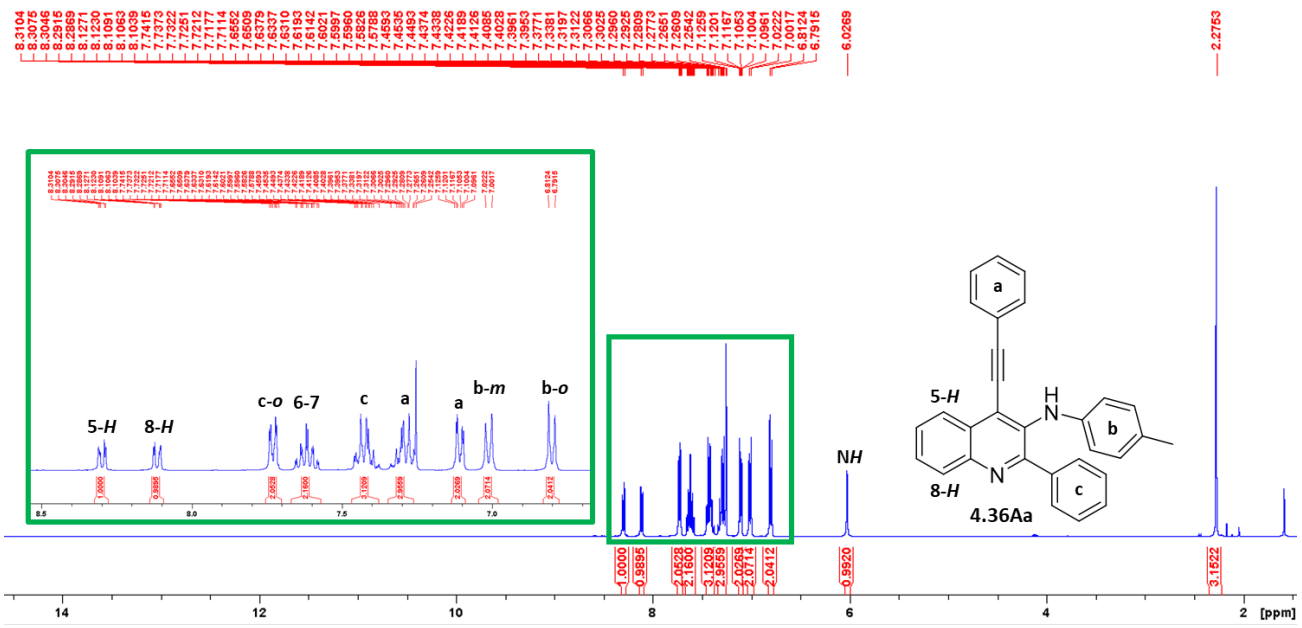


Figure 4.5 400 MHz ^{1}H NMR spectrum of **4.36Aa** in $CDCl_3$

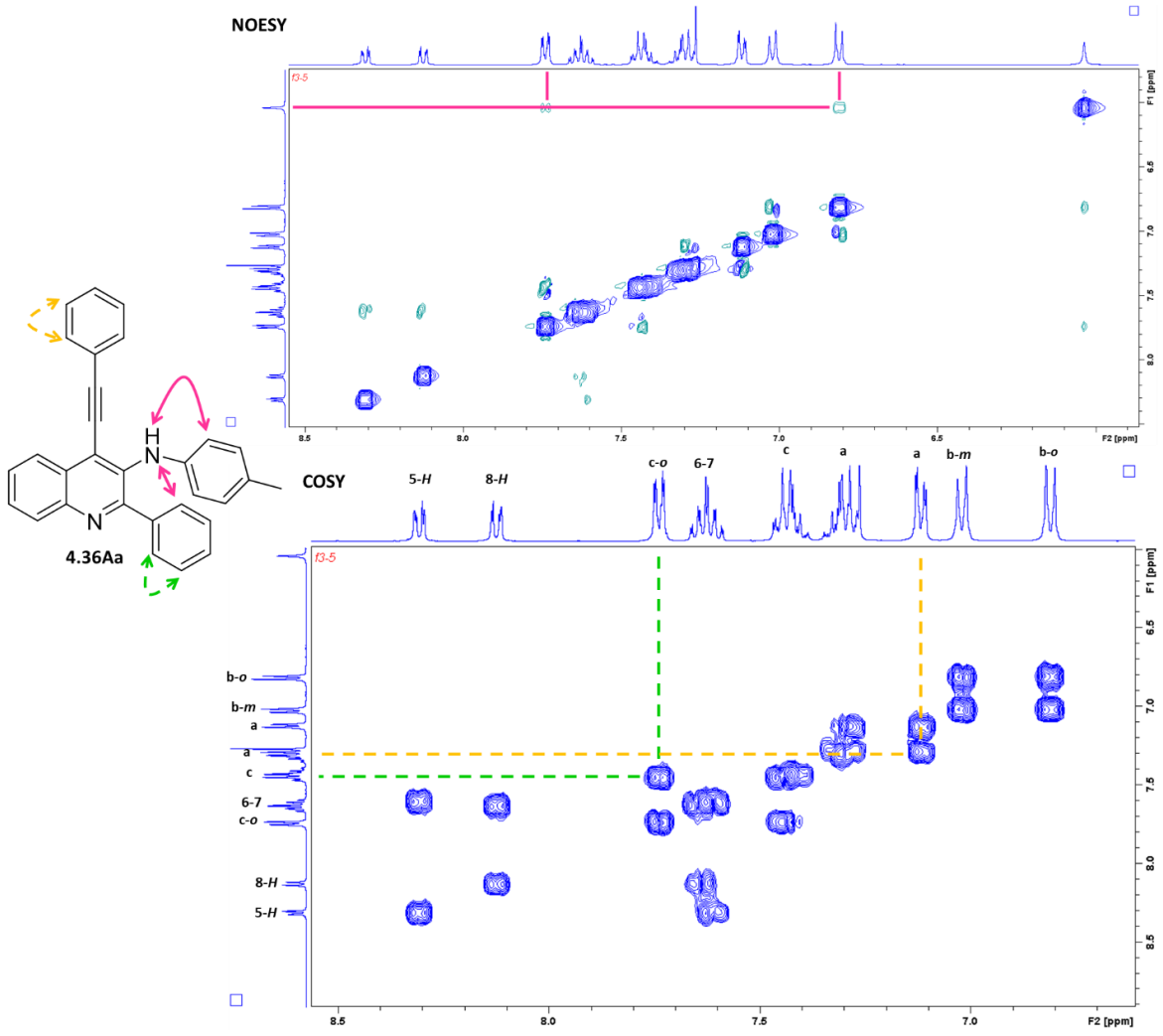
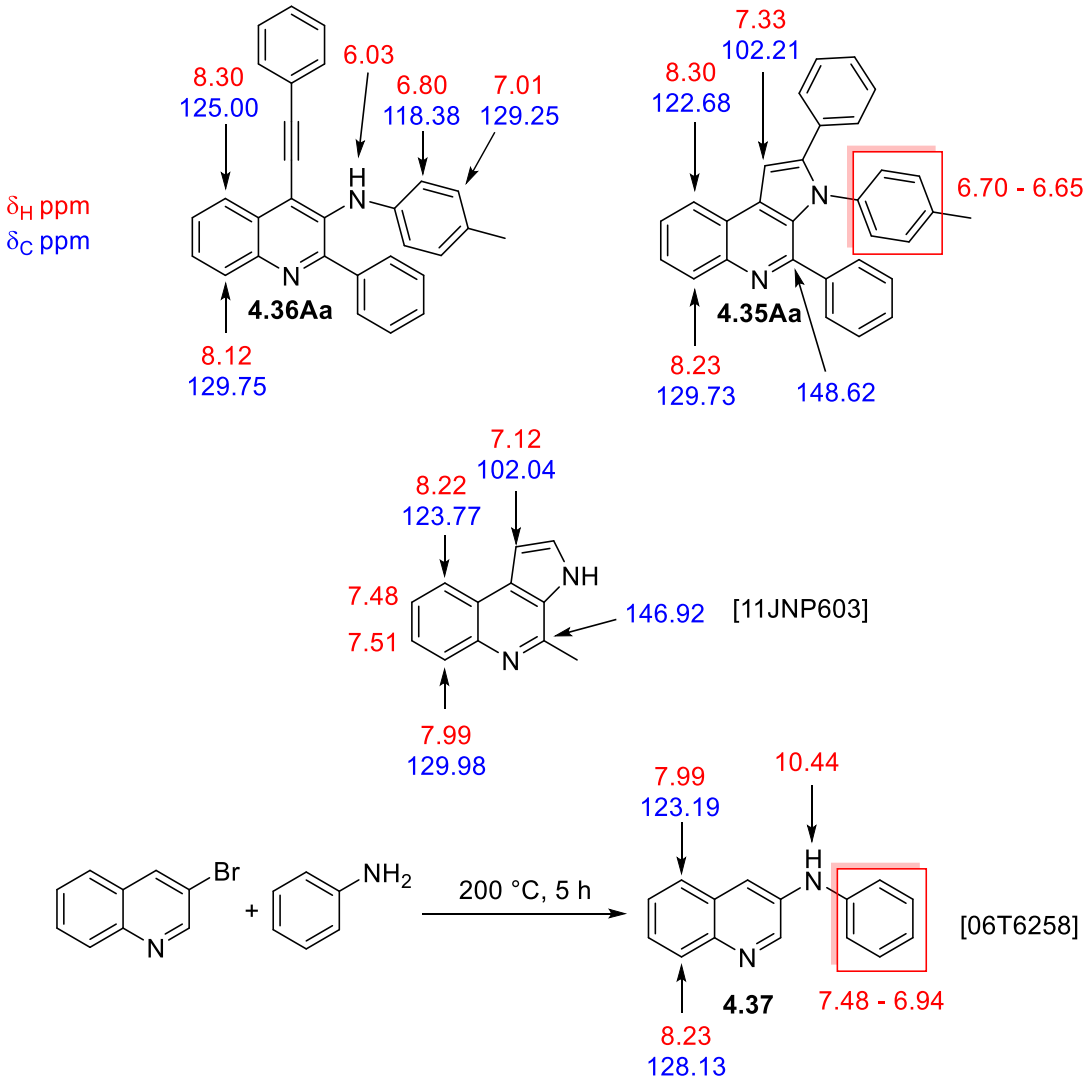


Figure 4.6 NOESY and COSY spectra of **4.36Aa**

The resonances for the 1-*H* position are similar to those of Marinoquinoline A (4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline) which exhibits resonances at δ_H 7.12 ppm and δ_C 102.04 ppm (Scheme 4.19) [11JNP603]. A feature observed in **4.35Aa** is the 7-*H* and 8-*H* protons absorb over a very small range (δ_H 7.65 and 7.59 ppm), which is also a feature in Marinoquinoline A (Scheme 4.19).

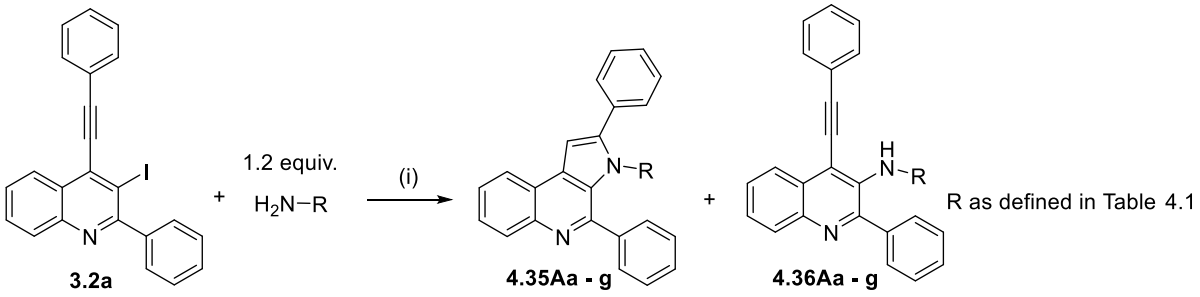
The ^{1}H NMR signals for the benzo ring protons in aminoquinoline **4.36Aa** differ to those found in 3-anilinoquinoline **4.37** (Scheme 4.19) [06T6258]. Of importance are the shifts of the 5-*H* and 8-*H* protons in 2-phenyl-4-(phenylethynyl)-*N*-(*p*-tolyl)quinolin-3-amine **4.36Aa**, in which the 5-*H* proton absorbs at δ_H 8.30 ppm and 8-*H* at δ_H 8.11 ppm. However, as described in Section 3.1, Scheme 3.3 the C-4 alkyne moiety in the quinoline ring imparts a pronounced deshielding effect on the (*peri*) 5-*H* proton. The phenyl ring protons of the amine **4.37** are deshielded compared with those observed in **4.36Aa** (δ_H 7.01 ppm and 6.80 ppm) for the electron-rich *p*-toluidine moiety.



Scheme 4.19

With the initial success of the Pd-catalysed amination-(hydroamination) reaction with *p*-toluidine the reaction of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** towards a range of amines or amides was investigated Scheme 4.20. The results of these reactions are documented in Table 4.1. In many cases the 3-aminoquinoline was the major product from the reaction and in every case eluted first on purification by column chromatography (non-polar).

The reaction was also extended to 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline **3.2b** and to 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline **3.2c**. In each case the amination-hydroamination reaction was investigated with *p*-toluidine and with aniline as substrates (Scheme 4.21). The results of these reactions are collated in Table 4.2.



(i) $Pd(OAc)_2$ (8 mol %), Xantphos (10 mol %), K_2CO_3 (3 equiv.), DMA (0.04 g/mL), 80 °C

Scheme 4.20

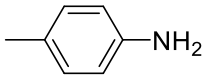
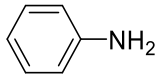
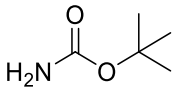
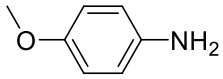
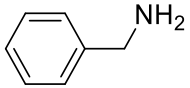
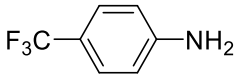
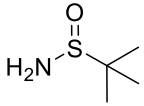
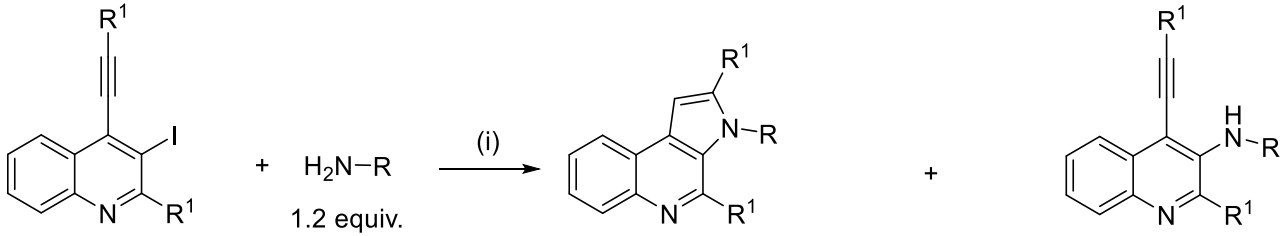
Entry	Iodoquinoline R^1	Amine or Amide	Pyrrolo[2,3-*c*]quinolines	Pyrrolo[2,3-*c*]quinoline Yield (%)	δ_H 1-*H* (ppm)	3-Aminoquinoline	3-Aminoquinoline Yield (%)	δ_H N*H* (ppm)
1	Ph		**4.35Aa**	21	7.33	**4.36Aa**	38	6.03
2	Ph		**4.35Ab**	74	7.41	**4.36Ab**	3	7.18
3	Ph		**4.35Ac**	0	–	**4.36Ac**	0	–
4	Ph		**4.35Ad**	35	7.52	**4.36Ad**	40	6.92
5	Ph		**4.35Ae**	0	–	**4.36Ae**	60	4.72
6	Ph		**4.35Af**	20	7.58	**4.36Af**	35	7.92
7	Ph		**4.35Ag**	0	–	**4.36Ag**	0	–

Table 4.1 Yields of **4.35A** and **4.36A** from amination-hydroamination reaction of 3-iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a**



3.2b, $R^1 = C_3H_7$
3.2c, $R^1 = 4\text{-}MeOC_6H_4$

3.35Ba, R = $4\text{-}MeC_6H_4$, $R^1 = C_3H_7$
3.35Bb, R = Ph, $R^1 = C_3H_7$
3.35Cb, R = $4\text{-}MeC_6H_4$, $R^1 = 4\text{-}MeOC_6H_4$
3.35Cb, R = Ph, $R^1 = 4\text{-}MeOC_6H_4$

3.36Ba, R = $4\text{-}MeC_6H_4$, $R^1 = C_3H_7$
3.36Bb, R = Ph, $R^1 = C_3H_7$
3.36Cb, R = $4\text{-}MeC_6H_4$, $R^1 = 4\text{-}MeOC_6H_4$
3.36Cb, R = Ph, $R^1 = 4\text{-}MeOC_6H_4$

(i) $Pd(OAc)_2$ (8 mol %), Xantphos (10 mol %), K_2CO_3 (3 equiv.), DMA (0.04 g/mL), 80 °C

Scheme 4.21

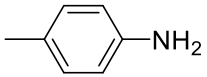
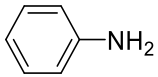
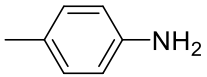
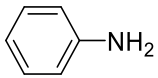
Entry	Iodoquinoline R^1	Amine or Amide	Pyrrolo[2,3-*c*]quinolines	Pyrrolo[2,3-*c*]quinoline Yield (%)	δ_H 1-*H* (ppm)	3-Aminoquinoline	3-Aminoquinoline Yield (%)	δ_H N*H* (ppm)
1	C_3H_7		**4.35Ba**	0	–	**4.36Ba**	0	–
2	C_3H_7		**4.35Bb**	0	–	**4.36Bb**	0	–
3	$4\text{-}MeOC_6H_4$		**4.35Ca**	40	7.25	**4.36Ca**	0	–
4	$4\text{-}MeOC_6H_4$		**4.35Cb**	37	7.27	**4.36Cb**	20	6.04

Table 4.2 Yields of **4.35B – C** and **4.36B – C** from amination-hydroamination reaction of 4-alkynyl-3-iodoquinoline **3.2b – c**

The Pd-catalysed amination of **3.2a** with *p*-toluidine provided a mixture of the pyrroloquinoline **4.35Aa** and the 3-aminoquinoline **4.36Aa** in which the latter predominated (entry 1, Table 4.1). Separation of the two compounds was readily accomplished by flash column chromatography on silica with 10% EtOAc – pet ether. Under these conditions the 3-aminoquinoline **4.36Aa** eluted first from the column. When aniline was coupled with **3.2a**, 2,3,4-triphenyl-3*H*-pyrrolo[2,3-*c*]quinoline **4.35Ab** was obtained in excellent yield (74%, entry 2, Table 4.1), together with a trace amount of the corresponding 3-aninoquinoline **4.36Ab**. However, near equal yields of both products **4.35Ad** and **4.36Ad** were obtained from the coupling of **3.2a** with *p*-anisidine (entry 4, Table 4.1). Although the electron deficient 4-trifluoromethylaniline coupled to **3.2a** to furnish modest yields of both the pyrroloquinoline **4.35Af** and the aminoquinoline **4.36Af**, the latter was obtained in slightly higher yield (entry 6, Table 4.1).

Amination of **3.2a** with benzylamine provided exclusively the 3-(benzylamino)quinoline derivative **4.36Ae**; none of the pyrroloquinoline **4.35Ae** was observed (entry 5, Table 4.1). It is difficult to rationalise the outcome of this latter hydroamination, that failed to provide any of the pyrroloquinoline, whilst the coupling of **3.2a** with aniline (a less nucleophilic amine) furnished the pyrroloquinoline **4.35Ab** in excellent yield. Attempts to effect Pd-catalysed amidation of the 3-iodoquinoline **3.2a** with either *tert*-butyl carbamate or with *tert*-butylsulfinamide were unsuccessful (entries 3 and 7 respectively, Table 4.1), these reactions are considered in more detail on page 224.

Efforts to accomplish the amination-hydroamination reaction with 3-iodo-4-(pent-1-yn-1-yl)-2-propylquinoline **3.2b** with either aniline or *p*-toluidine were unsuccessful and failed to afford tractable products (entry 1 and 2, Table 4.2). In contrast the Pd-mediated coupling of 3-iodo-2-(4-methoxyphenyl)-4-(4-methoxyphenylethynyl)quinoline **3.2c** with both amines was successful, *p*-toluidine provided the pyrroloquinoline **4.35Ca** as the only isolable product in 40% yield (entry 3, Table 4.2). Whereas, amination with aniline afforded both the pyrroloquinoline **4.35Cb** and a somewhat lower yield of the 3-anilino-quinoline **4.36Cb** (entry 4, Table 4.2).

Pyrrolo[2,3-*c*]quinolines **4.35A – C** and *N*-substituted-4-alkynylquinolin-3-amines **4.36A – C** were characterised by all the usual physical techniques. Interestingly the melting points of

the pyrroloquinolines **4.35A – C** were on average 50 °C higher than the 3-aminoquinolines **4.36A – C**.

The ^{1}H NMR spectrum of 2,4-diphenyl-3-(*p*-tolyl)pyrrolo[2,3-*c*]quinoline **4.35Aa** (cf. Figure 4.3) is shown in Figure 4.7 along with those of the analogues **4.35Ab**, **4.35Ad** and **4.35Af**. A notable characteristic of the spectra in that the 1-*H* signal resonances fall within the range δ_H 7.58 – 7.25 ppm. Although a contribution to these differences can be attributed to solvent effects, particularly noteworthy is the deshielding of the 1-*H* signal in the trifluoromethyl analogue **4.35Af** (δ_H 7.58 ppm) compared to the 3-(*p*-anisyl)pyrroloquinoline **4.35Ad** (δ_H 7.52 ppm), presumably a consequence of the electron withdrawing substituent in the former.

An interesting feature of the ^{1}H spectra of the pyrroloquinolines **4.35Ab**, **4.35Ad** and **4.35Af** is that all display non-first order splitting of the signals for the 6-*H* and 9-*H* protons and these together with 7-*H* and 8-*H* form part of an AA'XX' system. Clearly this feature cannot be attributed to solvent effects because of the similarity of the spectra of **4.35Ab** (in CD_2Cl_2) with **4.35Ad** and **4.35Af** (both in acetone-d_6). In contrast, the 6-*H* and 9-*H* signals in the 3-(*p*-tolyl)pyrroloquinoline **4.35Aa** both have first order-like appearance, giving rise to broadened double doublets (Figure 4.7, see also Figure 4.3). A similarity of all the pyrroloquinoline **4.35A** ^{1}H spectra is the narrow range in which the (superimposed) signals for 7-*H* and 8-*H* resonate (ca. δ_H 7.58 – 7.71 ppm) and this is also the case for the corresponding protons i.e. 6-*H* and 7-*H* in the aminoquinolines **4.36A** (Figure 4.8). Within this series the quinoline 5-*H* and 8-*H* protons appear as a broadened double doublet and are the most deshielded signals (cf. Figures 4.5 and 4.6). Deshielding of the anilino-substituted protons is observed with 2-phenyl-4-(phenylethynyl)-*N*-[4-(trifluoromethyl)phenyl]quinoline-3-amine **4.36Af** in which the ring protons *ortho* to the CF_3 group are deshielded and resonate at δ_H 7.50 ppm, a shift of ca. 0.5 ppm compared to those in the tolyl derivative **4.36Aa**.

The 3-(benzylamino)quinoline **4.36Ae** exhibits a broadened signal at δ_H 4.48 ppm which also displays partial splitting by virtue of coupling with the N*H* proton and because they are also diastereotopic (Figure 4.8).

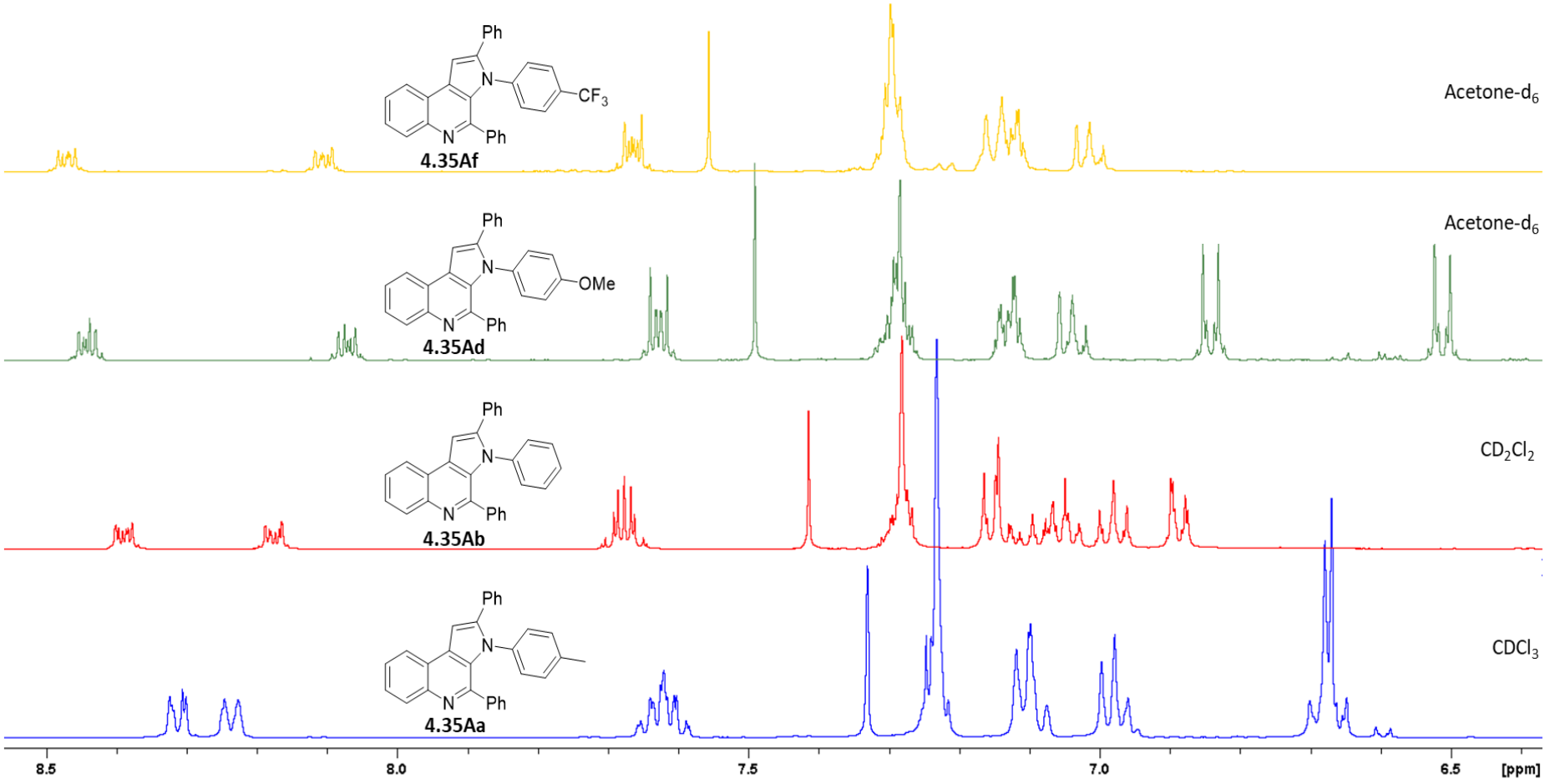


Figure 4.7 ^{1}H NMR spectra comparison of pyrrolo[2,3-*c*]quinolines **4.35Aa – f**

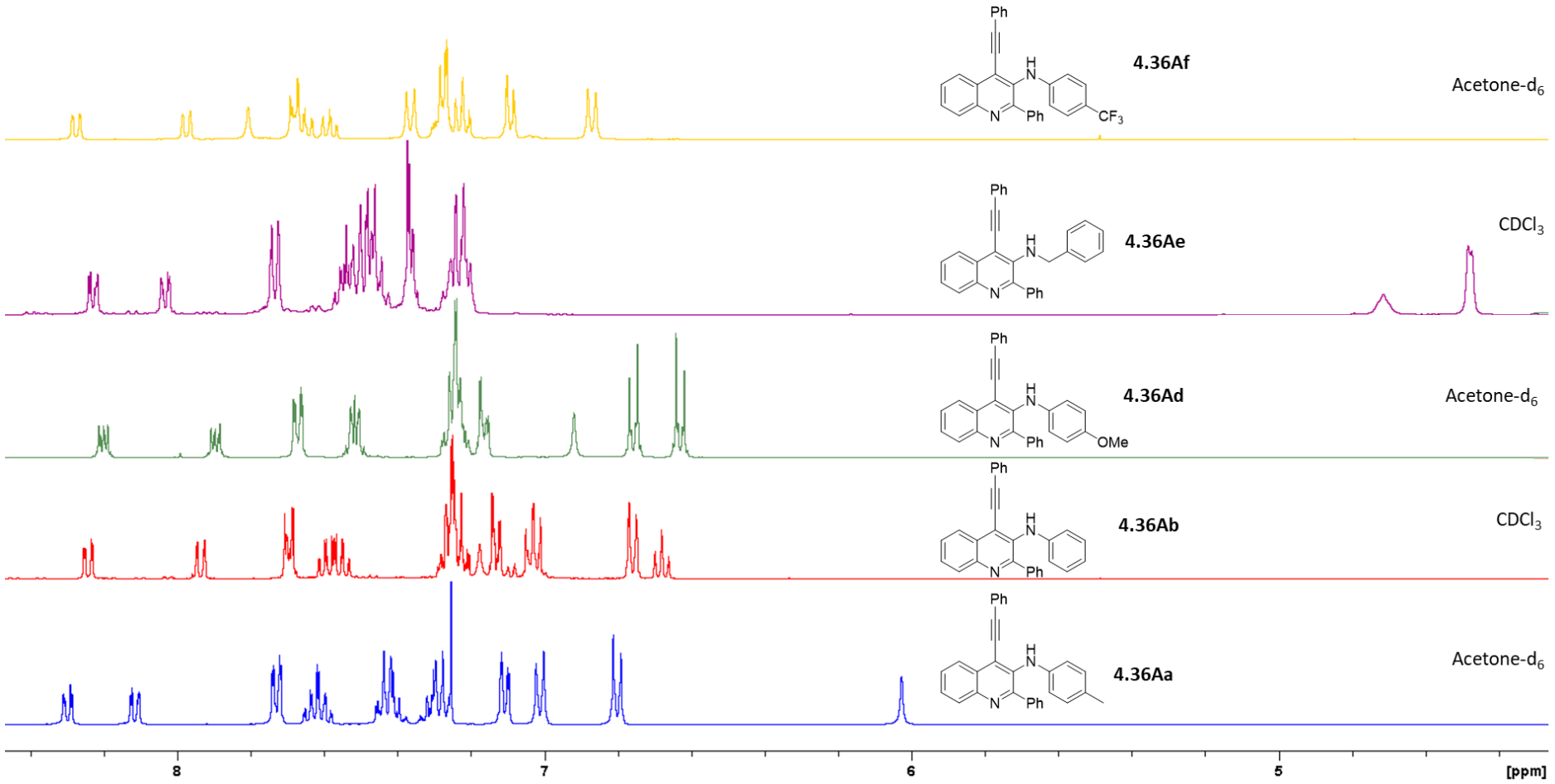
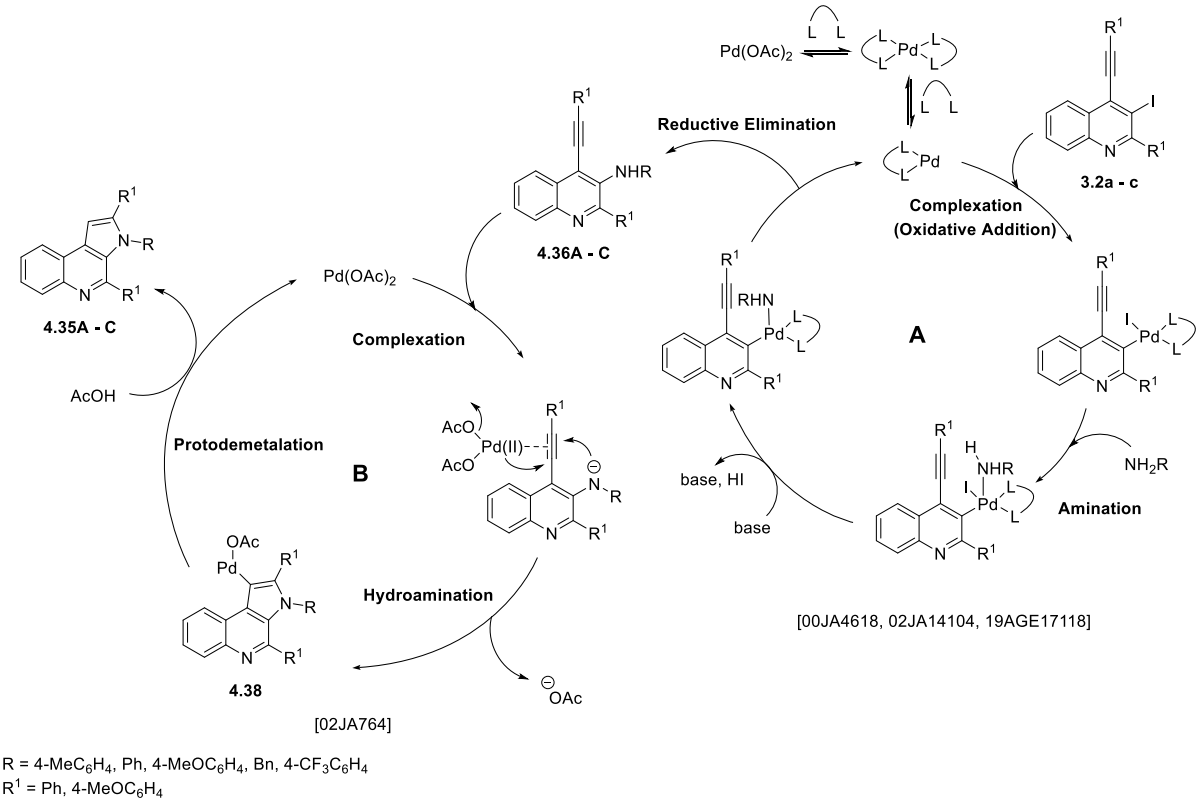


Figure 4.8 ^{1}H NMR spectra comparison of *N*-substituted-2-phenyl-4-(phenylethynyl)quinolin-3-amines **4.36Aa – f**

Formation of both *N*-substituted-4-(alkynyl)quinolin-3-amines **4.36A – C** and the pyrrolo[2,3-*c*]quinolines **4.35A – C** can be postulated to proceed by two competing catalytic cycles. Formation of *N*-substituted-4-(alkynyl)quinolin-3-amines **4.36A – C** is proposed to involve a Buchwald-Hartwig amination as shown in catalytic cycle **A** (Scheme 4.22). The cycle has been adapted for **4.36A – C** from the review by Dorel *et al*. for Pd-mediated amination with a bidentate ligand (in this case Xantphos) [00JA4618, 19AGE17118]. Aminoquinoline **4.36A – C** will then enter the next catalytic cycle **B**, in which hydroamination takes place. Palladium(II) will coordinate with the π-electrons of the triple bond, activating it to attack from the amino nitrogen to give the palladium complex **4.38** [02JA764]. Following protodemetalation, aided by acetic acid, the corresponding pyrrolo[2,3-*c*]quinolines **4.35A – C** will be obtained.

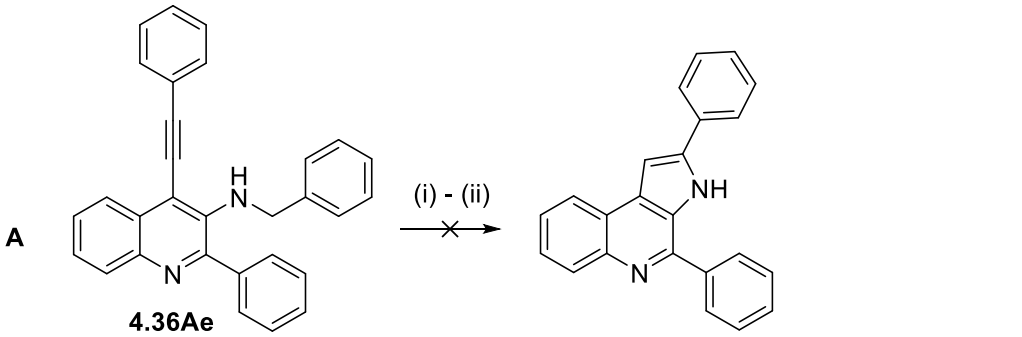


Scheme 4.22

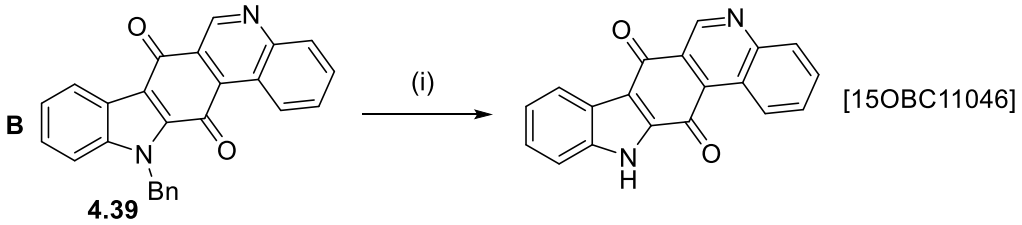
Surprisingly, 4-alkynyl-3-iodoquinolines **3.2b** ($R^1 = C_3H_7$) did not work with the amination-hydroamination conditions used (Scheme 4.21, entries 3 and 4, Table 4.2), with no identifiable products isolated from the reactions. As with the synthesis of the 3-iodoquinoline **3.2b**, different conditions are possibly needed for the alkyl substituted derivatives (Section 3.1, Scheme 3.13, page 151). Moreover when $R^1 = 4\text{-}MeOC_6H_4$ (**3.2c**) the

yields of pyrrolo[2,3-*c*]quinolines **3.35Ca – b** were higher than 4-alkynyl-3-aminoquinoline **3.36Ca – b** which is different to that seen for the phenyl derivatives (R^1 = Ph) **3.35Aa – f**. Evidently changing the substituents on the alkyne unit significantly affects the reactivity of the compound.

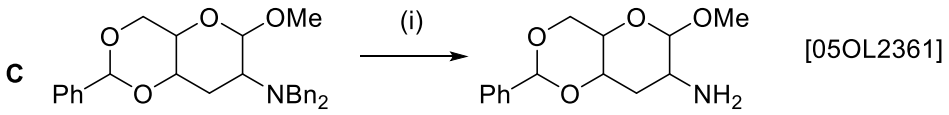
The use of amines possessing readily cleavable *N*-protecting groups can be envisaged to allow access to a free N*H* i.e. an *N*-3-unsubstuted 3*H*-pyrrolo[2,3-*c*]quinoline. Thus, benzylamine was an obvious choice. The reaction proceeded smoothly with **3.2a** to afford the aminoquinoline **4.36Ae** in a good yield (60%, entry 5, Table 4.1), this was the only Pd-mediated amination reaction in the series to produce an oil. With the *N*-protected compound to hand the removal of the Bn group and possible domino-hydroamination of the 4-alkynyl-3-aminoquinoline **4.36Ae** was attempted (**A**, Scheme 4.23) [05OL2361, 15OBC11046]. Thus, treatment of the latter with Pd/C and ammonium formate, which acts as a hydrogen source, in MeOH was attempted. Unfortunately, no tractable products could be isolated from the reaction. These conditions were taken from the hydrogenolysis depicted in **B** Scheme 4.23, in which the benzyl group was removed with ease to afford the indole derivative **4.39** in 71% yield. Another set of conditions attempted for the deprotection of the benzyl group from **4.36Ae**, was the use of NIS in DCM reported by Grayson and Davies (**C** Scheme 4.23) [05OL2361]. In the case of the latter conditions, it was hoped that along with benzyl deprotection the alkynophilicity of NIS would activate the triple bond to hydroamination and possible retention of an iodine substituent in the subsequent 3*H*-pyrrolo[2,3-*c*]quinoline structure (1-postion). However the use of NIS also failed to provide the desired 3*H*-pyrrolo[2,3-*c*]quinoline, with only starting material being isolated from the reaction.



(i) Pd/C 10 %, NH_4HCO_2 (excess), degassed MeOH, 21 h, Δ [15OBC11046]
(ii) NIS (5 equiv.), DCM, r.t., 24 h [05OL2361]



(i) Pd/C 10 %, NH_4HCO_2 (excess), MeOH, 3 h, Δ

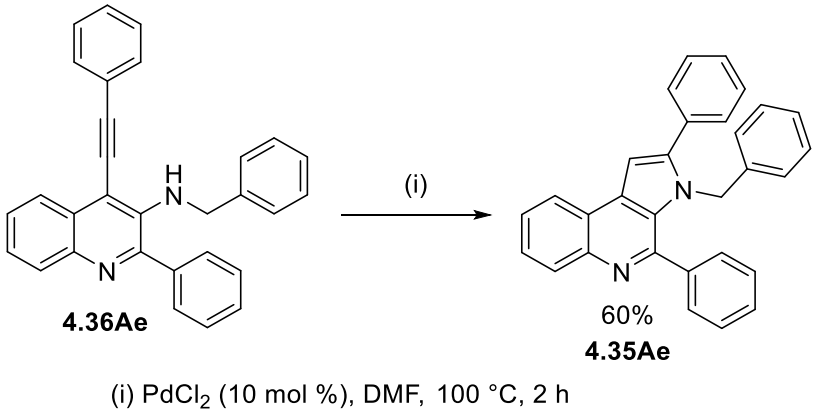


(i) NIS (5 equiv.), DCM, r.t., 2 h

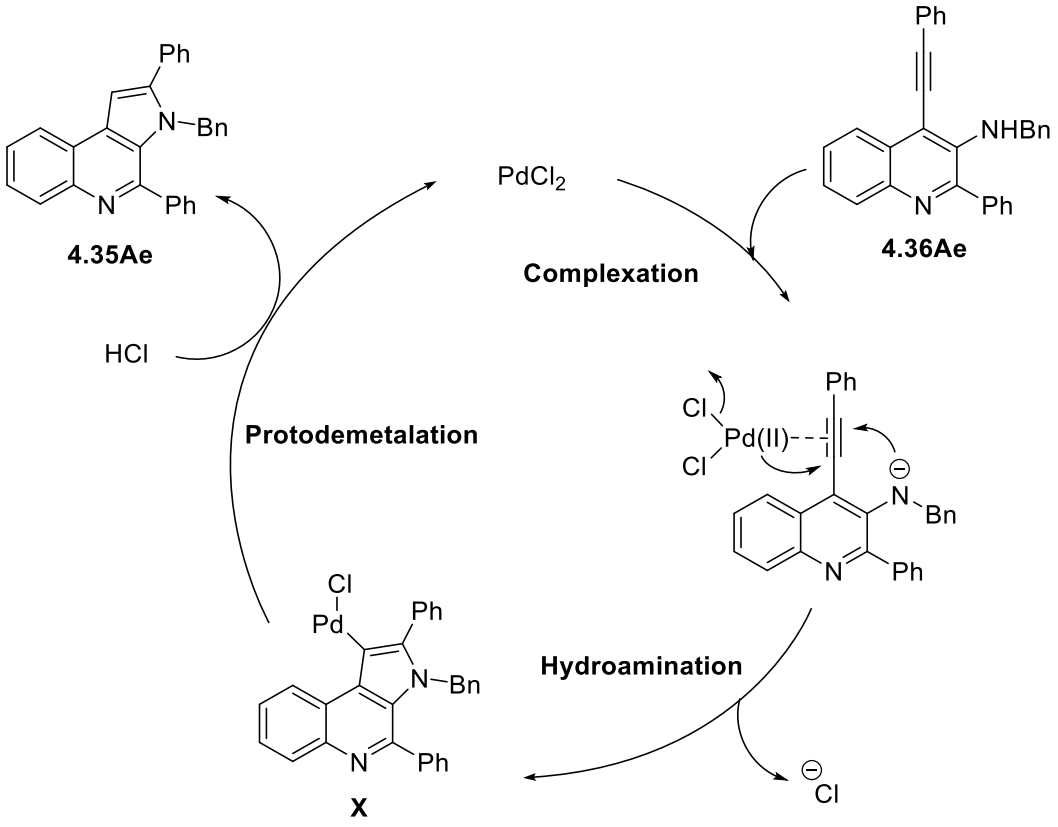
Scheme 4.23

Due to unsuccessful attempts to deprotect of the benzyl group from aminoquinoline **4.36Ae** attention turned to accessing 3-benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline **3.35Ae** by an alternative means. As discussed in **D** Scheme 4.13 (v), $PdCl_2$ in DMF has been shown to be effective in the hydroamination of 4-alkynyl-3-amino-2-quinolones to afford 3*H*-pyrrolo[2,3-*c*]quinolin-4(5*H*)-ones [13OBC7334]. Thus, *N*-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine **4.36Ae** was treated with $PdCl_2$ (10 mol %) in DMF for 2 h (Scheme 4.24), following purification of the crude mixture by flash column chromatography (10 % EtOAc – pet ether) a fast eluting fraction was isolated as a yellow oil. On inspection of the ^{1}H NMR spectrum the fraction was found to be 3-benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline **4.35Ae** in a 60% yield. It can be postulated that the hydroamination mechanism is similar to that with $Pd(OAc)_2$ (Scheme 4.22, cycle **B**); palladium(II) will coordinate with the π-electrons of the triple bond, activating it to attack from the amino nitrogen to give the palladium complex **X**.

Following protodemetalation, aided by HCl, 3-benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline **3.35Ae** will be obtained (Scheme 4.25).



Scheme 4.24



Scheme 4.25

The ^{1}H NMR spectrum of **4.35Ae** has similar features and chemical shifts to the other pyrrolo[2,3-*c*]quinolines **4.35Aa – f**; for example overlapping of the 7-*H* and 8-*H* protons, the 1-*H* proton resonance at δ_H 7.33 ppm which is identical to that in **4.35Aa**. However, a striking difference is the high field doublet at δ_H 6.11 ppm, integrating for two protons

corresponding to the benzyl group *ortho* protons (blue circle, Figure 4.9). The remarkable upfield shift is a consequence of the proximity of the benzylic *ortho* protons to the adjacent phenyl substituents at C-2 and C-4. Either, or both of these aryl groups will adopt an orthogonal disposition to the *N*-benzyl group, so exposing the *ortho* protons to an anisotropic shielding region. Similar structural fragments to **4.35Ae** possessing either *C*- or *N*- linked benzyl groups do no exhibit such high field signals for their aromatic protons (Scheme 4.26) [11JNP603, 17JOC4435, 20SL1613]. It is noteworthy that the aromatic proton signals in benzylamine for **4.36Ae** (pink and green circles, Figure 4.9) are in the range of δ_H 7.20 – 7.39 ppm ($CDCl_3$), those in **4.35Ae** are shielded by 1 ppm compared to the amine substrate.

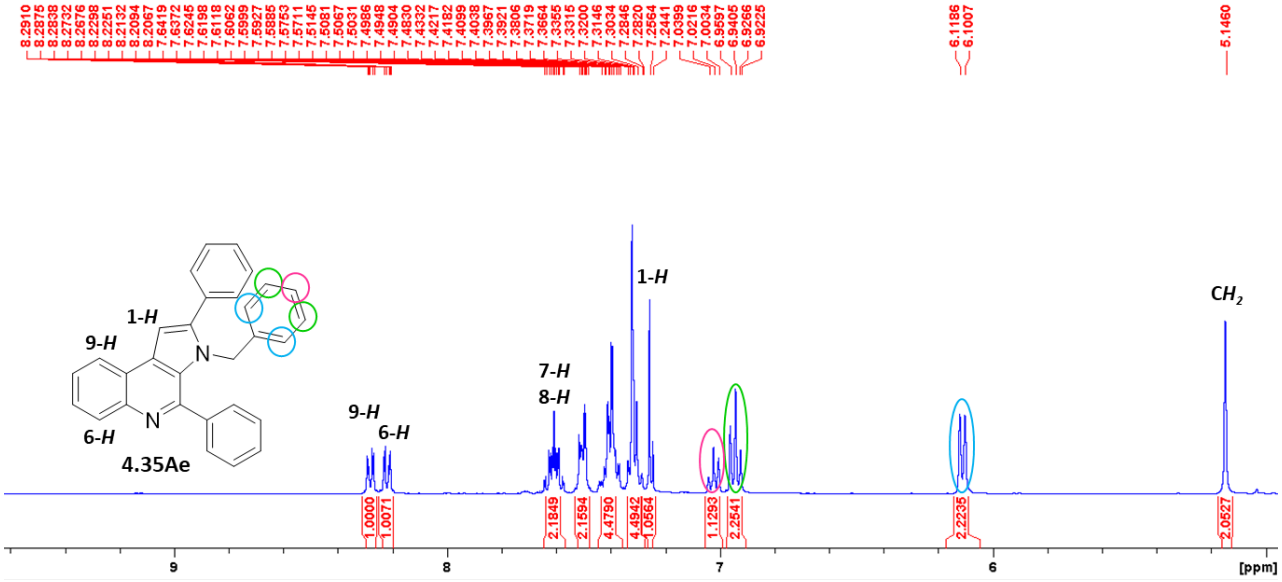
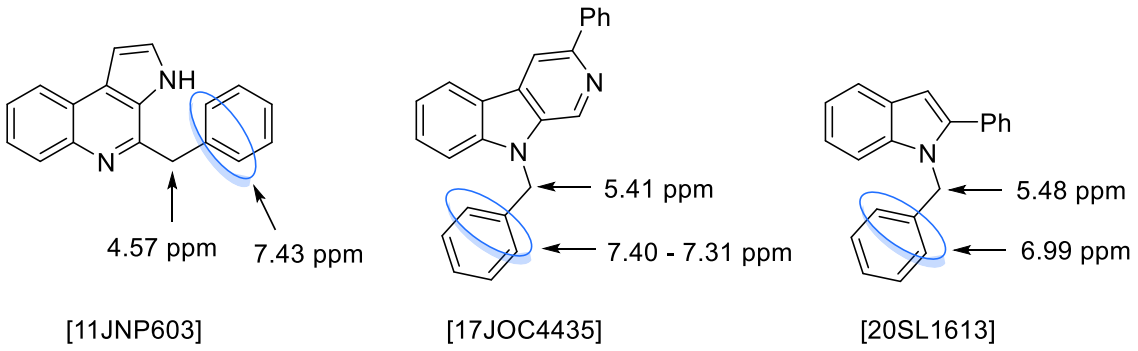


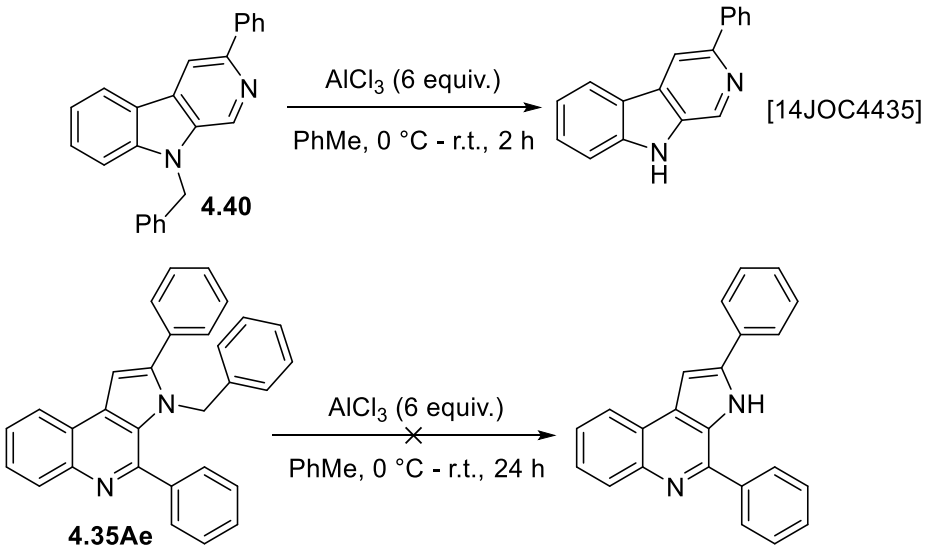
Figure 4.9 400 MHz ^{1}H NMR spectrum of **4.35Ae** in $CDCl_3$



[11JNP603] [17JOC4435] [20SL1613]

Scheme 4.26

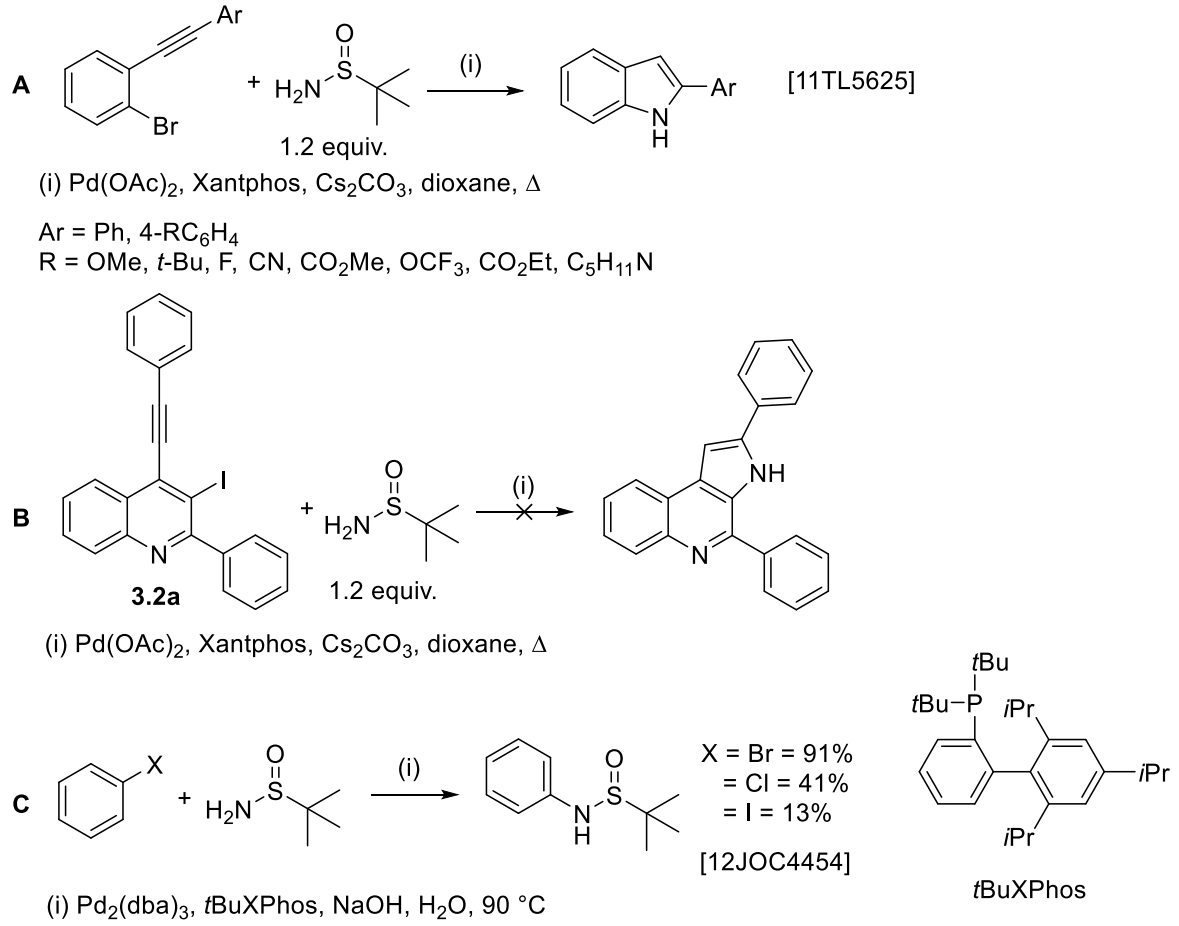
Donohoe and co-workers showed that β-carboline **4.40** undergoes benzyl deprotection in a high yield (88%) with excess $AlCl_3$ in PhMe at room temperature (Scheme 4.27) [17JOC4435]. Thus, pyrrolo[2,3-*c*]quinoline **4.35Ae** was dissolved in dry PhMe and added to a suspension of excess $AlCl_3$ (6 equiv.) in dry PhMe at 0 °C. The mixture was stirred for 30 minutes, after which it was allowed to warm to room temperature and stirred overnight. After quenching with aq. $NaHCO_3$ and isolation with EtOAc the ^{1}H NMR spectrum revealed only starting material (**4.35Ae**) was present (Scheme 4.27). The use of alternative protected amines or ammonia surrogates was therefore sought.



Scheme 4.27

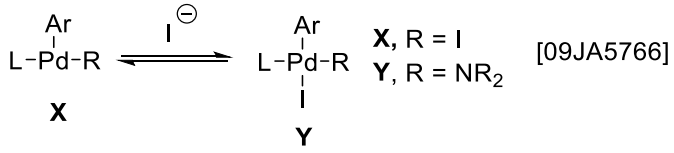
Attempts to couple *tert*-butyl carbamate ($BocNH_2$) with 3-iodoquinoline **3.2a** (entry 3, Table 4.1) were unsuccessful and only starting material could be isolated from the reaction mixture. $BocNH_2$ has been utilised extensively in palladium-catalysed C-N coupling reactions, which has been reviewed by Buchwald and Ruiz-Castillo [16CRV12564]. An alternative means to access an *N*-unsubstituted pyrroloquinoline was to employ *tert*-butylsulfinamide (*t*-$BuSONH_2$) because it has been utilised as an ammonia surrogate in the synthesis of 2-arylindoles (**A**, Scheme 4.28) [11TL5625]. However use of *tert*-butylsulfinamide was also unsuccessful and only starting material was isolated from the reaction mixture (entry 7, Table 4.1), even when the reaction was attempted using the same conditions reported by Sivakumar and co-workers (**B**, Scheme 4.27). It is possible that the failure of *tert*-butylsulfinamide to couple with **3.2a** is a consequence of the substrate being an iodo-compound. The palladium(0)-catalysed reaction of *tert*-butylsulfinamide with aryl halides (**C**,

Scheme 4.28) shows a significant difference in yields by changing the halide. Aryl bromides appear to couple most efficiently [12JOC4454].



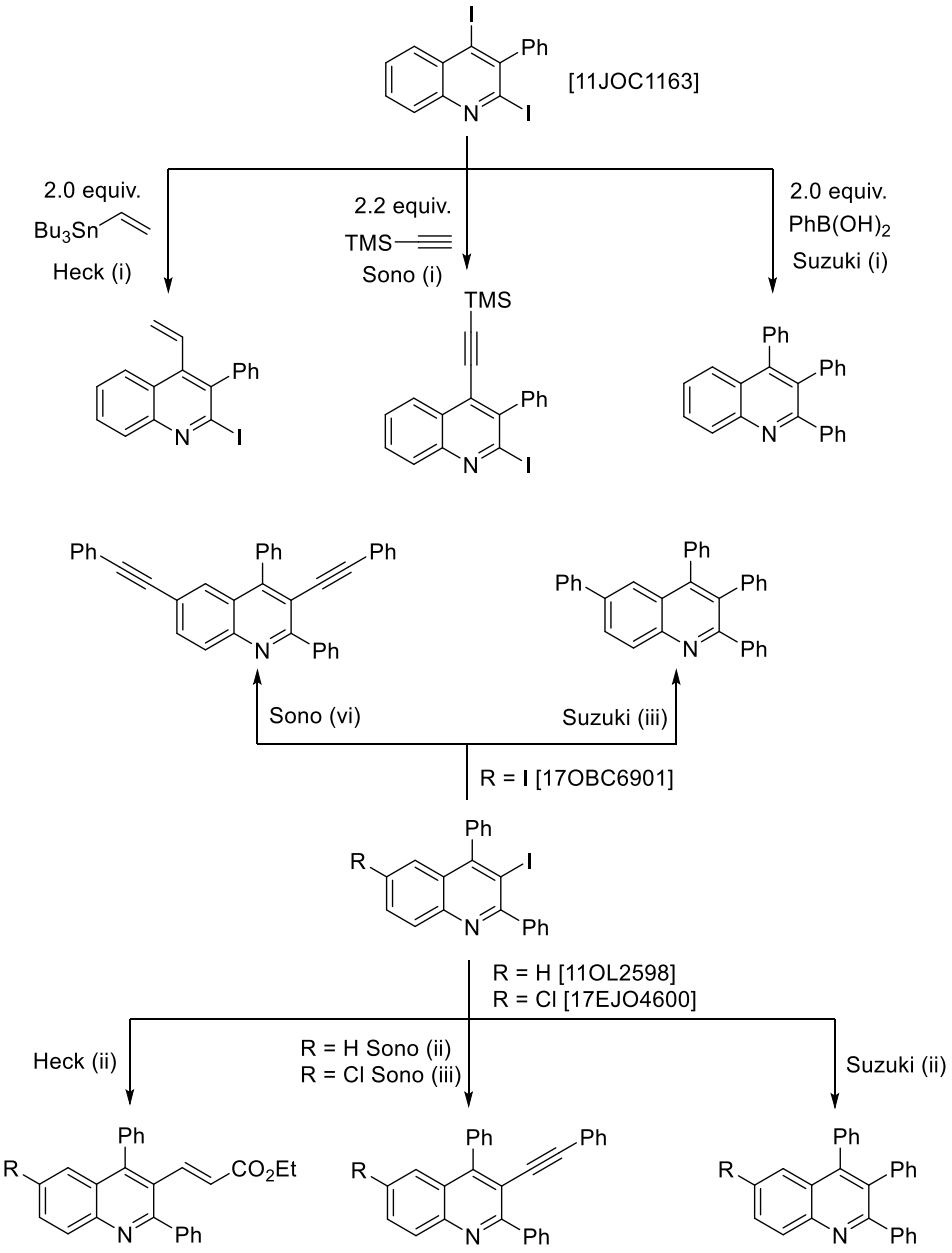
Scheme 4.28

Iodo-compounds are known to not react as successfully in the C-N forming reactions [09JA5766] in comparison to other halide substrates (bromides or chlorides). Buchwald and co-workers suggest the poor yields from aryl iodides in C-N bond formations is due to the iodide salt generation competing with the amine binding to the Pd(II) oxidative addition complex (**X**, Scheme 4.29) or iodide binding with the amino Pd(II) complex slowing the rate of reductive elimination (**Y**, Scheme 4.29). Of note is that these studies were carried out using different reactions conditions [09JA5766] to those described here. Therefore the use of an amide instead of an amine and the substrate being an iodo compound may be the reasons for the failure of $BocNH_2$ and *t*-$BuSONH_2$ to afford the corresponding amidation products (entries 3 and 7, Table 4.1); the scope and limitations of this reaction needs to be investigated further.



Scheme 4.29

Another simple way in which the 4-alkynyl-3-iodoquinoline structure could be functionalised or extended is by application in a Suzuki, Heck or Sonogashira coupling. Some examples of iodoquinolines subjected to these coupling reactions are shown in Scheme 4.30 [11JOC1163, 11OL2598, 17EJO4600, 17OBC6901, 18EJO1863]. Interestingly when 2,4-diiodo-3-phenylquinoline was subject to Heck or Sonogashira coupling conditions with excess alkene or acetylene (2.0 – 2.2 equiv.) the coupling would occur regioselectively at the 4-position [11JOC1163].



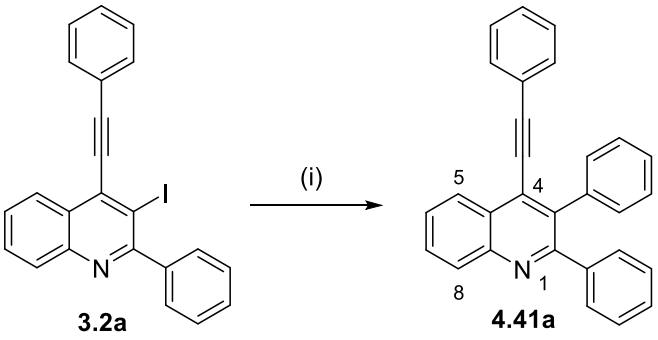
Heck reaction conditions = (i) $Pd(PPh_3)_4$ (5 mol %), MeCN, 100 °C; (ii) $Pd(OAc)_2$ (5 mol %), Bu_4NBr (1 equiv.), K_2CO_3, DMF, 80 °C, 3 equiv. ethyl acrylate

Sonogashira reaction conditions = (i) $PdCl_2(PPh_3)_2$ (1 mol %), CuI, Et_3N, 60 °C; (ii) $PdCl_2(PPh_3)_2$ (5 mol %), CuI, Et_3N, r.t., 1.3 equiv. phenylacetylene; (iii) $Pd(OAc)_2$ (2 mol %), DABCO, MeCN, 2.0 equiv. phenylacetylene, r.t.; (vi) $PdCl_2(PPh_3)_2$ (10 mol %), CuI, Na_2CO_3, DMF, 120 °C, 1.5 equiv. phenylacetylene

Suzuki reaction conditions = (i) $PdCl_2(PPh_3)_2$ (5 mol %), K_2CO_3, DMF/H_2O, 100 °C; (ii) $Pd(OAc)_2$ (5 mol %), Na_2CO_3, 1.3 equiv. $PhB(OH)_2$, DMF/H_2O, 100 °C; (iii) $Pd(PPh_3)_4$ (5 mol %), Na_2CO_3, 1.5 equiv. $PhB(OH)_2$, THF/H_2O, 70 °C

Scheme 4.30

3-Iodo-2-phenyl-4-(phenylethynyl)quinoline **3.2a** was coupled with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in a PhMe : EtOH mixture (50 : 50) and stirred at reflux for 22 h. After an aqueous work-up and purification by flash column chromatography (8% EtOAc – hexane) the 4-alkynyl-2,3,-diphenylquinoline **4.41a** was obtained as a white powder in 68% yield.



3.2a **4.41a**

(i) $Pd(PPh_3)_4$ (2.5 mol %), K_2CO_3 (2.4 equiv.), phenylboronic acid (2.3 equiv.), PhMe : EtOH, Δ, 22 h, N_2

Scheme 4.31

The 2,3-diphenyl-4-(phenylethynyl)quinoline **4.41a** was characterised by its ^1H and ^{13}C NMR spectra; the appearance of five extra aromatic protons corresponding to the new phenyl ring (^1H) as well as the disappearance of the C-3 quaternary carbon signal i.e. C-I (δ_C 102.29 ppm) were confirmative. The ^1H NMR spectrum of 2,3-diphenyl-4-(phenylethynyl)quinoline **4.41a** shows an upfield shift of all of the phenyl protons in comparison to those of the starting material **3.2a** (Figure 4.10).

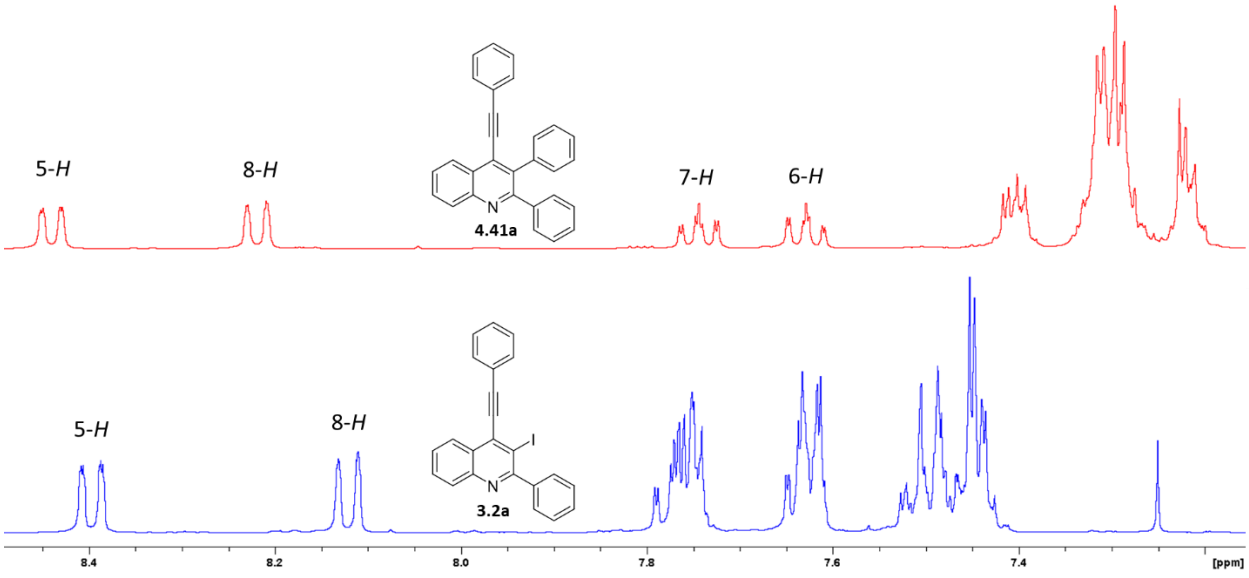
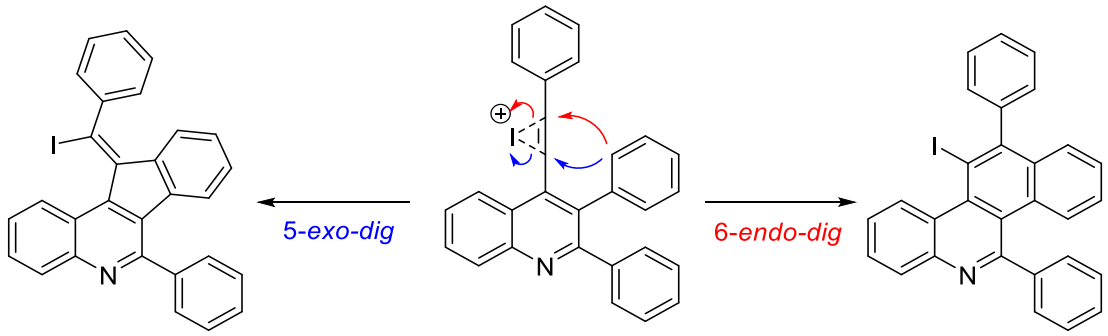


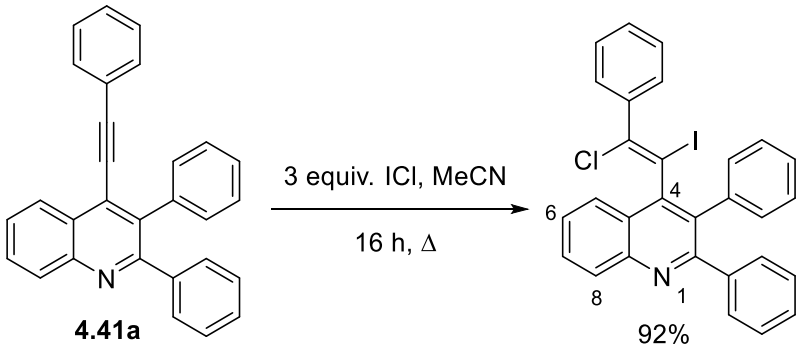
Figure 4.10 400 MHz ^1H NMR spectra; comparison of **3.2a** and **4.41a** in $CDCl_3$

It was envisaged that the alkyne moiety may undergo activation from treatment with an iodine electrophile thus rendering it susceptible to subsequent nucleophilic attack from the phenyl ring (Scheme 4.32), as observed for the cyclisation of 3,3-bis(phenylethynyl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide **2.59Ba** to 6-iodo-2-methyl-5-phenyl-6*a*-(phenylethynyl)-6*aH*-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide **2.66a-3**, Section 2.7, Scheme 2.71.



Scheme 4.32

Consequently, **4.41a** was dissolved in MeCN and following addition of 3 equiv. of ICl, the mixture was stirred at reflux overnight. After quenching the mixture with aqueous sodium thiosulfate, the resultant solid was washed with pentane. However the orange solid isolated was found to be neither of the two possible teracycles (Scheme 4.32) but the novel dihalogenated species **4.42a** (92% yield, Scheme 4.33). Confirmation of the presence of two halogen functions was established by HMRS that exhibited a molecular ion at *m/z* $[M+H]^+$ = 544.0314 corresponding to $C_{29}H_{19}{}^{35}ClIN$.



Scheme 4.33

Further confirmation that iodochlorination had occurred on the triple bond was derived from the upfield shift of the 5-*H* proton in comparison to the starting material (Figure 4.11). Assignment of the proton shift was determined by consideration of the 2D NMR data (HSQC) Figure 4.12 and with the aid of known ^{13}C shifts for other quinoline derivatives (see Section 3.1).

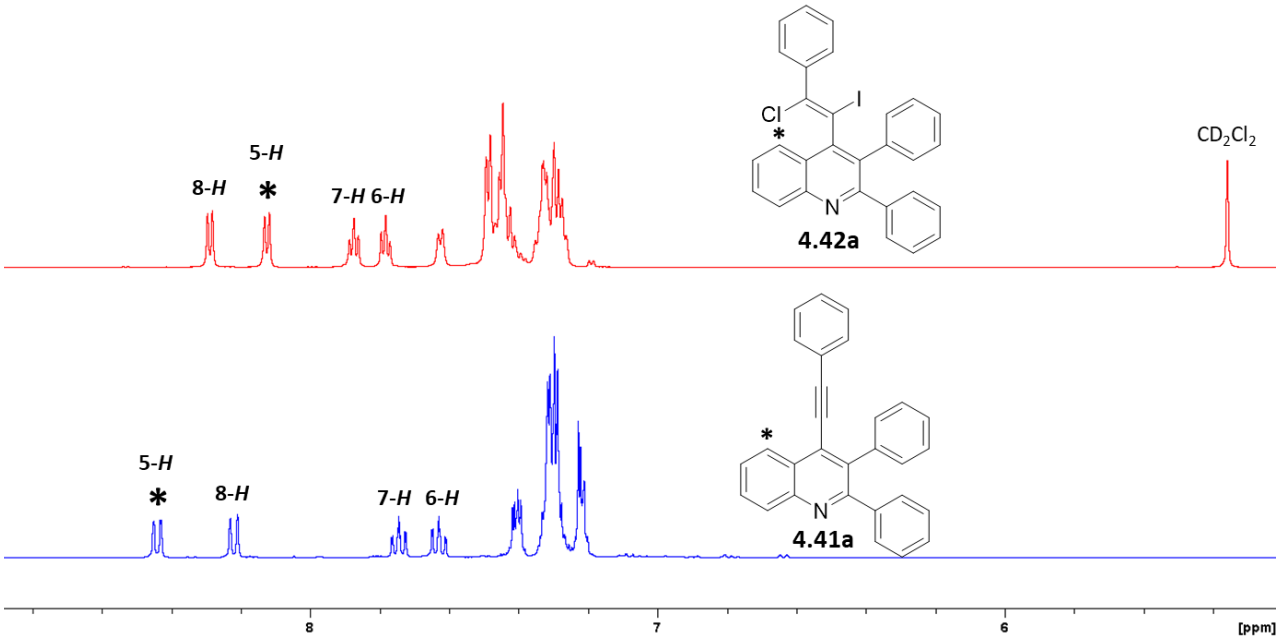


Figure 4.11 ^{1}H NMR spectra comparison of **4.41a** and **4.42a**

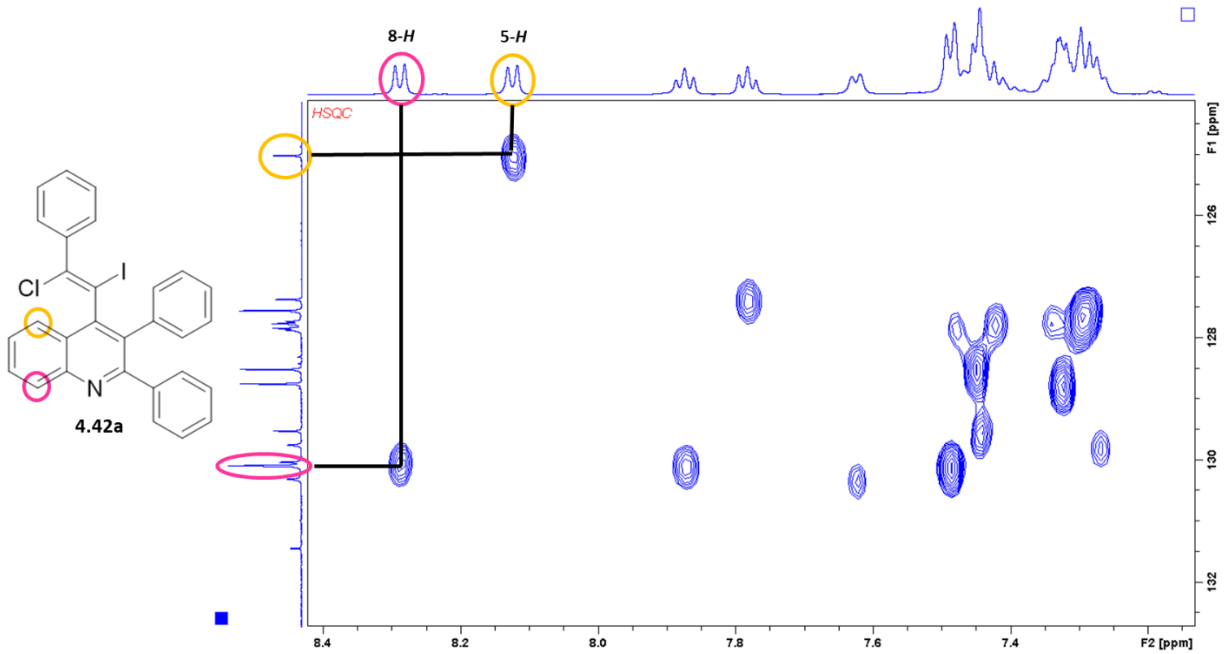
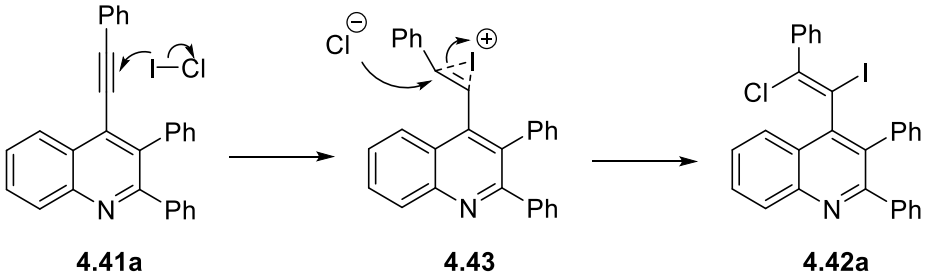


Figure 4.12 HSQC spectrum of **4.42a**

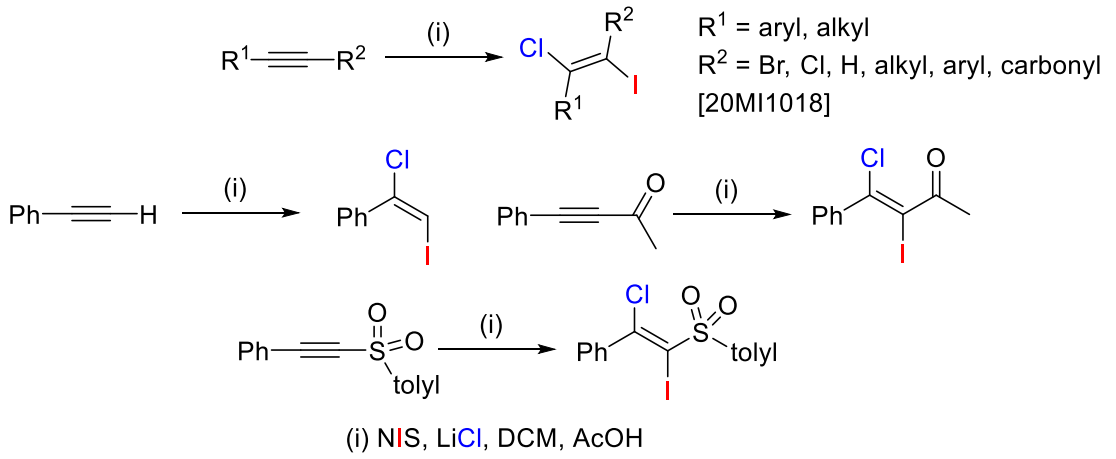
The *trans*-dihalo product will be formed in preference to the *cis* isomer due to the intermediacy of an iodonium intermediate **4.43**, which only enables attack of chloride on the opposite face (Scheme 4.34) [03JOC10175, 07MI1000]



4.41a **4.43** **4.42a**

Scheme 4.34

Recently Zeng *et al.* reported the regio- and stereoselective synthesis of dihaloalkenes from *in situ* generated ICl and various alkynes (Scheme 4.35) [20MI1018]. In all cases it was found that the *trans* isomer was the major or exclusive isomer obtained. The reason for the regioselectivity of the reaction was ascribed to addition of the chloride nucleophile to the most stabilised carbocation centre (neighbouring group stabilisation).

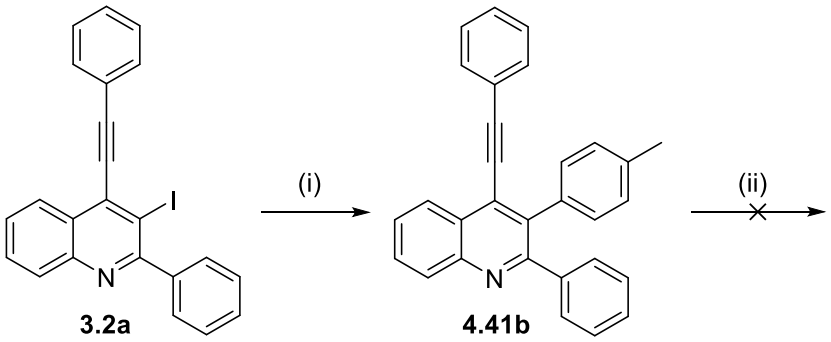


Scheme 4.35

In the case of **4.43** the most stable carbocation would be that adjacent to the phenyl ring, in comparison to the carbon adjacent to the quinoline ring which is electron deficient and therefore would exert a lesser stabilising effect. Consequently the structure is assigned as shown i.e. (*E*)-4-(2-chloro-1-iodo-2-phenylvinyl)-2,3-diphenylquinoline (Scheme 4.32). However, to fully ascertain the structure of **4.42a** and its regio- and stereochemistry a X-ray crystal structure would be required.

The results above clearly demonstrated the ease with which an iodonium ion can be generated from 4-alkynyl-2,3-diphenylquinoline **4.41a**. It was envisioned that the presence of a more electron rich 3-C aryl group may facilitate iodocarbocylisations shown in Scheme 4.32.

Accordingly, 4-tolylboronic acid was employed in the Suzuki coupling with **3.2a**, to give **4.41b** in a 70% yield (Scheme 4.36). The constitution of 2-phenyl-4-(phenylethynyl)-3-(*p*-tolyl)quinoline **4.41b** was confirmed by ^{1}H and ^{13}C NMR spectra and by HRMS that exhibited a molecular ion at *m/z* $[M+H]^+$ = 396.1739 corresponding to $C_{30}H_{21}N$. Addition of the methyl group in the *para* position of the aromatic ring should increase the overall electron density in the ring and thus facilitate the cyclisation (Scheme 4.32). Unfortunately, subsequent reaction with ICl in refluxing MeCN provided only unreacted starting material (Scheme 4.36). The reasons for this outcome are not clear and further work is required to understand the scope and limitations of this reaction.



3.2a **4.41b**

(i) $Pd(PPh_3)_4$ (2.5 mol %), K_2CO_3 (2.4 equiv.), $TolB(OH)_2$ (2.3 equiv.), PhMe : EtOH, Δ, 22 h, N_2; (ii) ICl (3 equiv.), MeCN, 24 h, Δ

Scheme 4.36

Chapter 5

Conclusions

Chapter 5 Conclusions

5.1 Chapter 2 Conclusions

- The synthesis of novel 3-(2-arenesulfonamidophenyl)penta-1,4-diyn-3-ols has been accomplished from addition of alkynyllithium reagents to methyl 2-(arenesulfonamido)benzoates in varying yields (11 – 90%). The electron density and thus nucleophilicity of the sulfonamide group could be attenuated by the nature of the arenesulfonyl function. Both electron rich and electron-deficient sulfonamides were prepared.
- The synthesis of novel 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols possessing unsymmetrical alkyne-terminal groups was readily accomplished in varying yields (28 – 88%) from the reaction of 3-aryl-1-(2-tosylamidophenyl)prop-2-yn-1-ones with alkynyllithiums or with HC≡CMgBr. The propynones could be accessed directly from the Weinreb amide, *N*-methoxy-*N*-methyl-2-(tosylamido)benzamide and an alkynyllithium reagent.
- The synthesis of *N*-arylsaccharins was achieved from a Chan-Lam-(Evans) coupling of arylboronic acids with saccharin. Subsequent addition of an alkynyllithium reagent resulted in an addition-ring opening-addition sequence giving access to the novel 1,5-disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols in varying yields (42 – 98%).
- Attempts to effect a base-mediated double desilylation of 1,5-bis(trimethylsilyl)-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol afforded, unexpectedly, a novel 3-ethynyl-2-methylene-1-tosylindolin-3-ol. A mechanism has been proposed to account for this transformation (Schemes 2.32 and 2.54)
    - This base-mediated 5-*exo*-*dig* ring closure was applicable to a range of 1-alkyl- or 1-aryl- 5-trimethylsilyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols as well as the 5-desilyl-derivatives. Both series of dialkynols provided high yields of 3-alkynyl-2-methylene-1-tosylindolin-3-ols and six examples were prepared.
    - The base-mediated dialkynol cyclisation was not applicable to internal 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols.

- Silver-catalysed cyclisation ($AgNO_3$ on silica) of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol underwent a 5-*exo*-*dig* cyclisation to the novel (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol in quantitative yield.
    - The stereochemistry of (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol was established by examination of 2D NMR spectra, primarily the NOESY spectrum.
    - A related, stereospecific 5-*exo*-*dig* cyclisation of 1,3-diphenyl-1-[2-(tosylamido)phenyl]prop-2-yn-1-ol with AgOAc to 2-benzylidene-3-phenyl-1-tosylindolin-3-ol has been reported by Chan and co-workers (Scheme 2.42) [12CEJ2666].
- Attempts to affect the cyclisation of other 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols with $AgNO_3$ proved unsuccessful.
- Treatment of 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols with silver(I) acetate brought about a 5-*exo*-*dig* cyclisation and subsequent isomerisation to afford the novel phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methanol in quantitative yield.
    - Exposure of 6-(2-tosylamidophenyl)undeca-4,7-diyn-6-ol to AgOAc initiated multiple reaction pathways. The major product was characterised as 1-[3-(pent-1-yn-1-yl)-1-tosyl-1*H*-indol-2-yl]butan-1-ol. The minor products were identified as the dehydration product (*E*)-2-but-1-en-1-yl-3-pentyn-1-yl-1-tosyl-1*H*-indole together with 4-pentyn-1-yl-2-propylquinoline from a 6-*endo*-*dig* pathway. All three products are novel.
    - However when the alkyne termini in 3-(2-tosylamidophenyl)penta-1,4-diyn-3-ols were substituted with TMS or *tert*-Bu groups, cyclisation did not procced to the expected 2-(α-hydroxyalkyl)indoles. Instead the (*Z*)-2-(trimethylsilylmethylene)- or (*Z*)-2(2,2-dimethylpropylidene)- derivatives of the 3-alkynyl-1-tosylindolin-3-ols were isolated. A plausible mechanism for these conversions has been postulated (Scheme 2.55). It is proposed that the presence of bulky groups hinders attack of water on the vinylic carbocation intermediate.
- Indium(III) triflate induced a remarkable and unexpected cascade cyclisation of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol to the novel the 2,4-diphenyl-1-tosyl-4,5-dihydrofuro[2,3-*c*]quinoline. It is proposed that an initial Meyer-Schuster rearrangement is followed by a 5-*exo*-*dig* cyclisation of an enynone from which a 6-

endo-trig ring closure ultimately ensues. Optimisation studies revealed that yields were maximised with 5 mol % $In(OTf)_3$in DCM at r.t.

- This novel cyclisation pathway was only applicable to 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol and none of the other 3-(2-tosylaminophenyl)penta-1,4-diyn-3-ol derivatives provided analogous, isolatable products.

- Treatment of 1,5-disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols with indium(III) triflate initiated dehydration (*via* an E_1 pathway) and subsequent cyclisation to afford novel 2-aryl-3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides in fair to high yields (37 – 100%). This cyclodehydration reaction could also be accomplished, but in lower yields, by treatment with iodine monochloride.
  - Iodine monochloride also induced cyclisation of 1,5-disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols to a novel 1,2-benzisothiazolo[2,3-*a*]quinoline that was characterised by X-ray crystallography. It was found that 2-aryl-3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides were intermediates of the reaction and a plausible mechanism for this unusual iodocyclisation reaction has been described (Scheme 2.71).
  - 1,2-Benzisothiazolo[2,3-*a*]quinolines could be generated from both a stepwise manner utilising preformed 2-aryl-3,3-di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides and in a one-pot domino reaction from 1,5-disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols by treatment with iodine monochloride.

5.2 Chapter 3 Conclusions

- Treatment of 1,5-diphenyl-3-(2-tosylamidophenyl)penta-1,4-diyn-3-ol with molecular iodine in refluxing MeOH initiates cyclisation *via* a 6-*endo*-*dig* pathway to afford the novel 3-iodo-2-phenyl-4-(phenylethynyl)quinoline in 25% yield.
    - Optimisation studies revealed that 2 equiv. ICl in MeCN at r.t. gave the best results providing the 3-iodoquinoline in 60% yield. (Table 3.1).
    - However when 6-(2-*p*-tosylamidophenyl)undeca-4,7-diyn-6-ol was treated with ICl in MeCN the reaction provided complex mixtures. Therefore, for the alkyl-terminated dialkynol derivatives molecular iodine (3 equiv.) in refluxing MeOH was used.
- Changing the electron density of the sulfonamide nitrogen affected the reaction rate and yields of the 4-alkynyl-3-iodo-2-substituted quinolines.
    - With an electron withdrawing 4-nitrophenylsulfonyl group, lower yields and slower reactions times were observed. In contrast, the more electron donating (4-methoxyphenylsulfonyl group provided higher yields of products and faster reaction rates were achieved.
- 3-(2-Tosylamidophenyl)penta-1,4-diyn-3-ols possessing unsymmetrical alkyne-terminal groups also underwent the 6-*endo*-*dig* cyclisation to 4-alkynyl-3-iodoquinolines, however only poor yields were achieved and many reactions failed to give any tractable products.
- 1,5-Disubstituted-3-[2-(*N*-arylsulfamoyl)phenyl]penta-1,4-diyn-3-ols underwent a silver-catalysed 6-*exo*-*dig* cyclisation to (*Z*)-3-alkylidene-4-alkynyl-2-aryl- and (*Z*)-4-alkynyl-2-aryl-3-arylidene- derivatives of 1,2-benzothiazin-4-ol 1,1-dioxides. Some sixteen examples were prepared in fair to excellent yields (30 – 96%). This reaction represents a novel means to assemble the 1,2-benzothiazine system.
    - The reaction was stereospecific giving the (*Z*)-isomer exclusively, the stereochemistry of the products was established from the 1D and 2D NMR (^{1}H and NOESY) spectra.
    - 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide and 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(thiophen-3-yl)benzenesulfonamide also cyclised

via a 7-*endo*-*dig* pathway to yield small amounts of the novel 1,2-benzothiazepine 1,1-dioxides (7% and 11% respectively).

5.3 Chapter 4 Conclusions

- A variety of reactions with 3-ethynyl-2-methylene-1-tosylindolin-3-ol (dehydration and interception with a nucleophile, cyclocondensation with 2-naphthol, 1,3-AAI and oxidation reactions) to extend the functionality of the ring system gave no tractable products (Scheme 4.5).
    - When (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol was treated with acetylacetone under acidic conditions facile dehydration and interception with the nucleophilic enolate tautomer was achieved in quantitative yield to afford 3-{phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methyl}pentane-2,4-dione.
    - However when the indole-linked 1,3-dione was subjected to basic conditions, cyclisation did not ensue. External electrophilic π-bond activators – Ag(I), In(III) and sources of I^+ – also failed to initiate cyclisation. Further work is needed to establish the scope and limitations of the reaction (Scheme 4.10).
- Palladium(0)catalysed coupling of 4-alkynyl-3-iodquinolines with various aniline derivatives and with benzylamine afforded both the amination [4-(alkynyl)quinolin-3-amine] and hydroamination (pyrrolo[2,3-*c*]quinoline) products. With many of the couplings affording the former, 4-(alkynyl)quinolin-3-amines as the major product. Formation of the pyrrolo[2,4-*c*]quinolines is of interest as it enables access to novel analogues of the biologically active marinoquinolines.
    - The Pd-medaiated amination reaction was also attempted with ammonia surrogates (*tert*-butyl carbamate and *tert*-butyl sulfinamide) but only starting material was isolated from these reactions.
    - In a separate reaction *N*-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine with $PdCl_2$ in DMF effected the hydroamination cyclisation to 3-benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline in 60% yield.
    - Attempts to deprotect the 3-benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline to achieve access to the *N*-unsubstituted 2,4-diphenyl-3*H*-pyrrolo[2,3-c]quinoline by dealkylation with excess $AlCl_3$ provided futile and only starting material was isolated.
    - 4-Pentyn-1-yl-2-propylquinoline did not afford any amination-hydroamination products, only starting material was isolated.

Chapter 6

Experimental

Chapter 6 Experimental

6.1 Equipments and Reagents

Unless otherwise stated, reagents were used as supplied. Reagents were purchased from Alfa Aesar, Fluorochem, TCI, Fisher and Sigma Aldrich.

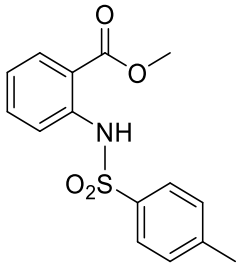
NMR spectra were recorded on a Bruker Avance 400 spectrometer (^{1}H 400 MHz and ^{13}C 100 MHz), unless otherwise stated. Coupling constants are given in Hz. Accurate mass measurements were obtained from the IPOS Mass Spectrometry Service at The University of Huddersfield. Single crystal studies were recorded on a Bruker D8 Venture with Dual IμS Microfocus Sources using Mo and/or Cu radiation. The temperature of data collection was 150 K.

Melting points were determined in capillary tubes, using a Stuart SMP10 melting point apparatus, and are uncorrected. FT-IR spectra were recorded on a Nicolet 380 Spectrum Spotlight system, equipped with a diamond probe ATR attachment (neat sample). TLC was performed on Merck TLC Aluminium sheets, silica gel 60 F254 using a range of eluent systems of differing polarity. Flash Chromatographic separations were performed on Aldrich, 35-70 μ, 60 Å silica gel, according to the literature procedure [78JOC2923]. When stated flash column chromatography separations were performed using Biotage® Isolera 4 Automated Purification System equipped with Biotage® Snap Ultra Biotage® HP-Sphere™ 25 μm cartridges.

6.2 Chapter 2.0 Experimental

6.2.1 Synthesis of 2-Sulfonamido- Benzoic Acid Derivatives

Synthesis of methyl 2-[(4-methylphenyl)sulfonamido]benzoate (2.4a)

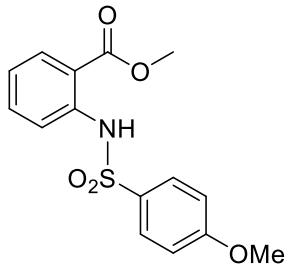


Under an inert (N_2) atmosphere methyl 2-aminobenzoate (9.71 mL, 75.0 mmol, 1.0 equiv.) was dissolved in DCM (75 mL). Pyridine (7.28 mL, 90.0 mmol, 1.2 equiv.) was added dropwise over 10 minutes and the solution stirred for 60 minutes. Toluene-4-sulfonyl chloride (17.2 g, 90.0 mmol, 1.2 equiv.) dissolved in DCM (100 mL) was added dropwise over 10 minutes and the reaction mixture was stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 100 mL). The organic phase was separated, washed with water and brine, dried (Na_2SO_4) and evaporated to give white crystals. The crude material was recrystallised from MeOH to give the title compound as white crystals (18.6 g, 81%) m.p. 113 – 114 °C (lit. m.p. 113 °C [04H(63)1113]).

δ_H ($CDCl_3$) 10.62 (1H, s, N*H*), 7.91 (1H, dd, *J* = 8.0, 1.6 Hz, 2-*H*), 7.74 (2H, d, *J* = 8.2 Hz, *o*-Ar-H), 7.68 (1H, dd, *J* = 8.0, 1.6 Hz, 5-*H*), 7.47 – 7.42 (1H, m, 4-*H*), 7.22 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 7.05 – 7.01 (1H, m, 3-*H*), 3.88 (3H, s, CO_2*Me*), 2.36 (3H, s, Ar-*Me*). δ_c 168.31 (C=O), 143.93 ($_q$C), 140.52 ($_q$C), 136.43 ($_q$C), 134.50 (CH), 131.17 (CH), 129.64 (CH), 127.29 (CH), 122.83 (CH), 118.97 (CH), 115.81 ($_q$C), 52.48 (CH_3), 21.54 (CH_3).

ν_{max}/cm^{-1}: 3131 b (NH), 1687 s (CO_2R), 1587 s (C=C), 1492 s (CH_3), 1316 s (SO_2), 1256 s (CO_2R), 1088 s (SO_2).

Synthesis of methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (2.4b)



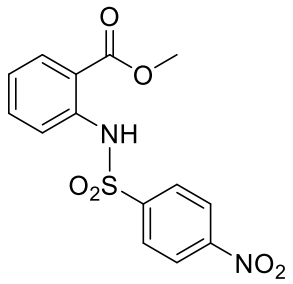
Under an inert (N_2) atmosphere methyl 2-aminobenzoate (3.15 mL, 24.2 mmol, 1.0 equiv.) was dissolved in chloroform (20 mL). Pyridine (5.85 mL, 72.6 mmol, 3.0 equiv.) was added dropwise over 10 minutes and the solution stirred for 60 minutes. 4-Methoxybenzenesulfonyl chloride (5.00 g, 24.2 mmol, 1.0 equiv.) dissolved in chloroform (30 mL) was added dropwise over 15 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with chloroform (approx. 30 mL). The organic phase was separated, washed with water and brine, dried (Na_2SO_4) and evaporated to give a light red oil. On standing the oil crystallised and subsequent recrystallisation from

EtOH to give the title compound as white crystals (4.85 g, 62%) m.p. 80 – 82 °C (lit. m.p. 81 – 85 °C [75USP3920687]).

δ_H ($CDCl_3$) 10.58 (1H, s, N*H*), 7.91 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.81 (2H, m, *o*-Ar-*H*), 7.68 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.47 – 7.43 (1H, m, 4-*H*), 7.05 – 7.01 (1H, m, 3-*H*), 6.90 – 6.87 (2H, m, *m*-Ar-*H*), 3.88 (3H, s, CO_2*Me*), 3.82 (3H, s, O-*Me*). δ_c 168.29 (C=O), 163.11 ($_q$C), 140.62 ($_q$C), 134.49 (CH), 131.16 (CH), 131.01 (CH), 129.47 (CH), 122.76 (CH), 119.02 (CH), 115.82 ($_q$C), 114.15 (CH), 55.58 (CH_3), 52.47 (CH_3).

ν_{max}/cm^{-1}: 3137 b (NH), 1682 s (CO_2R), 1588 s (C=C), 1490 s (CH_3), 1255 s (CO_2R), 1152 s (SO_2), 1087 s (SO_2).

Synthesis of methyl 2-[(4-nitrophenyl)sulfonamido]benzoate (2.4c)

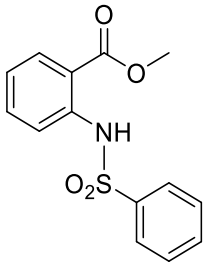


Under an inert (N_2) atmosphere methyl 2-aminobenzoate (2.70 mL, 21.4 mmol, 1.0 equiv.) was dissolved in DCM (30 mL). Pyridine (1.70 mL, 21.4 mmol, 1.0 equiv.) was added dropwise over 10 minutes and the solution was stirred for 60 minutes. 4-Nitrobenzenesulfonyl chloride (5.00 g, 21.4 mmol, 1.0 equiv.) dissolved in DCM (30 mL) was added dropwise over 20 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 30 mL). The organic phase was separated, washed with water and brine, dried (Na_2SO_4) and evaporated to give a red solid. The crude material was recrystallised from EtOH to give the title compound as yellow needles (4.97 g, 71%) m.p. 152 – 153 °C (lit. m.p. 154.9 – 155.7 °C [13MOL6883]).

δ_H ($CDCl_3$) 10.82 (1H, s, N*H*), 8.29 – 8.25 (2H, m, *m*-Ar-*H*), 8.05 – 8.01 (2H, m, *o*-Ar-*H*), 7.95 (1H, dd, *J* = 8.0, 1.5 Hz, 2-*H*), 7.73 (1H, dd, *J* = 8.0, 1.5 Hz, 5-*H*), 7.53 – 7.49 (1H, m, 4-*H*), 7.13 – 7.09 (1H, m, 3-*H*), 3.88 (3H, s, CO_2*Me*). δ_c 168.35 (C=O), 150.24 ($_q$C), 145.03 ($_q$C), 139.55 ($_q$C), 134.83 (CH), 131.48 (CH), 128.55 (CH), 124.27 (CH), 123.90 (CH), 119.36 (CH), 116.26 ($_q$C), 52.73 (CH_3).

ν_{max}/cm^{-1}: 3108 b (NH), 1698 s (CO_2R), 1600 s (C=C), 1586 w (NO_2), 1526 s (CH_3), 1349 s (NO_2), 1313 s (SO_2), 1265 s (CO_2R), 1088 s (SO_2).

Synthesis of methyl 2-(phenylsulfonamido)benzoate (2.4d)

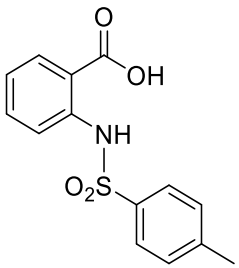


Under an inert (N_2) atmosphere methyl 2-aminobenzoate (9.80 mL, 75.0 mmol, 1.0 equiv.) was dissolved in DCM (75 mL). Pyridine (18.2 mL, 225 mmol, 3.0 equiv.) was added dropwise over 10 minutes and solution stirred for 60 minutes. Benzenesulfonyl chloride (12.5 mL, 97.5 mmol, 1.3 equiv.) dissolved in DCM (40 mL) was added dropwise over 5 minutes and stirred at r.t. overnight. After this time the mixture was quenched with 2M HCl, diluted with DCM (approx. 100 mL). The organic phase was separated, washed with water and brine, dried (Na_2SO_4) and evaporated to give white crystals. The crude material was recrystallised from MeOH to give the title compound as white crystals (15.3 g, 70%) m.p. 105 – 106 °C (lit. m.p. not quoted [06BMC5562]).

δ_H ($CDCl_3$) 10.65 (1H, s, N*H*), 7.91 (2H, dd, *J* = 8.0, 1.4 Hz, 2-*H*), 7.86 – 7.84 (2H, m, *o*-Ar-*H*) 7.70 (1H, app. d, 5-*H*), 7.75 – 7.41 (4H, m, Ar-*H*), 7.06 – 7.02 (1H, m, 3-*H*), 3.87 (3H, s, CO_2*Me*). δ_c 168.29 (C=O), 140.36 ($_qC$), 139.36 ($_qC$), 134.53 (CH), 133.03 (CH), 131.17 (CH), 129.01 (CH), 127.25 (CH), 123.03 (CH), 119.22 (CH), 116.00 ($_qC$), 52.51 (CH_3).

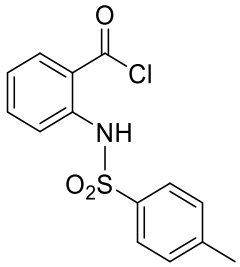
ν_{max}/cm^{-1}: 3157 b (NH), 1681 s (CO_2R), 1582 s (C=C), 1489 s (CH_3), 1315 s (SO_2), 1265 s (CO_2R), 1087 s (SO_2).

Synthesis of 2-[(4-methylphenyl)sulfonamide]benzoic acid (2.12)



Anthranilic acid (5.00 g, 36.46 mmol, 1 equiv.) and toluene-4-sulfonyl chloride (8.32 g, 43.6 mmol, 1.2 equiv.) was suspended in water (400 mL). To this NaOH (1.50 g, 37.5 mmol, 1.0 equiv.) was added portion wise over 10 minutes and the solution was stirred at r.t. overnight. After this time the mixture was filtered and washed with water, the crude material was used without further purification (8.80 g, 83%) m.p. 200 – 202 °C (literature m.p. 112 °C. [07JME1219]).

Synthesis of 2-[(4-methylphenyl)sulfonamide]benzoyl chloride (2.13)



Under an inert (N_2) atmosphere 2-[(4-methylphenyl)sulfonamide]benzoic acid (8.72 g, 29.9 mmol, 1.0 equiv) was suspended in anhydrous DCM (100 mL). Oxalyl chloride (3.80 mL, 44.3 mmol, 1.5 equiv) was added dropwise to the cold solution (0 °C), a catalytic amount of DMF was then added to the solution. The solution was stirred at r.t. for 2 h. After this time the mixture was evaporated to give the title compound as an off white solid. The crude material was used without further purification (8.30 g, 90%) m.p. 115 – 117 °C (literature m.p. 117 – 118 °C. [14MI435]).

6.2.2 Synthesis of *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

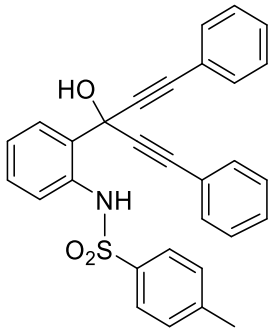
General Method for Synthesis of *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

Method **A**: Under an inert (N_2) atmosphere *n*-BuLi (3.5 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 3.5 equiv.) in anhydrous THF (approx. 100 mL). A solution of the appropriate sulfonamide (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 60 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give

the crude material which was purified by recrystallisation or by flash column chromatography. The following compounds were synthesised by this method.

Method **B**: Under an inert (N_2) atmosphere 1-bromo-1-propene (X mmol, 3.5 equiv.) was added to a cold (-75 °C) solution of LDA 3.5 equiv. (DIPA, 2.1 equiv. and *n*-BuLi, 3.5 equiv.) in anhydrous THF (approx. 50 mL) and was stirred for 3 h. A solution of the appropriate sulfonamide (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 30 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give the crude material which was purified by recrystallisation or by flash column chromatography. The following compounds were synthesised by this method.

_N_-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.5a)



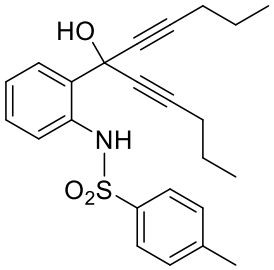
Using Method **A** from phenylacetylene (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (19.7 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (7.99 g, 85%) m.p. 137 – 138 °C; HRMS found $[M+Na]^+$ = 500.1287; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H ($CDCl_3$) 8.66 (1H, s, N*H*), 7.91 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.79 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.60 (1H, app. d, 5-*H*), 7.53 – 7.51 (4H, m, Ph-*H*), 7.41 – 7.33 (6H, m, Ph-*H*), 7.30 – 7.27* (1H, m, 3-*H*), 7.08 – 7.01 (3H, m, Ar-*H*), 3.34 (1H, s, O*H*), 2.28 (3H, s, Ar-*Me*). δ_c 143.63 ($_q$C), 136.89 ($_q$C), 135.93 ($_q$C), 132.01 (CH), 130.05 (CH), 129.52 (CH), 129.28 (CH), 128.41 (CH), 128.06 ($_q$C), 127.89 (CH), 127.52 (CH), 123.24 (CH), 121.42 ($_q$C), 119.23 (CH), 87.01 ($_q$C), 86.87 ($_q$C), 66.27 ($_q$C), 21.52 (CH_3).

ν_{max}/cm^{-1}: 3409 b (OH), 3282 w (NH), 2981 w (Ar-H), 1583 s (C=C), 1488 s (CH_3), 1326 s (SO_2), 1087 s (R-OH), 1012 s (SO_2).

*Overlapping with $CDCl_3$ signal

_N_-[2-(6-Hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonamide (2.5b)

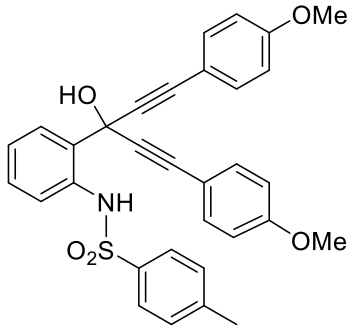


Using Method **A** from 1-pentyne (23.0 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (6.57 mmol) to give a yellow oil. The product crystallised on standing. The crude material was then recrystallised from hexane – EtOAc to give the title compound as a beige powder (2.09 g, 78%) m.p. 88 – 89 °C; HRMS found $[M+Na]^+$ = 432.1589; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 432.1589.

δ_H ($CDCl_3$) 8.51 (1H, s, N*H*), 7.81 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.50 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.24 – 7.19 (3H, m, Ar-*H*), 7.00 (1H, app. t, 3-*H*), 2.80 (1H, s, O*H*), 2.37 (3H, s, Ar-*Me*), 2.26 (4H, t, *J* = 7.3 Hz, CH_2), 1.59 (4H, sxt, *J* = 7.3 Hz, CH_2), 1.00 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 143.60 ($_q$C), 137.18 ($_q$C), 135.74 ($_q$C), 129.64 (CH), 129.53 (CH), 128.99 ($_q$C), 127.64 (CH), 127.48 (CH), 123.07 (CH), 119.20 (CH), 87.79 ($_q$C), 79.40 ($_q$C), 65.36 ($_q$C), 21.71 (CH_2), 21.55 (CH_3), 20.82 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3400 b (OH), 3285 m (NH), 2963 w (Ar-H), 2932 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 1588 s (C=C), 1492 s (CH_2), 1456 s (CH_3), 1333 s (SO_2), 1184 w (R-OH), 1090 s (SO_2).

***N*-{2-[3-Hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.5c)**



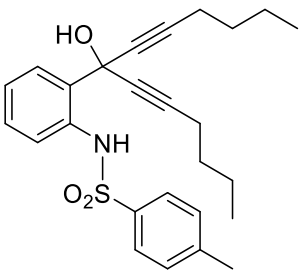
Using Method **A** from 1-ethynyl-4-methoxybenzene (34.5 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (9.86 mmol) to give the title compound as a golden powder (4.77 g, 90%) m.p. 132 – 134 °C; HRMS found $[M+Na]^+$ = 560.1491; $C_{32}H_{27}NO_5SNa$ $[M+Na]^+$ requires = 560.1502.

δ_H ($CDCl_3$) 8.68 (1H, s, N*H*), 7.90 (1H, dd, *J* = 7.9, 1.4 Hz, 2-*H*), 7.79 (2H, d, *J* = 8.3 Hz, Ar-*H*), 7.56 (1H, dd, *J* = 7.9, 1.4 Hz, 5-*H*), 7.46 (4H, d, *J* = 8.8 Hz, Ar-*H*), 7.28 – 7.24* (1H, m, 4-*H*), 7.07 – 7.03 (3H, m, Ar-*H,* 3-*H*), 6.87 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.83 (6H, s, O-*Me*), 2.30 (3H, s, Ar-*Me*). δ_c 160.28 ($_q$C), 143.58 ($_q$C), 136.94 ($_q$C), 133.59 (CH), 133.57 [2 X C ($_q$C)(CH)], 129.88 (CH), 129.53 (CH), 127.85 ($_q$C), 127.55 (CH), 123.17 (CH), 119.14 (CH), 114.02 (CH), 113.50 ($_q$C), 86.85 ($_q$C), 86.00 ($_q$C), 66.27 ($_q$C), 55.36 (CH_3), 21.54 (CH_3).

ν_{max}/cm^{-1}: 3383 b (OH), 3273 w (NH), 2228 s (C≡C), 1604 s (C=C), 1399 w (CH_3), 1307 w (SO_2), 1174 s (R-OH), 1154 s (SO_2).

*Overlapping with $CDCl_3$ signal

***N*-[2-(7-Hydroxytrideca-5,8-diyn-7-yl)phenyl]-4-methylbenzenesulfonamide (2.5d)**



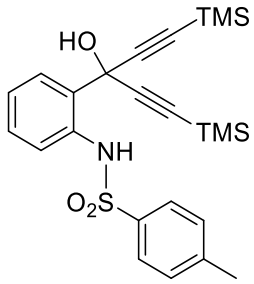
Using Method **A** from 1-hexyne (69.0 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (19.7 mmol) to give the title compound as off white

crystals (7.71 g, 89%) m.p. 80 – 82 °C; HRMS found $[M+Na]^+$ = 460.1926; $C_{26}H_{31}NO_3SNa$ $[M+Na]^+$ requires = 460.1917.

δ_H ($CDCl_3$) 8.54 (1H, s, N*H*), 7.81 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.50 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.24 – 7.19 (3H, m, Ar-*H*), 7.00 (1H, app. t, 3-*H*), 2.80 (1H, s, O*H*), 2.37 (3H, s, Ar-*Me*), 2.26 (4H, t, *J* = 7.3 Hz, CH_2), 1.59 (4H, sxt, *J* = 7.3 Hz, CH_2), 1.00 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 143.60 ($_q$C), 137.18 ($_q$C), 135.74 ($_q$C), 129.64 (CH), 129.53 (CH), 128.99 ($_q$C), 127.64 (CH), 127.48 (CH), 123.07 (CH), 119.20 (CH), 87.79 ($_q$C), 79.40 ($_q$C), 65.36 ($_q$C), 21.71 (CH_2), 21.55 (CH_3), 20.82 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 2956 m (Ar-H), 2930 m (CH_2, CH_3), 2871 m (CH_2, CH_3), 1599 s (C=C), 1494 w (CH_2), 1456 w (CH_3), 1379 w (SO_2), 1158 s (R-OH), 1008 s (SO_2).

_N_-{2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.5e)



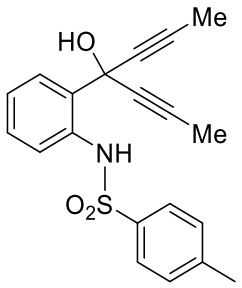
Using Method **A** from (trimethylsilyl)acetylene (34.6 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (9.89 mmol) to give a red oil. The product crystallised on standing. The crude material was purified by flash column chromatography (30% EtOAc – hexane) to give the title compound as an off white powder (1.80 g, 39%) m.p. 138 – 140 °C decomp; HRMS found $[M+Na]^+$ = 463.1304; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 463.1298.

δ_H ($CDCl_3$) 8.34 (1H, s, N*H*), 7.82 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.80 (1H, dd, *J* = 8.0, 1.3 Hz, 2-*H*), 7.41 (1H, app. d, 5-*H*), 7.25 – 7.20* (3H, m, Ar-*H*), 7.02 (1H, app. t, 3-*H*), 2.38 (3H, s, Ar-*Me*), 0.24 (18H, s, Si-*Me*$_3$). δ_c 143.71 ($_q$C), 137.17 ($_q$C), 135.81 ($_q$C), 129.97 (CH), 129.63 (CH), 127.86 (CH), 127.68 ($_q$C), 127.51 (CH), 123.23 (CH), 119.53 (CH), 102.21 ($_q$C), 92.62 ($_q$C), 65.33 ($_q$C), 21.57 (CH_3), -0.44 (Si-Me_3).

ν_{max}/cm^{-1}: 3373 b (OH), 3285 m (NH), 2962 w (CH_3), 1586 s (C=C), 1494 s (CH_3), 1325 s (SO_2), 1149 s (R-OH), 1090 s (SO_2).

*Overlapping with $CDCl_3$ signal

_N_-[2-(4-Hydroxyhepta-2,5-diyn-4-yl)phenyl]-4-methylbenzenesulfonamide (2.5g)

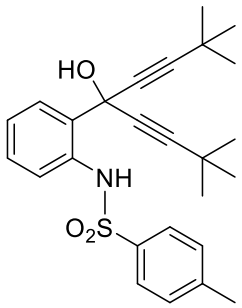


Using Method **B** from 1-bromo-1-propene (22.9 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (6.55 mmol) to give the title compound as a white powder (0.36 g, 16%) m.p. 140 °C decomp; HRMS found $[M+Na]^+$ = 376.0973; $C_{20}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 376.0978.

δ_H ($CDCl_3$) 8.51 (1H, s, N*H*), 7.81 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.75 (1H, dd, *J* = 7.9, 1.4 Hz, 2-*H*), 7.52 (1H, app. d, 5-*H*), 7.24 – 7.20 (3H, m, *m*-Ar-*H,* 4-*H*), 7.01 (1H, app. t, 3-*H*), 2.37 (3H, s, Ar-*Me*), 1.92 (6H, s, *Me*). δ_c 143.64 ($_qC$), 137.20 ($_qC$), 135.73 ($_qC$), 129.69 (CH), 129.53 (CH), 128.96 ($_qC$), 127.65 (CH), 127.48 (CH), 123.16 (CH), 119.31 (CH), 83.56 ($_qC$), 78.31 ($_qC$), 65.40 ($_qC$), 21.55 (CH_3), 3.91 (CH_3).

ν_{max}/cm^{-1}: 3392 b (OH), 3244 m (NH), 2921 w (CH_3), 1597 s (C=C), 1406 w (CH_3), 1319 s (SO_2), 1191 s (R-OH), 1152 s (SO_2).

_N_-[2-(5-Hydroxy-2,2,8,8-tetramethylnona-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.5j)



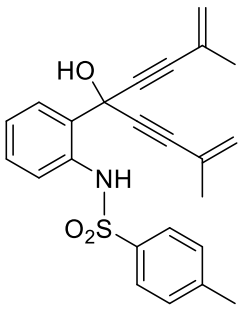
Using Method **A** from 3,3-dimethyl-1-butyne (5.74 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (1.64 mmol) to give the title compound as a white

solid (0.56 g, 79%) m.p. 138 – 140 °C decomp; HRMS found $[M+Na]^+$ = 460.1915; $C_{26}H_{31}NO_3SNa$ $[M+Na]^+$ requires = 460.1917.

δ_H ($CDCl_3$) 8.50 (1H, s, N*H*), 7.82 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.75 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.40 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.24 – 7.17 (3H, m, *m*-Ar-*H,* 4-*H*), 7.00 (1H, td, *J* = 7.9, 1.5 Hz, 3-*H*), 2.82 (1H, s, O*H*), 2.37 (3H, s, Ar-*Me*), 1.28 (18H, s, *Me*$_3$). δ_c 143.61 ($_q$C), 137.33 ($_q$C), 135.78 ($_q$C), 129.61 (CH), 129.55 (CH), 129.21 ($_q$C), 127.60 (CH), 127.45 (CH), 123.01 (CH), 119.22 (CH), 95.54 ($_q$C), 78.00 ($_q$C), 64.98 ($_q$C), 30.50 (CH_3), 27.60 ($_q$C), 21.56 (CH_3).

ν_{max}/cm^{-1}: 3409 b (OH), 3263 m (NH), 2964 m (CH_3), 2866 w (Ar-H), 2240 w (C≡C), 1599 s (C=C), 1400 w (CH_3), 1335 s (SO_2), 1158 s (R-OH), 1121 s (SO_2).

_N_-[2-(5-Hydroxy-2,8-dimethylnona-1,8-dien-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.5k)

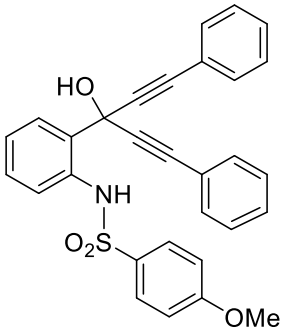


Using Method **A** from 2-methyl-1-buten-3-yne (11.5 mmol) and methyl 2-[(4-methylphenyl)sulfonamido]benzoate (3.27 mmol) to give the title compound as a yellow solid (0.86 g, 65%) m.p. 138 – 139 °C; HRMS found $[M+K]^+$ = 444.1368; $C_{24}H_{23}NO_3SK$ $[M+K]^+$ requires = 444.1030.

δ_H ($CDCl_3$) 8.49 (1H, s, N*H*), 7.85 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.49 (1H, app. d, 5-*H*), 7.27 – 7.23 (3H, m, *m*-Ar-*H,* 4-*H*), 7.04 (1H, app. t, 3-*H*), 5.47 (2H, s, C*H*$_2$), 5.39 (2H, s, C*H*$_2$), 2.39 (3H, s, Ar-*Me*), 1.96 (6H, s, *Me*). δ_c 143.70 ($_q$C), 137.04 ($_q$C), 135.84 ($_q$C), 129.92 (CH), 129.62 (CH), 128.04 ($_q$C), 127.73 (CH), 127.54 (CH), 127.30 (CH), 125.47 ($_q$C), 124.18 (CH_2), 123.12 (CH), 119.13 (CH), 87.88 ($_q$C), 85.92 ($_q$C), 65.89 ($_q$C), 22.99 (CH_3), 21.56 (CH_3).

ν_{max}/cm^{-1}: 3370 b (OH), 3288 m (NH), 2917 w (CH_3), 1602 s (C=C), 1493 s (CH_3), 1335 s (SO_2), 1175 s (SO_2), 1089 s (R-OH), 987 s (C=CH_2), 905 s (C=CH_2).

***N*-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methoxybenzenesulfonamide (2.6a)**

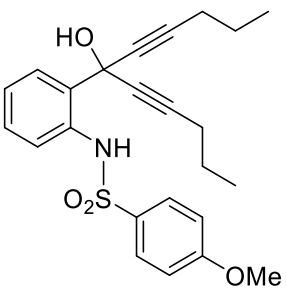


Using Method **A** from phenylacetylene (21.8 mmol) and methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (6.22 mmol) to give an orange oil. The product crystallised on standing, which was then recrystallised from hexane – EtOAc to give the title compound as an off white powder (2.16 g, 70%) m.p. 126 °C decomp; HRMS found $[M+Na]^+$ = 516.1230; $C_{30}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 516.1240.

δ_H ($CDCl_3$) 8.64 (1H, s, N*H*), 7.91 (1H, dd, *J* = 7.8, 1.2 Hz, 2-*H*), 7.85 – 7.82 (2H, m, *o*-Ar-*H*), 7.61 (1H, dd, *J* = 7.8, 1.2 Hz, 5-*H*), 7.53 – 7.51 (4H, m, Ph-*H*), 7.41 – 7.33 (6H, m, Ph-*H*), 7.29 – 7.28 (1H, m, 4-*H*), 7.06 (1H, td, *J* = 7.8, 1.2 Hz, 3-*H*), 6.69 – 6.66 (2H, m, *m*-Ar-*H*), 3.73 (3H, s, O-*Me*), 3.31 (1H, s, O*H*). δ_c 162.93 ($_q$C), 135.96 ($_q$C), 132.01 (CH), 131.30 ($_q$C), 130.04 (CH), 129.75 (CH), 129.27 (CH), 128.43 (CH), 128.04 ($_q$C), 127.89 (CH), 123.18 (CH), 121.44 ($_q$C), 119.13 (CH), 114.00 (CH), 87.09 ($_q$C), 86.82 ($_q$C), 66.27 ($_q$C), 55.44 (CH_3).

ν_{max}/cm^{-1}: 3413 b (OH), 3305 w (NH), 1596 s (C=C), 1489 s (CH_3), 1329 w (SO_2), 1148 s (SO_2), 1093 s (R-OH), 748 s (Ph-H), 689 s (Ph-H).

***N*-[2-(6-Hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methoxybenzenesulfonamide (2.6b)**



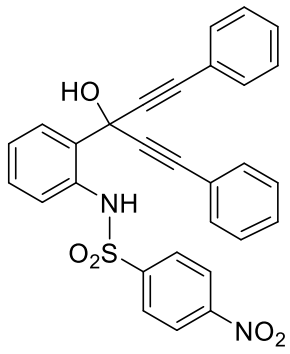
Using Method **A** from 1-pentyne (21.8 mmol) and methyl 2-[(4-methoxyphenyl)sulfonamido]benzoate (6.22 mmol) to give a yellow oil. The product

crystallised on standing, the resultant solid was washed with hexane to give the title compound an orange solid (1.87 g, 73%) m.p. 84 – 85 °C; HRMS found $[M+Na]^+$ = 448.1541; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 448.1553.

δ_H ($CDCl_3$) 8.49 (1H, s, N*H*), 7.87 – 7.83 (2H, m, *o*-Ar-*H*), 7.77 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.51 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.24 – 7.19 (1H, m, 4-*H*), 7.00 (1H, app. t, 3-*H*), 6.91 – 6.87 (2H, m, *m*-Ar-*H*), 3.82 (3H, s, O-*Me*), 2.87 (1H, s, O*H*), 2.27 (4H, t, *J* = 7.2 Hz, CH_2), 1.59 (4H, sxt, *J* = 7.2 Hz, CH_2), 1.00 (6H, t, *J* = 7.2 Hz, CH_3). δ_c 162.94 ($_q$C), 135.77 ($_q$C), 131.66 ($_q$C), 129.65 (CH), 129.62 (CH) 127.65 (CH), 123.05 (CH), 119.22 (CH), 114.03 (CH), 87.77 ($_q$C), 79.44 ($_q$C), 65.35 ($_q$C), 55.54 (CH_3), 21.72 (CH_2), 20.82 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3407 b (OH), 3287 m (NH), 2963 w (Ar-H), 2932 w (CH_2, CH_3), 2840 w (CH_2, CH_3), 1597 s (C=C), 1493 s (CH_2), 1458 w (CH_3), 1331 w (SO_2), 1186 s (R-OH), 1091 s (SO_2).

***N*-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-nitrobenzenesulfonamide (2.7a)**



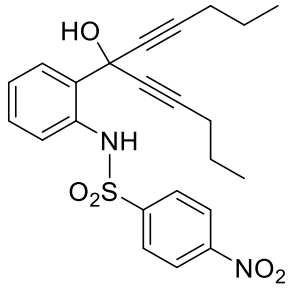
Using Method **A** from phenylacetylene (20.9 mmol) and methyl 2-[(4-nitrophenyl)sulfonamido]benzoate (5.98 mmol) to give an orange oil. The product crystallised on trituration with hexane – EtOAc, which was then recrystallised from hexane – EtOAc to give the title compound as a fine orange powder (0.31 g, 10%) m.p. 180 °C decomp; HRMS found $[M+Na]^+$ = 531.0967; $C_{29}H_{20}N_2O_5SNa$ $[M+Na]^+$ requires = 531.0985.

δ_H [$(CD_3)_2CO$] 10.16 (1H, s, N*H*), 8.12 – 8.10 (2H, m, *m*-Ar-*H*), 7.92 – 7.90 (2H, m, *o*-Ar-*H*), 7.70 (1H, dd, *J* = 7.6, 1.5 Hz, 2-*H*), 7.55 (1H, app. d, 5-*H*), 7.48 – 7.45 (4H, m, Ph-*H*), 7.39 – 7.36 (6H, m, Ph-*H*), 6.97 (1H, m, 4-*H*), 6.62 (1H, app. t, 3-*H*). δ_c 153.57 ($_q$C), 148.08 ($_q$C), 147.17 ($_q$C), 131.45 (CH), 131.23 ($_q$C), 128.41 (CH), 128.25 (CH), 127.95 (CH), 127.82 (CH),

126.30 (CH), 123.28 ($_q$C), 122.94 (CH), 118.93 (CH), 117.17 (CH), 92.19 ($_q$C), 82.23 ($_q$C), 67.53 ($_q$C).

ν_{max}/cm^{-1}: 1593 m (C=C), 1532 s (NO_2), 1439 s (CH_3), 1362 s (NO_2), 1287 s (SO_2), 1234 s (R-OH), 1099 m (SO_2).

_N_-[2-(6-Hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-nitrobenzenesulfonamide (2.7b)

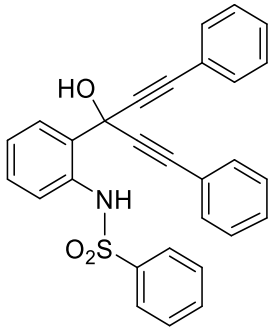


Using Method **A** from 1-pentyne (20.8 mmol) and methyl 2-[(4-nitrophenyl)sulfonamide]benzoate (5.95 mmol) to give an orange oil. The product crystallised on standing and the crude material was recrystallised from hexane – EtOAc to give a brick red powder. From the liquor subsequent recrystallised from $EtOH_{(aq)}$ to give the title compound as straw crystals (total = 0.29 g, 11%) m.p. 100 – 101 °C; HRMS found $[M+Na]^+$ = 463.1304; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 463.1298.

δ_H [$(CD_3)_2CO$] 9.38 (1H, s, N*H*), 8.43 – 8.39 (2H, m, *m*-Ar-*H*), 8.23 – 8.19 (2H, m, *o*-Ar-*H*), 7.81 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.58 (1H, app. d, 5-*H*), 7.29 (1H, app. t, 4-*H*), 7.08 (1H, td, *J* = 7.9, 1.5 Hz, 3-*H*), 6.78 (1H, s, O*H*), 2.24 – 2.20 (4H, m, CH_2), 1.53 (4H, sxt, *J* = 7.2 Hz, CH_2), 0.98 (6H, t, *J* = 7.2 Hz, CH_3). δ_c 145.71 ($_q$C), 135.44 ($_q$C), 130.55 ($_q$C), 129.31 (CH), 128.82 (CH), 127.81 (CH), 124.35 (CH), 123.51 (CH), 118.64 (CH), 86.19 ($_q$C), 80.18 ($_q$C), 64.96 ($_q$C), 21.61 (CH_2), 20.12 (CH_2), 12.79 (CH_3).

ν_{max}/cm^{-1}: 2961 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 1594 m (C=C), 1528 s (NO_2), 1477 s (CH_2), 1360 s (NO_2), 1292 s (SO_2), 1132 s (R-OH), 1096 m (SO_2).

***N*-[2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]benzenesulfonamide (2.8a)**

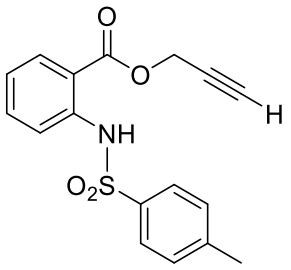


Using Method **A** from phenylacetylene (69.0 mmol) and methyl 2-(phenylsulfonamido)benzoate (19.7 mmol) to give an orange oil. The product crystallised on standing, which was then recrystallised from hexane – EtOAc to give the title compound as a white powder (6.19 g, 65%) m.p. 127 – 128 °C; HRMS found $[M+Na]^+$ = 486.1134; $C_{29}H_{21}NO_3SNa$ $[M+Na]^+$ requires = 486.1134.

δ_H ($CDCl_3$) 8.69 (1H, s, N*H*), 7.93 – 7.90 (3H, m, Ar-*H*), 7.58 (1H, dd, *J* = 8.0, 1.0 Hz, 5-*H*), 7.55 – 7.52 (4H, m, Ph-*H*), 7.43 – 7.33 (7H, m, Ar-*H*), 7.30 – 7.24 (4H, m, Ar-*H*), 7.07 (1H, td, *J* = 8.0, 1.0 Hz, 3-*H*). δ_c 139.96 ($_q$C), 135.82 ($_q$C), 132.85 (CH), 132.02 (CH), 130.08 (CH), 129.31 (CH), 128.89 (CH), 128.42 (CH), 128.14 ($_q$C), 127.92 (CH), 127.47 (CH), 123.37 (CH), 121.37 ($_q$C), 119.27 (CH), 86.96 ($_q$C), 86.94 ($_q$C), 66.28 ($_q$C).

ν_{max}/cm^{-1}: 3344 b (OH), 3224 m (NH), 2230 w (C≡C), 1583 s (C=C), 1324 s (SO_2), 1148 s (R-OH), 1107 s (SO_2).

Prop-2-yn-1-yl 2-[(4-methylphenyl)sulfonamide]benzoate (2.14)



Under and inert N_2 atmosphere *n*-BuLi (3.5 equiv.) was added to a cold (-75 °C) solution of propargyl alcohol (0.96 mL, 11.3 mmol, 3.5 equiv.) in anhydrous THF (approx. 50 mL). A solution of 2-[(4-methylphenyl)sulfonamide]benzoyl chloride (1.00 g, 3.23 mmol, 1.0 equiv.) in anhydrous THF (approx. 20 mL) was added dropwise to the cold (0 °C) solution and the

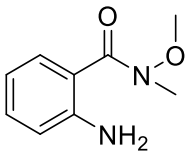
mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give the title compound as a cream powder (0.75 g, 70%) m.p. 150 – 151 °C; HRMS found $[M+Na]^+$ = 352.0613; $C_{17}H_{15}NO_4SNa$ $[M+Na]^+$ requires = 352.0613.

δ_H ($CDCl_3$) 10.43 (1H, s, N*H*), 7.96 (1H, dd, *J* = 8.0, 1.5 Hz, 2-*H*), 7.74 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.69 (1H, app. d, 5-*H*), 7.49 – 7.45 (1H, m, 4-*H*), 7.22 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 7.07 – 7.03 (1H, m, 3-*H*), 4.86 (2H, d, *J* = 2.5 Hz, CH_2), 2.55 (1H, d, *J* = 2.5 Hz, C*H*), 2.37 (3H, s, Ar-*Me*), 1.59 (1H, s, O*H*). δ_c 167.03 ($_q$C), 143.99 ($_q$C), 140.75 ($_q$C), 136.37 ($_q$C), 134.95 (CH), 131.38 (CH), 129.68 (CH), 127.32 (CH), 122.89 (CH), 119.08 (CH), 115.16 ($_q$C), 77.23 ($_q$C), 75.62 (CH), 52.90 (CH_2), 21.56 (CH_3).

ν_{max}/cm^{-1}: 3273 s (C≡C-H), 3171 w (CH_2), 1683 s (RCO_2R), 1597 s (C=C), 1490 s (CH_3), 1326 s (SO_2), 1153 s (SO_2), 1084 s (R-OH).

6.2.3 Synthesis of Ynones

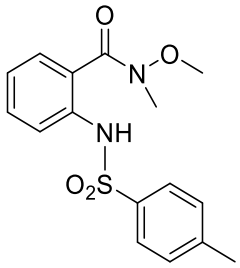
2-Amino-*N*-methoxy-*N*-methylbenzamide (2.20)



N,O-Dimethylhydroxylamine hydrochloride (7.29 g, 74.5 mmol, 1.5 equiv.) was dissolved in 90% $EtOH_{(aq)}$ (60 mL). Triethylamine (10.4 mL, 74.5 mmol, 1.5 equiv.) was added dropwise over 10 minutes and the solution stirred for 10 minutes at r.t., a solution of isatoic anhydride (8.13 g, 49.8 mmol, 1.0 equiv.) in 90% $EtOH_{(aq)}$ (50 mL) was added portion-wise over 20 minutes. The mixture was then refluxed for 2 h. After this time the mixture was poured onto equal volumes of ice and saturated aqueous Na_2CO_3 and the EtOH was removed under reduced pressure. The aqueous solution was diluted with EtOAc (approx. 100 mL). The organic phase was separated, washed with brine, dried (Na_2SO_4) and evaporated to give dark orange oil. The crude material was purified by flash column chromatography (10% EtOAc – hexane) to give the title compound as an orange oil (5.74 g, 64%) [14CC12293].

δ_H ($CDCl_3$) 7.36 (1H, app. d, Ar-*H*), 7.21 – 7.16 (1H, m, Ar-*H*), 6.71 – 6.67 (2H, m, Ar-*H*), 4.64 (2H, s, NH_2), 3.60 (3H, s, O-*Me*), 3.35 (3H, s, N-*Me*). δ_c 170.03 ($_q$C), 146.78 ($_q$C), 131.43 (CH), 129.21 (CH), 117.25 ($_q$C), 116.87 (CH), 116.68 (CH), 61.12 (CH_3), 34.35 (CH_3).

_N_-Methoxy-_N_-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (2.21)



Under an inert (N_2) atmosphere, 2-amino-*N*-methoxy-*N*-methylbenzamide (5.74 g, 31.9 mmol, 1.0 equiv.) was dissolved in pyridine (40 mL) and to this toluene-4-sulfonyl chloride (7.59 g, 39.6 mmol, 1.3 equiv.) was added in one portion. The mixture was refluxed overnight. Then cooled and diluted with EtOAc and washed with 2M HCl. The organic phase was separated, washed with water and brine, dried (Na_2SO_4) and evaporated to give dark orange oil. The crude material was purified by flash column chromatography (10% EtOAc – hexane) to give an orange oil which crystallised on trituration with ether to afford the title compound as an off-white solid (7.50 g, 70%) m.p. 109 – 110 °C (lit m.p. not quoted [16JOC2930]).

δ_H ($CDCl_3$) 8.96 (1H, s, N*H*), 7.70 – 7.65 (3H, m, 2-*H, o*-Ar-*H*), 7.48 (1H, app. d, 5-*H*), 7.40 – 7.36 (1H, m, 4-*H*), 7.22 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 7.10 – 7.06 (1H, m, 3-*H*), 3.19 (6H, s, O-*Me,* N-*Me*), 2.35 (3H, s, Ar-*Me*). δ_c 167.85 ($_q$C), 143.65 ($_q$C), 136.87 ($_q$C), 136.73 ($_q$C), 131.72 (CH), 129.58 (CH), 129.21 (CH), 127.31 (CH), 123.75 (CH), 123.23 ($_q$C), 122.87 (CH), 60.94 (CH_3), 33.69 (CH_3), 21.48 (CH_3).

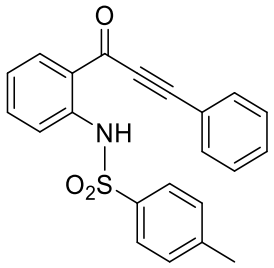
ν_{max}/cm^{-1}: 3166 b (NH), 2937 w (CH_3), 1616 s (C=O), 1594 s (C=C), 1450 w (CH_3), 1334 s (SO_2), 1157 s (SO_2).

General Method for Synthesis of Ynones

Under and inert (N_2) atmosphere *n*-BuLi (2.2 equiv.) was added to a cold (-75 °C) solution of an acetylene derivative (X mmol, 2.2 equiv.) in anhydrous THF (50 – 100 mL). The solution was warmed to 0 °C and *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamide]benzamide

(Y mmol, 1.0 equiv.) in anhydrous THF (15 – 30 mL) was added dropwise to the solution. When addition was complete the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated. The following were synthesised by this method.

1-[2-(4-Toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (2.17A)

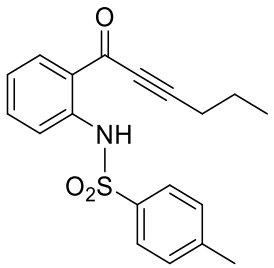


From phenylacetylene (39.5 mmol) and *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (17.9 mmol) to give an orange oil which on trituration with ether gave the title compound as a bright yellow solid (3.76 g, 56%) m.p. 138 – 140 °C (lit m.p. 149 – 152 °C [16AGE7737]).

δ_H ($CDCl_3$) 11.25 (1H, s, N*H*), 8.28 (1H, app. d, 2-*H*), 7.78 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.73 (1H, app. d, 5-*H*), 7.67 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 7.53 – 7.49 (2H, m, Ar-*H*), 7.45 – 7.42 (2H, m, Ar-*H*), 7.24 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.13 (1H, app. t, 3-*H*), 2.36 (3H, s, Ar-*Me*). δ_c 180.51 (C=O), 144.08 ($_q$C), 140.94 ($_q$C), 136.46 ($_q$C), 135.73 (CH), 134.77 (CH), 133.11 (CH), 131.22 (CH), 129.76 (CH), 128.80 (CH), 127.33 (CH), 122.62 (CH), 122.49 ($_q$C), 118.42 (CH), 95.27 ($_q$C), 86.61 ($_q$C), 21.56 (CH_3).

ν_{max}/cm^{-1}: 3056 w (NH), 2202 m (C≡C), 1706 s (C=O), 1591 s (C=C), 1449 s (CH_3), 1363 s (SO_2), 1167 s (SO_2).

***N*-[2-(Hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.17B)**

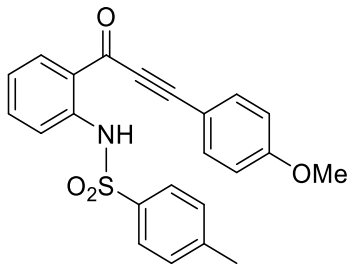


From 1-pentyne (15.8 mmol) and *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (7.18 mmol) to give an orange oil which on trituration with ether gave the title compound as a baby pink solid (1.62 g, 66%) m.p. 93 – 94 °C; HRMS found $[M+H]^+$ = 341.1072; $C_{19}H_{20}NO_3S$ $[M+H]^+$ requires = 342.1158.

δ_H ($CDCl_3$) 11.25 (1H, s, N*H*), 8.18 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.76 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.68 (1H, app. d, 5-*H*), 7.49 – 7.45 (1H, m, 4-*H*), 7.23 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 7.08 (1H, app. t, 3-*H*), 2.48 (2H, t, *J* = 7.2 Hz, CH_2), 2.37 (3H, s, Ar-*Me*), 1.69 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.07 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 180.80 (C=O), 144.01 ($_q$C), 140.85 ($_q$C), 136.48 ($_q$C), 135.50 (CH), 134.93 (CH), 129.72 (CH), 127.31 (CH), 122.47 (CH), 122.38 ($_q$C), 118.21 (CH), 99.08 ($_q$C), 79.55 ($_q$C), 21.56 (CH_3), 21.26 (CH_2), 21.24 (CH_2), 13.64 (CH_3).

ν_{max}/cm^{-1}: 3272 w (NH), 2980 w (CH_2, CH_3), 2214 m (C≡C), 1604 s (C=C), 1175 s (SO_2).

***N*-{2-[3-(4-Methoxyphenyl)propioloyl]phenyl}-4-methylbenzenesulfonamide (2.17C)**



From 1-ethynyl-4-methoxybenzene (39.5 mmol) and *N*-methoxy-*N*-methyl-2-[(4-methylphenyl)sulfonamide]benzamide (17.9 mmol) to give an orange oil which on trituration with ether gave the title compound as a bright yellow solid (4.83 g, 66%) m.p. 163 – 165 °C (lit m.p. 134 – 136 °C [16AGE7737]).

δ_H ($CDCl_3$) 11.31 (1H, s, N*H*), 8.26 (1H, dd, *J* = 8.0, 1.5 Hz, 2-*H*), 7.77 (2H, d, *J* = 8.1 Hz, *o*-Ar-*H*), 7.71 (1H, app. d, 5-*H*), 7.64 – 7.60 (2H, m, *o*-Ar-*H*), 7.52 – 7.47 (1H, m, 4-*H*), 7.23 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 7.15 – 7.11 (1H, m, 3-*H*), 6.96 – 6.92 (2H, m, *m*-Ar-*H*), 3.87 (3H, s, O-*Me),* 2.35 (3H, s, Ar-*Me*). δ_c 180.52 (C=O), 162.10 ($_q$C), 144.03 ($_q$C), 140.82 ($_q$C), 136.46 ($_q$C), 135.47 (CH), 135.27 ($_q$C), 135.28 (CH), 134.64 (CH), 129.74 (CH), 127.31 (CH), 122.62 ($_q$C), 122.60 (CH), 118.47 (CH), 114.55 (CH), 111.33 ($_q$C), 96.70 ($_q$C), 86.78 ($_q$C), 55.52 (CH_3), 21.56 (CH_3).

ν_{max}/cm^{-1}: 3033 w (NH), 2184 m (C≡C), 1602 s (C=C), 1328 w (SO_2), 1126 s (SO_2).

6.2.4 Synthesis of Unsymmetrical *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

General Method for the Synthesis of Unsymmetrical *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

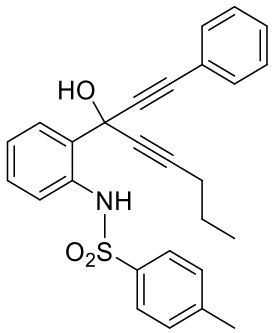
Method **A**: Under an inert (N_2) atmosphere *n*-BuLi (2.1 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 2.1 equiv.) in anhydrous THF (50 – 100 mL). The solution was warmed to 0 °C and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one derivative (Y mmol, 1 equiv.) in anhydrous THF (30 – 60 mL) was added dropwise to the solution. When the addition was complete the mixture was allowed to warm to r.t., then stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give crude material which was purified by recrystallisation or washing with cold hexane. The following were synthesised by this method.

Method **B**: Under an inert (N_2) atmosphere ethynylmagnesium bromide (2.1 equiv., 0.5M in THF) was added to a warm (40 °C) solution of 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one derivative (X mmol, 1 equiv.) in anhydrous THF (30 mL). The solution was refluxed until the reaction was complete by TLC. After this time the mixture was allowed to cool and was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give crude material which was purified by flash column chromatography (10% EtOAc – pet ether, unless otherwise stated). The following were synthesised by this method.

Method **C**: Under an inert (N_2) atmosphere 1-bromo-1-propene (X mmol, 2.5 equiv.) was added to a cold (-75 °C) solution of LDA 2.5 equiv. (DIPA, 1.1 equiv. and *n*-BuLi, 2.5 equiv.) in anhydrous THF (approx. 50 mL) and was stirred for 3 h. The solution was warmed to 0 °C and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one derivative (Y mmol, 1 equiv.) in anhydrous THF (30 mL) was added dropwise to the solution. When the addition was complete the mixture was allowed to warm to r.t. and then stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give crude material which was

purified by recrystallisation or washing with cold hexane. The following were synthesised by this method.

_N_-[2-(3-Hydroxy-1-phenylocta-1,4-diyn-3-yl)phenyl)]-4-methylbenzenesulfonamide (2.19Ab)



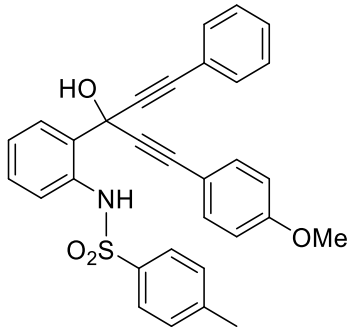
Using Method **A** from 1-pentyne (8.40 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (4.00 mmol) to give the title compound as an orange solid (1.52 g, 86%) m.p. 127 – 129 °C; HRMS found $[M+Na]^+$ = 466.1452; $C_{27}H_{25}NO_3SNa$ $[M+Na]^+$ requires = 466.1447.

δ_H ($CDCl_3$) 8.59 (1H, s, N*H*), 7.84 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.79 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.55 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.50 – 7.47 (2H, m, Ph-*H*), 7.37 – 7.31 (3H, m, Ph-*H*), 7.26 – 7.22* (1H, m, 4-*H*), 7.10 (1H, d, *J* = 7.9 Hz, *m*-Ar-*H*), 7.03 (1H, td, *J* = 7.9, 1.5 Hz, 3-*H*), 3.13 (1H, s, O*H*), 2.32 – 2.28 (5H, m, Ar-*Me*, CH_2), 1.62 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.03 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 143.61 ($_q$C), 137.00 ($_q$C), 135.84 ($_q$C), 131.96 (CH), 129.83 (CH), 129.52 (CH), 129.11 (CH), 128.53 ($_q$C), 128.35 (CH), 127.78 (CH), 127.50 (CH), 123.14 (CH), 121.59 ($_q$C), 119.17 (CH), 88.74 ($_q$C), 87.64 ($_q$C), 85.91 ($_q$C), 78.91 ($_q$C), 65.80 ($_q$C), 21.70 (CH_2), 21.53 (CH_3), 20.88 (CH_2), 13.63 (CH_3).

ν_{max}/cm^{-1}: 3348 b (OH), 3254 m (NH), 2968 w (Ar-H), 2931 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 2359 w (C≡C), 1597 s (C=C), 1490 s (CH_2), 1324 s (SO_2), 1150 s (SO_2), 1087 s (R-OH).

*Overlapping with $CDCl_3$ signal

***N*-{2-[3-Hydroxy-1-(4-methoxyphenyl)-5-phenylpenta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.19Ac)**



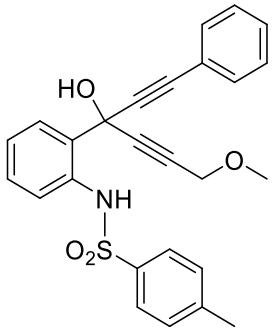
Using Method **A** from 1-ethynyl-4-methoxybenzene (8.40 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (4.00 mmol) to give the title compound as an off white powder (1.75 g, 86%) m.p. 139 – 140 °C decomp; HRMS found $[M+Na]^+$ = 530.1395; $C_{31}H_{25}NO_4SNa$ $[M+Na]^+$ requires = 530.1397.

δ_H ($CDCl_3$) 8.65 (1H, s, N*H*), 7.90 (1H, dd, *J* = 7.8, 1.4 Hz, 2-*H*), 7.79 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.58 (1H, app. d, 5-*H*), 7.54 – 7.51 (2H, m, Ph-*H*), 7.49 – 7.45 (2H, m, *o*-Ar-*H*), 7.41 – 7.34 (3H, m, Ph-*H*), 7.29 – 7.25* (1H, m, 4-*H*), 7.08 – 7.04 (3H, m, *m*-Ar-*H,* 3-*H*), 6.89 – 6.86 (2H, m, *m*-Ar-*H*), 3.83 (3H, s, O-*Me*), 3.20 (1H, s, O*H*), 2.29 (3H, s, Ar-*Me*). δ_c 160.33 ($_qC$), 143.60 ($_qC$), 136.91 ($_qC$), 135.91 ($_qC$), 133.58 (CH), 132.00 (CH), 129.97 (CH), 129.52 (CH), 129.22 (CH), 128.40 (CH), 128.22 ($_qC$), 127.86 (CH), 127.53 (CH), 123.20 (CH), 121.50 ($_qC$), 119.17 (CH), 114.03 (CH), 113.40 ($_qC$), 87.19 ($_qC$), 86.65 ($_qC$), 85.74 ($_qC$), 78.91 ($_qC$), 66.23 ($_qC$), 55.37 (CH_3), 21.53 (CH_3).

ν_{max}/cm^{-1}: 3402 b (OH), 3274 s (NH), 2224 s (C≡C), 1604 s (C=C), 1324 s (SO_2), 1153 s (SO_2), 1089 s (R-OH).

*Overlapping with $CDCl_3$ signal

***N*-[2-(3-Hydroxy-6-methoxy-1-phenylhexa-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Af)**

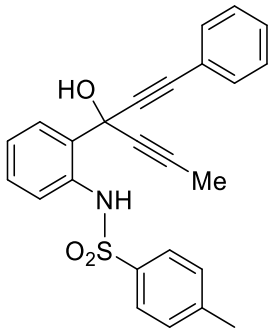


Using Method **A** from methyl propargylic ether (2.79 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a golden powder (0.45 g, 73%) m.p. 141 °C decomp; HRMS found $[M+Na]^+$ = 468.1238; $C_{26}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 468.1240.

δ_H $[(CD_3)_2CO]$ 9.19 (1H, s, N*H*), 7.87 – 7.83 (3H, m, 2-*H, o*-Ar-*H*), 7.56 (1H, app. d, 5-*H*), 7.50 – 7.48 (2H, m, Ph-*H*), 7.45 – 7.42 (3H, m, Ph-*H*), 7.31 – 7.24 (3H, m, 4-*H, m*-Ar-*H*), 7.06 (1H, app. t, 3-*H*), 4.21 (2H, AB_q, *J* = 16.1 Hz, CH_aH_b), 3.35 (3H, s, O-*Me*), 2.22 (3H, s, Ar-*Me*). δ_c 143.86 ($_q$C), 137.36 ($_q$C), 136.43 ($_q$C), 131.64 (CH), 129.60 (CH), 129.56 (CH), 129.23 (CH), 128.64 (CH), 128.47 ($_q$C), 127.66 (CH), 127.43 (CH), 122.77 (CH), 121.72 ($_q$C), 118.05 (CH), 88.04 ($_q$C), 85.19 ($_q$C), 84.85 ($_q$C), 82.54 ($_q$C), 65.39 ($_q$C), 59.20 (CH_2), 56.89 (CH_3), 20.49 (CH_3).

ν_{max}/cm^{-1}: 3255 b (OH), 2361 m (C≡C), 2342 m (C≡C), 1597 s (C=C), 1490 s (CH_2), 1335 s (SO_2), 1183 s (SO_2), 1088 s (R-OH).

***N*-[2-(3-Hydroxy-1-phenylhexa-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ag)**

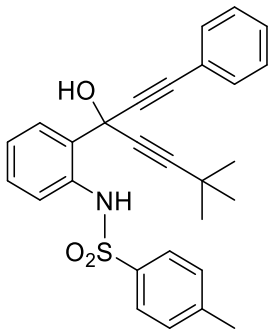


Using Method **C** from 1-bromo-1-propene (12.3 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (5.86 mmol) to give an orange oil which on trituration with hexane – EtOAc gave the title compound as an a pale pink solid (0.31 g, 28%) m.p. 127 °C decomp; HRMS found $[M+Na]^+$ = 438.1128; $C_{25}H_{21}NO_3SNa$ $[M+Na]^+$ requires = 438.1134.

δ_H [$(CD_3)_2CO$] 9.24 (1H, s, N*H*), 7.85 – 7.81 (3H, m, 2-*H, o*-Ar-*H*), 7.77 (1H, dd, *J* = 8.2, 1.1 Hz, 5-*H*), 7.49 – 7.46 (2H, m, Ph-*H*), 7.44 – 7.40 (3H, m, Ph-*H*), 7.29 – 7.23 (3H, m, *m*-Ar-*H,* 4-*H*), 7.03 (1H, td, *J* = 8.2, 1.1 Hz, 3-*H*), 2.32 (3H, s, Ar-*Me*), 1.92 (3H, s, *Me*). δ_c 143.82 ($_q$C), 137.45 ($_q$C), 136.35 ($_q$C), 131.60 (CH), 129.57 (CH), 129.33 (CH), 129.09 (CH), 128.62 (CH), 127.69 (CH), 127.42 (CH), 122.69 (CH), 121.91 ($_q$C), 117.90 (CH), 88.67 ($_q$C), 84.55 ($_q$C), 82.83 ($_q$C), 78.42 ($_q$C), 65.40 ($_q$C), 20.49 (CH_3), 2.64 (CH_3).

ν_{max}/cm^{-1}: 3392 b (OH), 3255 m (NH), 2980 w (CH_3), 2336 w (C≡C), 1597 s (C=C), 1489 s (CH_3), 1330 s (SO_2), 1153 s (SO_2).

***N*-[2-(3-Hydroxy-6,6-dimethyl-1-phenylhepta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Aj)**



Using Method **A** from 3,3-dimethyl-1-butyne (2.79 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a yellow oil (0.54 g, 88%); HRMS found $[M+K]^+$ = 496.1339; $C_{28}H_{27}NO_3SK$ $[M+K]^+$ requires = 496.1343.

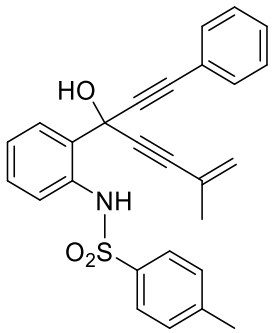
δ_H ($CDCl_3$) 8.60 (1H, s, N*H*), 7.84 – 7.79 (3H, m, 2-*H, o*-Ar-*H*), 7.53 – 7.47 (3H, m, 5-*H*, Ph-*H*), 7.39 – 7.31 (3H, m, Ph-*H*), 7.26 – 7.22* (1H, m, 4-*H*), 7.10 (2H, d, *J* = 7.9 Hz, *m*-Ar-*H*), 7.01 (1H, td, *J* = 7.8, 1.2 Hz, 3-*H*), 3.09 (1H, s, O*H*), 2.31 (3H, s, Ar-*Me*), 1.32 (9H, s, *Me*$_3$). δ_c 143.60 ($_q$C), 137.05 ($_q$C), 135.85 ($_q$C), 131.95 (CH), 129.80 (CH), 129.55 (CH), 129.06 (CH), 128.62

($_q$C), 128.35 (CH), 127.72 (CH), 127.49 (CH), 123.11 (CH), 121.70 ($_q$C), 119.15 (CH), 96.65 ($_q$C), 87.75 ($_q$C), 85.71 ($_q$C), 65.60 ($_q$C), 30.54 (CH_3), 27.71 ($_q$C), 21.53 (CH_3).

ν_{max}/cm^{-1}: 3392 b (OH), 3269 m (NH), 2968 w (CH_3), 2235 w (C≡C), 2205 w (C≡C), 1598 s (C=C), 1492 s (CH_3), 1332 s (SO_2), 1153 s (SO_2), 1092 s (R-OH).

*Overlapping with $CDCl_3$ signal

_N_-[2-(3-Hydroxy-6-methyl-1-phenylhepta-6-en-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ak)

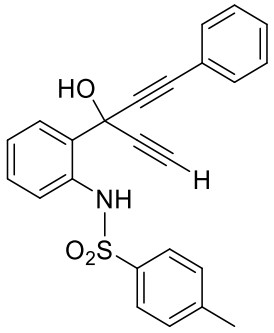


Using Method **A** from 2-methyl-1-buten-3-yne (12.3 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (5.85 mmol) to give the title compound as a straw solid (0.90 g, 76%) m.p. 120 – 123 °C; HRMS found $[M+K]^+$ = 480.1038; $C_{27}H_{23}NO_3SK$ $[M+K]^+$ requires = 480.1030.

δ_H [$(CD_3)_2CO$] 7.85 – 7.83 (3H, m, *o*-Ar-*H*, 2-*H*), 7.54 (1H, app. d, 5-*H*), 7.51 – 7.48 (2H, m, Ph-*H*), 7.45 – 7.40 (3H, m, Ph-*H*), 7.27 (1H, app. t, 4-*H*), 7.22 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 7.04 (1H, app. t, 3-*H*), 5.41 – 5.39 (2H, m, CH_2), 2.87 (1H, s, O*H*) 3.31 (3H, s, Ar-*Me*), 1.92 (3H, s, CH_3).
δ_c 143.76 ($_q$C), 137.52 ($_q$C), 136.66 ($_q$C), 131.65 (CH), 129.59 (CH), 129.49 (CH), 129.19 (CH), 128.63 (CH), 127.60 (CH), 127.38 (CH), 125.92 ($_q$C), 123.18 (CH_2), 122.68 (CH), 121.80 ($_q$C), 118.04 (CH), 88.17 ($_q$C), 87.09 ($_q$C), 86.65 ($_q$C), 85.14 ($_q$C), 65.67 ($_q$C), 22.48 ($_q$C), 22.27 (CH_3), 20.51 (CH_3).

ν_{max}/cm^{-1}: 3655 m (OH), 3388 m (NH), 3256 w (Ar-H), 2980 s (C=C-H), 2889 s (CH_3), 2202 w (C≡C), 1594 s (C=C), 1491 s (CH_3), 1327 s (SO_2), 1153 s (SO_2), 1090 s (R-OH), 997 s (C=CH_2), 940 s (C=CH_2).

***N*-[2-(3-Hydroxy-1-phenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Ai)**



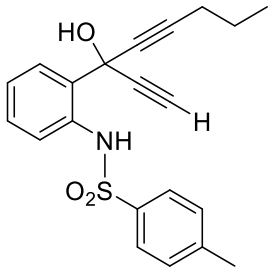
Using Method **B** ethynylmagnesium bromide (5.61 mmol) and *N*-[2-(hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.67 mmol) to give the title compound as an orange oil (0.69 g, 65%); HRMS found $[M+Na]^+$ = 424.0990; $C_{24}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 424.0978.

δ_H ($CDCl_3$) 8.78 (1H, s, N*H*), 7.85 (1H, dd, *J* = 1.4, 7.9 Hz, 2-*H*), 7.80 (2H, d, *J* = 8.0 Hz, *o*-Ar-*H*), 7.61 (1H, dd, *J* = 1.4, 7.9 Hz, 5-*H*), 7.48 – 7.45 (2H, m, Ph-*H*), 7.35 – 7.26* (4H, m, Ph-*H,* 4-*H*), 7.09 – 7.02 (3H, m, *m*-Ar-*H*, 3-*H*), 4.48 (1H, s, O*H*), 2.78 (1H, s, C*H*), 2.27 (3H, s, Ar-*Me*). δ_c 143.80 ($_qC$), 136.85 ($_qC$), 135.87 ($_qC$), 131.99 (CH), 130.05 (CH), 129.57 (CH), 129.26 (CH), 128.39 (CH), 128.02 ($_qC$), 127.89 (CH), 127.53 (CH), 123.40 (CH), 121.36 ($_qC$), 119.42 (CH), 86.87 ($_qC$), 86.65 ($_qC$), 82.03 ($_qC$), 75.25 (CH), 65.55 ($_qC$), 21.52 (CH_3).

ν_{max}/cm^{-1}: 3279 b (OH), 2227 w (C≡C), 1598 s (C=C), 1490 s (CH_3), 1328 s (SO_2), 1153 s (SO_2), 1089 s (R-OH), 753 s (Ph-H), 689 s (Ph-H).

*Overlapping with $CDCl_3$ signal

***N*-[2-(3-Hydroxyocta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.19Bi)**



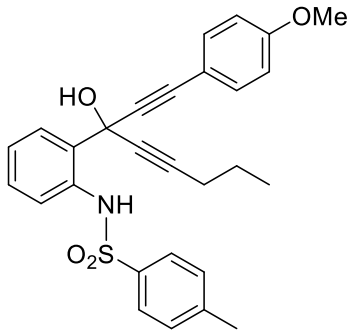
Using Method **B** ethynylmagnesium bromide (6.15 mmol) and *N*-[2-(hex-2-ynoyl)phenyl]-4-methylbenzenesulfonamide (2.93 mmol) to give a brown oil. The crude material was

purified by flash column chromatography to give the title compound as yellow oil (0.57 g, 64%); HRMS found $[M+Na]^+$ = 390.1133; $C_{24}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 390.1134.

δ_H ($CDCl_3$) 8.64 (1H, s, N*H*), 7.80 – 7.76 (3H, m, *o*-Ar-*H*, 2-*H*), 7.56 (1H, dd, *J* = 7.7, 1.1 Hz, 5-*H*), 7.25 – 7.18 (3H, m, 4-*H, m*-Ar-*H*), 7.00 (1H, td, *J* = 7.7, 1.1 Hz, 3-*H*), 3.92 (1H, s, O*H*), 2.66 (1H, s, C*H*), 2.32 (3H, s, Ar-*Me*), 2.23 (2H, t, *J* = 7.2 Hz, CH_2), 1.56 (2H, sxt, *J* = 7.2 Hz, CH_2), 0.97 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 143.78 ($_q$C), 137.00 ($_q$C), 135.75 ($_q$C), 129.86 (CH), 129.57 (CH), 128.45 ($_q$C), 127.78 (CH), 127.51 (CH), 123.32 (CH), 119.43 (CH), 88.68 ($_q$C), 82.56 ($_q$C), 78.60 ($_q$C), 74.29 (CH), 65.11 ($_q$C), 21.64 (CH_2), 21.53 (CH_3), 20.77 (CH_2), 13.60 (CH_3).

ν_{max}/cm^{-1}: 3278 b (OH), 2970 s (CH_2, CH_3), 2236 s (C≡C), 1599 s (C=C), 1493 s (CH_2), 1331 s (SO_2), 1155 s (SO_2), 1090 s (R-OH).

_N_-{2-[3-Hydroxy-1-(4-methoxyphenyl)octa-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.19Cb)



Using Method **A** from 1-pentyne (5.19 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (2.47 mmol) to give the title compound as an white solid (0.87 g, 74%) m.p. 122 – 123 °C; HRMS found $[M+K]^+$ = 512.1310; $C_{28}H_{27}NO_4SK$ $[M+K]^+$ requires = 512.1292.

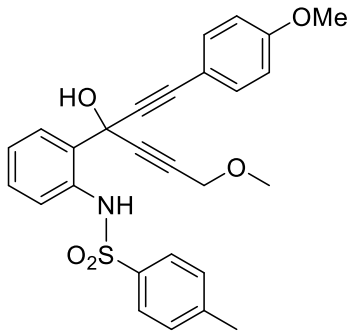
δ_H ($CDCl_3$) 8.57 (1H, s, N*H*), 7.85 – 7.89 (3H, m, 2-*H,* Ar-*H*), 7.53 (1H, dd, *J* = 8.2, 1.0 Hz, 5-*H*), 7.45 – 7.41 (2H, m, Ar-*H*), 7.24* (1H, td, *J* = 8.2, 1.0 Hz, 4-*H*), 7.13 (2H, d, *J* = 8.1 Hz, Ar-*H*), 7.03 (1H, td, *J* = 8.2, 1.0 Hz, 3-*H*), 6.88 – 6.84 (2H, m, Ar-*H*), 3.83 (3H, s, O-*Me*), 2.98 (1H, s, O*H*), 2.33 – 2.29 (5H, m, Ar-*Me*, CH_2), 1.62 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.03 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 160.21 ($_q$C), 143.59 ($_q$C), 137.04 ($_q$C), 135.81 ($_q$C), 133.52 (CH), 129.76 (CH), 129.53 (CH), 128.68 ($_q$C), 127.75 (CH), 127.52 (CH), 123.12 (CH), 119.15 (CH), 113.98 (CH), 113.57

($_q$C), 88.56 ($_q$C), 86.36 ($_q$C), 86.15 ($_q$C), 79.04 ($_q$C), 65.81 ($_q$C), 55.35 (CH_3), 21.71 (CH_2), 21.55 (CH_3), 20.88 (CH_2), 13.63 (CH_3).

ν_{max}/cm^{-1}: 3386 b (OH), 3230 m (NH), 2960 w (Ar-H), 2935 w (CH_2, CH_3), 2872 w (CH_2, CH_3), 2229 w (C≡C), 1605 s (C=C), 1440 s (CH_2), 1325 s (SO_2), 1153 s (SO_2), 1089 s (R-OH).

*Overlapping with $CDCl_3$ signal

_N_-{2-[3-Hydroxy-6-methoxy-1-(4-methoxyphenyl)hexa-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.19Cf)

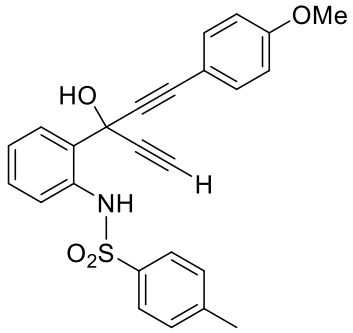


Using Method **A** from methyl propargylic ether (2.79 mmol) and 1-[2-(4-toluenesulfonamido)phenyl]-3-phenylprop-2-yn-1-one (1.33 mmol) to give the title compound as a golden powder (0.45 g, 73%) m.p. 141 °C decomp; HRMS found $[M+Na]^+$ = 468.1238; $C_{26}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 468.1240.

δ_H [$(CD_3)_2CO$] 9.19 (1H, s, N*H*), 7.87 – 7.83 (3H, m, 2-*H, o*-Ar-*H*), 7.56 (1H, app. d, 5-*H*), 7.50 – 7.48 (2H, m, Ph-*H*), 7.45 – 7.42 (3H, m, Ph-*H*), 7.31 – 7.24 (3H, m, 4-*H, m*-Ar-*H*), 7.06 (1H, app. t, 3-*H*), 4.23 (2H, AB_q, *J* = 15.8 Hz, CH_aH_b), 3.35 (3H, s, O-*Me*), 2.22 (3H, s, O-*Me*). δ_c 143.86 ($_q$C), 137.36 ($_q$C), 136.43 ($_q$C), 131.64 (CH), 129.60 (CH), 129.56 (CH), 129.23 (CH), 128.64 (CH), 128.47 ($_q$C), 127.66 (CH), 127.43 (CH), 122.77 (CH), 121.72 ($_q$C), 118.05 (CH), 88.04 ($_q$C), 85.19 ($_q$C), 84.85 ($_q$C), 82.54 ($_q$C), 65.39 ($_q$C), 59.20 (CH_2), 56.89 (CH_3), 20.49 (CH_3).

ν_{max}/cm^{-1}: 3255 b (OH), 2980 m (CH_2, CH_3), 2233 m (C≡C), 1606 s (C=C), 1340 s (SO_2), 1184 s (SO_2), 1091 s (R-OH).

***N*-{2-[Hydroxy-1-(4-methoxyphenyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (2.19Ci)**



Using Method **B** ethynylmagnesium bromide (5.19 mmol) and *N*-{2-[3-(4-methoxyphenyl)propioloyl]phenyl}-4-methylbenzenesulfonamide (2.47 mmol) to give a brown oil. The crude material was purified by flash column chromatography (15% acetone – pet ether) and recrystallisation from hexane – EtOAc to give the title compound as white needles (0.68 g, 64%) m.p. 108 – 110 °C; HRMS found $[M+Na]^+$ = 454.1083; $C_{25}H_{21}NO_4SNa$ $[M+Na]^+$ requires = 454.1083.

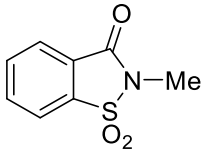
δ_H ($CDCl_3$) 8.58 (1H, s, N*H*), 7.83 (1H, dd, *J* = 7.9, 1.5 Hz, 2-*H*), 7.79 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.60 (1H, dd, *J* = 7.9, 1.5 Hz, 5-*H*), 7.42 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.30 – 7.24* (1H, m, 4-*H*), 7.14 (2H, d, *J* = 8.3 Hz, *m*-Ar-*H*), 7.04 (1H, td, *J* = 7.9, 1.5 Hz, 3-*H*), 6.85 (2H, d, *J* = 8.3 Hz, *m*-Ar-*H*), 3.81 (3H, s, Ar-*Me*), 3.53 (1H, s, O*H*), 2.76 (1H, s, C*H*), 2.32 (3H, s, O-*Me*). δ_c 160.35 ($_q$C), 143.71 ($_q$C), 136.99 ($_q$C), 135.83 ($_q$C), 133.57 (CH), 130.08 (CH), 129.54 (CH), 127.95 ($_q$C), 127.82 (CH), 127.53 (CH), 123.37 (CH), 119.56 (CH), 114.04 (CH), 113.19 ($_q$C), 87.14 ($_q$C), 85.38 ($_q$C), 82.05 ($_q$C), 75.08 (CH), 65.62 ($_q$C), 55.37 (CH_3), 21.54 (CH_3).

ν_{max}/cm^{-1}: 3295 b (OH), 3287 s (C≡C-H), 2226 s (C≡C), 1604 s (C=C), 1322 s (SO_2), 1153 s (SO_2), 1087 (R-OH).

*Overlapping with $CDCl_3$ signal

6.2.5 Synthesis of *N*-Substituted Saccharins

2-Methylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25A)



Sodium saccharin (4.00 g, 19.5 mmol, 1.0 equiv.) was dissolved in DMF (100 mL). Iodomethane (4.50 mL, 68.3 mmol, 3.5 equiv.) was added dropwise and the solution was stirred at 100 °C overnight. After this time the mixture was quenched with water and filtered [17CC901] to give the title compound as a white solid (2.73 g, 63%) m.p. 134 – 135 °C (literature m.p. 130 – 131 °C [51JOC1582]).

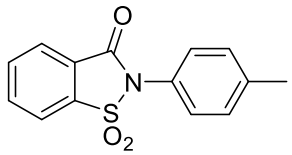
δ_H ($CDCl_3$) 8.09 – 8.07 (1H, m, 4-*H*), 7.96 – 7.94 (1H, m, 7-*H*), 7.90 – 7.82 (2H, m, 5-*H,* 6-*H*), 3.28 (3H, s, *Me*). δ_c 158.74 (C=O), 137.63 ($_qC$), 134.69 (CH), 134.36 (CH), 127.62 ($_qC$), 125.16 (CH), 121.02 (CH), 23.27 (CH_3).

ν_{max}/cm^{-1}: 3095 w (Ar-H), 2980 w (CH_3), 1735 s (C=O), 1594 s (C=C), 1468 s (CH_3), 1311 s (SO_2), 1055 s (SO_2).

<u>General Method for the Synthesis of *N*-Aryl Substituted Saccharins</u>

Saccharin (X mmol, 1.0 equiv.) and an appropriate boronic acid (Y mmol, 2.0 equiv.) was suspended in DCM (10 – 15 mL/g). To this pyridine (Y mmol, 2.0 equiv.) and then $Cu(OAc)_2$ (Y mmol, 2.0 equiv.) were added, the reaction mixture was stirred at r.t. for 48 h. After this time the mixture was quenched with water and diluted with DCM (approx. 100 mL). The mixture was acidified with HCl and filtered. The organic phase was separated, dried (Na_2SO_4) and evaporated to give the title compound. The following were synthesised by this method [98TL2933].

2-(*p*-Tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25B)

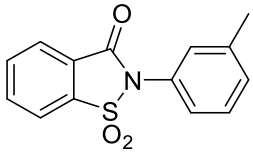


From *p*-tolylboronic acid (0.22 mol) to give the title compound as a white solid (28.4 g, 95%) m.p. 200 °C (literature m.p. 210 – 212 °C [15CEJ5332]).

δ_H ($CDCl_3$) 8.16 (1H, app. d, 4-*H*), 8.00 (1H, app. d, 7-*H*), 7.90 – 7.82 (2H, m, 5-*H,* 6-*H*), 7.41 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.36 (2H, d, *J* = 8.3 Hz, *m*-Ar-*H*), 3.28 (3H, s, Ar-*Me*). δ_c 158.52 (C=O), 140.53 ($_qC$), 137.67 ($_qC$), 135.01 (CH), 134.41 (CH), 130.63 (CH), 128.64 (CH), 127.31 ($_qC$), 125.78 ($_qC$), 125.62 (CH), 121.26 (CH), 21.36 (CH_3).

ν_{max}/cm^{-1}: 1730 s (C=O), 1613 w (C=C), 1402 s (CH_3), 1310 s (SO_2), 1159 s (SO_2).

2-(*m*-Tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25C)

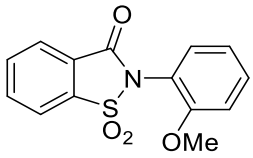


From *m*-tolylboronic acid (65.5 mmol) to give the title compound as a beige solid which was recrystallised from EtOH – EtOAc to give a white powder (4.35 g, 59%) m.p. 149 – 150 °C (literature m.p. not quoted [14CEJ14321]).

δ_H ($CDCl_3$) 8.16 (1H, app. d, 4-*H*), 8.00 (1H, app. d, 7-*H*), 7.95 – 7.86 (2H, m, 5-*H,* 6-*H*), 7.46 – 7.42 (1H, m, Ar-*H*), 7.34 – 7.33 (3H, m, Ar-*H*), 2.43 (3H, s, Ar-*Me*). δ_c 158.46 (C=O), 140.14 ($_q$C), 137.66 ($_q$C), 135.05 (CH), 134.44 (CH), 131.04 (CH), 129.71 (CH), 129.29 (CH), 128.47 ($_q$C), 127.26 ($_q$C), 125.79 (CH), 125.63 (CH), 121.26 (CH), 21.35 (CH_3).

ν_{max}/cm^{-1}: 1721 s (C=O), 1602 s (C=C), 1455 w (CH_3), 1333 s (SO_2), 1179 s (SO_2).

2-(2-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25D)

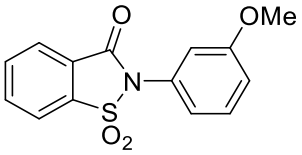


From 2-methoxyphenylboronic acid (0.11 mol) to give the title compound as a beige solid (7.56 g, 48%) m.p. 184 – 185 °C (literature m.p. not quoted [17SYN2000]).

δ_H ($CDCl_3$) 8.17 – 8.14 (1H, m, 4-*H*), 8.04 – 7.99 (1H, m, 7-*H*), 7.94 – 7.87 (2H, m, 5-*H,* Ar-*H*), 7.55 – 7.48 (2H, m, 6-*H,* Ar-*H*), 7.13 – 7.08 (2H, m, Ar-*H*), 3.84 (3H, s, O-*Me*). δ_c 158.52 (C=O), 140.53 ($_q$C), 137.67 ($_q$C), 135.01 (CH), 134.41 (CH), 130.63 (CH), 128.64 (CH), 127.31 ($_q$C), 125.78 ($_q$C), 125.62 (CH), 121.26 (CH), 21.36 (CH_3).

ν_{max}/cm^{-1}: 3094 w (Ar-H), 2945 w (CH_3), 1734 s (C=O), 1593 m (C=C), 1499 s (CH_3), 1323 s (SO_2), 1182 s (SO_2).

2-(3-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25E)

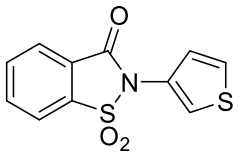


From 3-methoxyphenylboronic acid (32.8 mmol) to give the title compound as a golden powder (3.90 g, 82%) m.p. 170 – 172 °C (literature m.p. 207 – 209 °C [15CEJ5332]).

δ_H ($CDCl_3$) 8.16 (1H, app. d, 4-*H*), 8.00 (1H, app. d, 7-*H*), 7.95 – 7.87 (2H, m, 5-*H,* 6-*H*), 7.47 – 7.43 (1H, m, Ar-*H*) 7.13 (1H, app. d, Ar-*H*), 7.07 – 7.06 (2H, m, Ar-*H*), 3.35 (3H, s, O-*Me*). δ_c 160.61 (C=O), 158.34 ($_q$C), 137.32 ($_q$C), 135.10 (CH), 134.47 (CH), 130.55 (CH), 129.61 ($_q$C), 127.18 ($_q$C), 125.67 (CH), 121.25 (CH), 120.74 (CH), 116.31 (CH), 113.96 (CH), 55.34 (CH_3).

ν_{max}/cm^{-1}: 1721 s (C=O), 1602 m (C=C), 1509 s (CH_3), 1333 s (SO_2), 1179 s (SO_2).

2-(Thiophen-3-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25G)

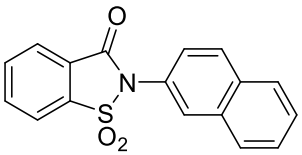


From 3-thienylboronic acid (10.9 mmol) to give the title compound as a red solid (0.94 g, 65%) m.p. 170 – 172 °C (literature m.p. 173 – 175 °C [15CEJ5332]).

δ_H ($CDCl_3$) 8.16 (1H, app. d, 4-*H*), 8.01 (1H, app. d, 7-*H*), 7.96 – 7.86 (2H, m, 5-*H,* 6-*H*), 7.72 (1H, m, Ar-*H*), 7.50 (1H, dd, *J* = 3.2, 5.2 Hz, Ar-*H*), 7.35 (1H, dd, *J* = 1.2, 5.2 Hz, Ar-*H*). δ_c 157.80 (C=O), 137.32 ($_q$C), 135.15 ($_q$C), 134.61 (CH), 127.06 ($_q$C), 126.44 (CH), 125.62 (CH), 124.73 (CH), 122.27 (CH), 121.31 (CH).

ν_{max}/cm^{-1}: 3093 w (Ar-H), 1716 s (C=O), 1593 m (C=C), 1332 s (SO_2), 1175 s (SO_2).

2-(Naphthalen-*2*-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (2.25H)



From 2-naphthelene boronic acid (65.5 mmol) to give the title compound as a beige solid which was recrystallised from EtOH – EtOAc to give a beige powder (8.77 g, 87%) m.p. 184 – 185 °C (literature m.p. 219 – 221 °C [15CEJ5332]).

δ_H ($CDCl_3$) 8.18 (1H, app. d, 4-*H*), 8.09 (1H, app. s, Ar-*H*), 8.01 (2H, d, *J* = 8.3 Hz, Ar-*H*), 7.95 – 7.86 (4H, m, Ar-*H*), 7.61 – 7.54 (3H, m, Ar-*H*). δ_c 158.60 (C=O), 137.71 ($_qC$), 135.15 (CH), 134.52 (CH), 133.62 ($_qC$), 133.49 ($_qC$), 130.05 (CH), 128.43 (CH), 128.23 (CH), 127.89 (CH), 127.55 (CH), 127.26 ($_qC$), 126.98 (CH), 126.09 ($_qC$), 125.68 (CH), 125.40 (CH), 121.31 (CH).

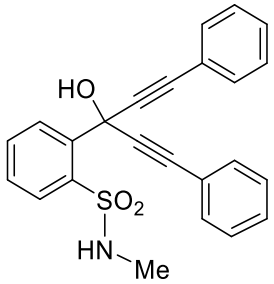
ν_{max}/cm^{-1}: 1739 s (C=O), 1504 w (C=C), 1329 s (SO_2), 1182 s (SO_2).

6.2.6 Synthesis of 3-[2-(Aminosulfamoyl)phenyl]penta-1,4-diyn-3-ols

General Method for the Synthesis of 3-[2-(Aminosulfamoyl)phenyl]penta-1,4-diyn-3-ols

Under an inert (N_2) atmosphere *n*-BuLi (2.5 M, 2.5 equiv.) was added to a cold (-75 °C) solution of the appropriate alkyne (X mmol, 2.5 equiv.) in anhydrous THF (approx. 100 mL). A solution of the appropriate *N*-substituted saccharin (Y mmol, 1.0 equiv.) in anhydrous THF (approx. 60 mL) was added dropwise to the cold (0 °C) solution and the mixture was allowed to warm to r.t. and stirred for 1 h. After this time the mixture was quenched with aqueous NH_4Cl and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give the crude material which was purified by recrystallisation or by washing with cold hexane. The following compounds were synthesised by this method.

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-methylbenzenesulfonamide (2.23Aa)

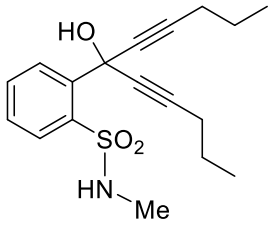


From phenylacetylene (12.9 mmol) and 2-methylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5.07 mmol) to give the title compound as an off white solid (1.99 g, 98%) m.p. 145 – 146 °C; HRMS found $[M+Na]^+$ = 424.0981; $C_{24}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 424.0978.

δ_H ($CDCl_3$) 8.44 (1H, dd, *J* = 7.9, 1.1 Hz, 2-*H*), 8.16 (1H, dd, *J* = 7.9, 1.1 Hz, 5-*H*), 7.67 (1H, td, *J* = 7.9, 1.1 Hz, 3-*H*), 7.58 – 7.52 (5H, m, 4-*H,* Ph-*H*), 7.40 – 7.32 (6H, m, Ph-*H*), 5.95 (1H, s, O*H*), 5.63 (1H, app. s, N*H*), 2.62 (3H, d, *J* = 5.3 Hz, *Me*). δ_c 139.82 ($_qC$), 135.50 ($_qC$), 133.28 (CH), 132.29 (CH), 131.89 (CH), 130.65 (CH), 129.33 (CH), 129.12 (CH), 128.51 (CH), 121.39 ($_qC$), 88.54 ($_qC$), 86.61 ($_qC$), 67.02 ($_qC$), 29.74 (CH_3).

ν_{max}/cm^{-1}: 3413 b (OH), 3320 m (NH), 2233 w (C≡C), 1489 m (C=C), 1372 w (CH_3), 1325 s (SO_2), 1164 s (R-OH), 1045 s (SO_2), 751 s (Ph-H), 688 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide (2.23Ab)

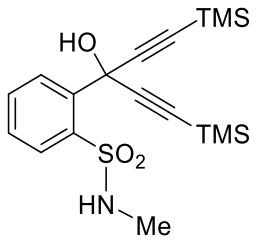


From 1-pentyne (12.7 mmol) and 2-methylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5.07 mmol) to give the title compound as an orange oil (1.64 g, 97%); HRMS found $[M+Na]^+$ = 356.1304; $C_{18}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 356.1291.

δ_H ($CDCl_3$) 8.28 (1H, dd, *J* = 7.9, 1.1 Hz, 2-*H*), 8.10 (1H, dd, *J* = 7.9, 1.1 Hz, 5-*H*), 7.60 (1H, td, *J* = 7.9, 1.1 Hz, 3-*H*), 7.49 (1H, td, *J* = 7.9, 1.1 Hz, 4-*H*), 5.68 (1H, q, *J* = 5.2 Hz, N*H*), 5.51 (1H, s, O*H*), 2.62 (3H, d, *J* = 5.2 Hz, *Me*), 2.29 (4H, t, *J* = 7.1 Hz, CH_2), 1.59 (4H, sxt, *J* = 7.1 Hz, CH_2), 1.00 (6H, t, *J* = 7.1 Hz, CH_3). δ_c 140.70 ($_qC$), 135.00 ($_qC$), 132.98 (CH), 131.92 (CH), 130.71 (CH), 128.59 (CH), 87.23 ($_qC$), 81.04 ($_qC$), 66.29 ($_qC$), 29.69 (CH_3), 21.70 (CH_2), 20.85 (CH_2), 13.55 (CH_3).

ν_{max}/cm^{-1}: 3413 b (OH), 3315 b (NH), 2965 m (Ar-H), 2934 w (CH_2, CH_3), 2873 w (CH_2, CH_3), 2236 w (C≡C), 1463 s (CH_2), 1393 s (CH_3), 1317 s (SO_2), 1156 s (R-OH), 1034 s (SO_2).

2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-methylbenzenesulfonamide (2.23Ae)

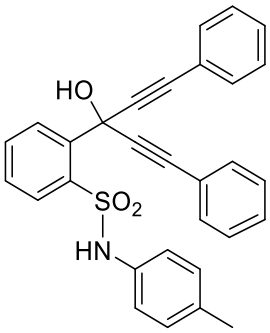


From (trimethylsilyl)acetylene (11.2 mmol) and 2-methylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5.07 mmol) to give the title compound as a brown solid (1.36 g, 68%) m.p. 71 – 73 °C; HRMS found $[M+Na]^+$ = 416.1140; $C_{18}H_{27}NO_3SSi_2Na$ $[M+Na]^+$ requires = 416.1142.

δ_H ($CDCl_3$) 8.18 (1H, dd, *J* = 7.9, 1.2 Hz, 2-*H*), 7.91 (1H, dd, *J* = 7.9, 1.2 Hz, 5-*H*), 7.45 (1H, td, *J* = 7.9, 1.2 Hz, 3-*H*), 7.35 (1H, td, *J* = 7.9, 1.2 Hz, 4-*H*), 5.79 (1H, s, O*H*), 5.70 (1H, q, *J* = 5.2 Hz, N*H*), 2.42 (3H, d, *J* = 5.2 Hz, *Me*), 0.19 (18H, s, Si-*Me*$_3$). δ_c 138.55 ($_q$C), 135.19 ($_q$C), 133.25 (CH), 132.26 (CH), 130.73 (CH), 129.07 (CH), 92.14 ($_q$C), 87.10 ($_q$C), 66.30 ($_q$C), 29.43 (CH_3), -0.29 (Si-Me_3).

ν_{max}/cm^{-1}: 3342 b (NH), 2960 m (CH_3), 2167 w (C≡C), 1315 m (SO_2), 1160 s (R-OH).

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.23Ba)



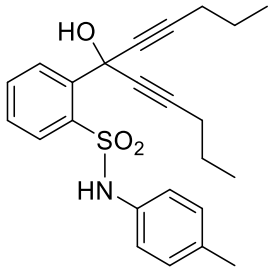
From phenylacetylene (9.15 mmol) and 2-(*p*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.66 mmol) to give the title compound as an pale orange powder (1.40 g, 80%) m.p. 145 – 147 °C; HRMS found $[M+Na]^+$ = 500.1291; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H ($CDCl_3$) 8.45 (1H, dd, *J* = 7.9, 1.1 Hz, 2-*H*), 7.68 (1H, dd, *J* = 7.9, 1.1 Hz, 5-*H*), 7.61 – 7.56 (6H, m, 3-*H,* Ph-*H*), 7.38 – 7.28 (7H, m, Ph-*H,* 4-*H,* N*H*), 6.97 (2H, d, *J* = 8.3 Hz, *m*-Ar-*H*), 6.90 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 6.10 (1H, s, O*H*), 2.25 (3H, s, Ar-*Me*). δ_c 139.34 ($_q$C), 136.48 ($_q$C),

135.46 ($_q$C), 133.36 (CH), 133.19 ($_q$C), 132.37 (CH), 131.91 (CH), 130.33 (CH), 129.78 (CH), 129.39 (CH), 128.55 (CH), 128.30 (CH), 124.15 (CH), 121.29 ($_q$C), 88.80 ($_q$C), 86.92 ($_q$C), 67.05 ($_q$C), 20.93 (CH_3).

ν_{max}/cm^{-1}: 3400 b (OH), 3268 w (NH), 2224 w (C≡C), 1508 s (C=C), 1436 w (CH_3), 1325 s (SO_2), 1159 s (R-OH), 1163 s (SO_2).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.23Bb)

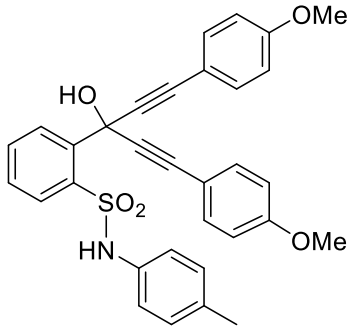


From 1-pentyne (9.15 mmol) and 2-(*p*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.66 mmol) to give the title compound as a pale yellow powder (1.13 g, 76%) m.p. 102 – 103 °C; HRMS found [M+Na]$^+$ = 432.1608; $C_{24}H_{27}NO_3SNa$ [M+Na]$^+$ requires = 432.1604.

δ_H ($CDCl_3$) 8.31 (1H, dd, *J* = 7.9, 1.0 Hz, 2-*H*), 7.71 (1H, s, N*H*), 7.59 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.52 (1H, td, *J* = 7.9, 1.0 Hz, 3-*H*), 7.23 (1H, td, *J* = 7.9, 1.0 Hz, 4-*H*), 7.99 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 6.90 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 5.83 (1H, s, O*H*), 2.33 (4H, t, *J* = 7.0 Hz, CH_2), 2.27 (3H, s, Ar-*Me*), 1.66 – 1.57 (4H, m, CH_2), 1.02 (6H, t, *J* = 7.0 Hz, CH_3). δ_c 140.07 ($_q$C), 136.56 ($_q$C), 135.06 ($_q$C), 133.34 ($_q$C), 133.10 (CH), 132.01 (CH), 130.39 (CH), 129.75 (CH), 128.45 (CH), 124.38 (CH), 87.62 ($_q$C), 81.44 ($_q$C), 66.28 ($_q$C), 21.71 (CH_2), 20.95 (CH_3), 20.91 (CH_2), 13.60 (CH_3).

ν_{max}/cm^{-1}: 3405 b (OH), 3264 m (NH), 2955 m (Ar-H), 2933 m (CH_2, CH_3), 2870 w (CH_2, CH_3), 2240 w (C≡C), 1508 s (C=C), 1437 w (CH_2), 1389 w (CH_3), 1299 s (SO_2), 1165 s (R-OH), 1064 s (SO_2).

2-[3-Hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (2.23Bc)



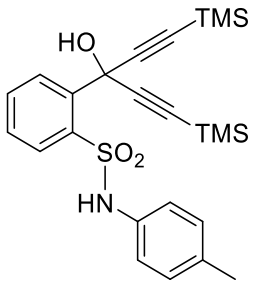
From 1-ethynyl-4-methoxybenzene (27.5 mmol) and 2-(*p*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (11.0 mmol) to give the title compound as a pale orange powder (5.50 g, 93%) m.p. 145 – 146 °C; HRMS found $[M+Na]^+$ = 560.1505; $C_{32}H_{27}NO_5SNa$ $[M+Na]^+$ requires = 560.1507.

δ_H ($CDCl_3$) 8.44 (1H, dd, *J* = 7.8, 1.1 Hz, 2-*H*), 7.64 (1H, app. d, 5-*H*), 7.57 (1H, td, *J* = 7.9, 1.1, Hz, 3-*H*), 7.50 (4H, m, Ar-*H*), 7.28* (1H, td, *J* = 7.8, 1.1 Hz, 4-*H*), 6.96 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 6.90 – 6.85 (6H, m, *o*-Ar-*H,* Ar-*H*), 6.10 (1H, s, N*H*), 3.81 (6H, s, O-*Me*), 2.24 (3H, s, Ar-*Me*). δ_c 160.37 ($_qC$), 139.68 ($_qC$), 136.44 ($_qC$), 135.34 ($_qC$), 133.45 (CH), 133.32 (CH), 133.25 ($_qC$), 132.33 (CH), 130.33 (CH), 129.75 (CH), 128.75 (CH), 124.17 (CH), 114.18 (CH), 113.30 ($_qC$), 87.78 ($_qC$), 86.92 ($_qC$), 67.06 ($_qC$), 55.35 (CH_3), 20.93 (CH_3).

ν_{max}/cm^{-1}: 3291 b (OH), 2955 w (NH), 2226 w (C≡C), 1605 s (C=C), 1456 w (CH_3), 1390 w (SO_2), 1164 s (R-OH), 1029 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (2.23Be)



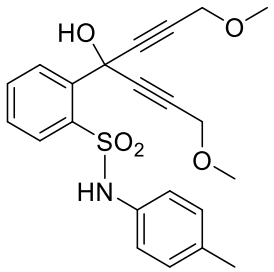
From (trimethylsilyl)acetylene (27.5 mmol) and 2-(*p*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (11.0 mmol) to give the title compound as an orange oil (3.27 g, 63%); HRMS found $[M+Na]^+$ = 492.1464; $C_{24}H_{31}NO_3SSi_2Na$ $[M+Na]^+$ requires = 492.1455.

δ_H ($CDCl_3$) 8.38 (1H, app. d, 2-*H*), 7.92 (1H, s, N*H*), 7.54 (1H, td, *J* = 7.7, 1.1 Hz, 3-*H*), 7.49 (1H, app. d, 5-*H*), 7.24* (1H, app. t, 4-*H*), 7.01 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 6.99 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 6.24 (1H, s, O*H*), 2.27 (3H, s, Ar-*Me*), 0.25 (18H, s, Si-*Me*$_3$). δ_c 138.41 ($_q$C), 137.51 ($_q$C), 135.62 ($_q$C), 133.80 (CH), 133.40 ($_q$C), 132.82 (CH), 130.84 (CH), 130.24 (CH), 129.33 (CH), 125.63 (CH), 105.25 ($_q$C), 93.09 ($_q$C), 66.83 ($_q$C), 21.49 (CH_3), 0.00 (Si-Me_3).

ν_{max}/cm^{-1}: 3420 w (OH), 3261 w (NH), 2960 m (CH_3), 1509 s (C=C), 1334 m (SO_2), 1163 s (R-OH), 1053 m (SO_2).

*Overlapping with $CDCl_3$ signal

2-(4-Hydroxy-1,7-dimethoxyhepta-2,5-diyn-4-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.23Bf)



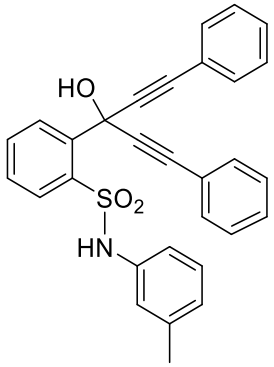
From methyl propargyl ether (9.15 mmol) and 2-(*p*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.66 mmol) to give the title compound as a beige powder (0.99 g, 66%) m.p. 110 – 111 °C; HRMS found $[M+K]^+$ = 452.0930; $C_{22}H_{23}NO_5SK$ $[M+K]^+$ requires = 452.0937.

δ_H ($CDCl_3$) 8.29 (1H, app. d, 2-*H*), 7.95 (1H, s, N*H*), 7.55 – 7.50 (2H, m, 5-*H,* 3-*H*), 7.24* (1H, app. t, 4-*H*), 7.04 – 6.97 (4H, m, Ar-*H*), 6.28 (1H, s, O*H*), 4.27 (4H, AB_q, *J* = 15.7 Hz, CH_aH_b), 3.41 (6H, s, *Me*), 2.29 (3H, s, Ar-*Me*). δ_c 138.62 ($_q$C), 136.46 ($_q$C), 136.06 ($_q$C), 133.15 ($_q$C), 133.10 (CH), 132.59 (CH), 129.74 (CH), 129.62 (CH), 128.87 (CH), 124.60 (CH), 85.84 ($_q$C), 82.84 ($_q$C), 65.72 ($_q$C), 60.15 (CH_2), 58.47 (CH_3), 20.97 (CH_3).

ν_{max}/cm^{-1}: 3386 b (OH), 3281 m (NH), 2939 w (CH_2, CH_3), 2824 w (CH_2, CH_3), 1508 s (C=C), 1434 w (CH_2), 1394 w (CH_3), 1328 m (SO_2), 1167 s (R-OH), 1093 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*m*-tolyl)benzenesulfonamide (2.23Ca)

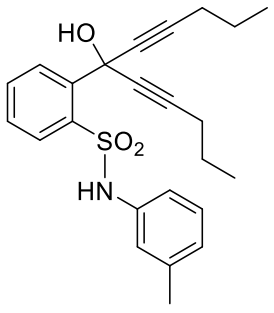


From phenylacetylene (18.3 mmol) and 2-(*m*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (7.32 mmol) to give the title compound as an orange powder (3.28 g, 94%) m.p. 178 – 180 °C; HRMS found $[M+Na]^+$ = 500.1291; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1297.

δ_H ($CDCl_3$) 8.44 (1H, dd, *J* = 7.9, 1.2 Hz, 2-*H*), 7.74 (1H, dd, *J* = 7.9, 1.2 Hz, 5-*H*), 7.61 – 7.56 (6H, m, 3-*H,* Ph-*H*), 7.40 – 7.29 (7H, m, Ph-*H,* 4-*H*), 7.05 – 7.02 (1H, m, *m*-Ar-*H*), 6.93 – 6.91 (1H, m, *o*-Ar-*H*), 6.82 – 6.80 (2H, m, Ar-*H*), 6.04 (1H, s, N*H*), 2.19 (3H, s, Ar-*Me*). δ_c 139.43 ($_q$C), 139.24 ($_q$C), 135.85 ($_q$C), 135.59 ($_q$C), 133.36 (CH), 132.27 (CH), 131.92 [2 X C (CH)], 130.36 (CH), 129.34 (CH), 128.93 (CH), 128.88 (CH), 128.54 [2 X C (CH)], 127.11 (CH), 124.30 (CH), 121.33 ($_q$C), 120.36 (CH), 88.82 ($_q$C), 86.90 ($_q$C), 67.08 ($_q$C), 21.23 (CH_3).

ν_{max}/cm^{-1}: 3383 b (OH), 3292 m (NH), 2224 s (C≡C), 1608 w (C=C), 1385 s (CH_3), 1326 s (SO_2), 1169 s (SO_2), 1155 s (R-OH), 729 w (Ph-H), 688 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(*m*-tolyl)benzenesulfonamide (2.23Cb)

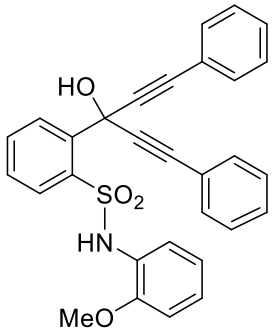


From 1-pentyne (18.3 mmol) and 2-(*m*-tolyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (7.32 mmol) to give the title compound as a pale pink powder (2.51 g, 84%) m.p. 117 – 118 °C; HRMS found $[M+Na]^+$ = 432.1607; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 432.1610.

δ_H ($CDCl_3$) 8.31 (1H, dd, *J* = 7.9, 1.3 Hz, 2-*H*), 7.72 (1H, s, N*H*), 7.64 (1H, dd, *J* = 7.9, 1.3 Hz, 5-*H*), 7.52 (1H, td, *J* = 7.9, 1.3 Hz, 3-*H*), 7.24 (1H, td, *J* = 7.9, 1.3 Hz, 4-*H*), 7.08 (1H, app. t, *m*-Ar-*H*), 6.96 – 6.94 (1H, m, *o*-Ar-*H*), 6.89 (1H, app. s, *o*-Ar-*H*), 6.81 – 6.79 (1H, m, *p*-Ar-*H*), 5.76 (1H, s, O*H*), 2.33 (4H, t, *J* = 7.1 Hz, CH_2), 2.25 (3H, s, Ar-*Me*), 1.63 (4H, sxt, *J* = 7.3 Hz, CH_2), 1.03 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 140.16 ($_q$C), 139.21 ($_q$C), 136.01 ($_q$C), 135.19 ($_q$C), 133.10 (CH), 131.90 (CH), 130.41 (CH), 128.89 (CH), 128.41 (CH), 127.27 (CH), 124.72 (CH), 120.84 (CH), 87.59 ($_q$C), 81.46 ($_q$C), 66.31 ($_q$C), 21.71 (CH_2), 21.27 (CH_3), 20.91 (CH_2), 13.57 (CH_3).

ν_{max}/cm^{-1}: 3403 b (OH), 3278 m (NH), 2961 w (Ar-H), 2932 w (CH_2, CH_3), 2870 w (CH_2, CH_3), 1590 s (C=C), 1494 w (CH_2, CH_3), 1392 s (SO_2), 1173 s (R-OH), 1107 w (SO_2).

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (2.23Da)

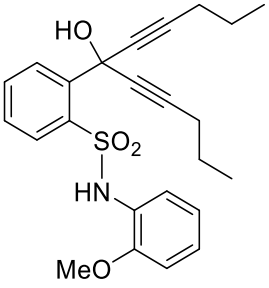


From phenylacetylene (8.65 mmol) and 2-(2-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.46 mmol) to give the title compound as a golden powder (1.09 g, 59%) m.p. 133 – 135 °C; HRMS found $[M+Na]^+$ = 516.1248; $C_{30}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 516.1240.

δ_H [$(CD_3)_2CO$] 8.45 (1H, app. d, 2-*H*), 7.91 (1H, dd, *J* = 7.9, 0.9 Hz, 5-*H*), 7.72 (1H, td, *J* = 7.9, 0.9 Hz, 3-*H*), 6.91 (1H, app. t, Ar-*H*), 6.85 (1H, app. d, Ar-*H*), 7.59 – 7.53 (5H, m, Ar-*H,* Ph-*H*), 7.49 – 7.40 (7H, m, 4-*H*, Ph-*H*), 7.06 (1H, td, *J* = 7.9, 1.4 Hz, Ar-*H*), 3.56 (3H, s, O-*Me*). δ_c 150.74 ($_q$C), 140.17 ($_q$C), 137.51 ($_q$C), 133.08 (CH), 131.61 (CH), 131.43 (CH), 129.73 (CH), 129.05 (CH), 128.58 (CH), 128.57 (CH), 126.56 ($_q$C), 125.55 (CH), 122.43 (CH), 122.16 ($_q$C), 120.65 (CH), 111.22 (CH), 89.63 ($_q$C), 85.31 ($_q$C), 66.41 ($_q$C), 55.21 (CH_3).

ν_{max}/cm^{-1}: 3411 w (OH), 3243 w (NH), 2221 w (C≡C), 1596 w (C=C), 1447 m (CH_3), 1259 m (SO_2), 1168 s (R-OH), 1048 w (SO_2), 750 s (Ph-H), 686 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (2.23Db)

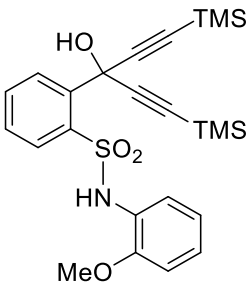


From 1-pentyne (8.65 mmol) and 2-(2-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (3.46 mmol) to give the title compound as a red oil (1.08 g, 74%); HRMS found $[M+Na]^+$ = 448.1562; $C_{24}H_{27}NO_4SNa$ $[M+Na]^+$ requires = 448.1553.

δ_H ($CDCl_3$) 8.29 (1H, dd, *J* = 7.9, 1.0 Hz, 2-*H*), 7.95 (1H, s, N*H*), 7.58 (1H, dd, *J* = 7.9, 1.5 Hz, Ar-*H*), 7.52 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.45 (1H, td, *J* = 7.9, 1.0 Hz, 3-*H*), 7.19 (1H, td, *J* = 7.9, 1.0 Hz, 4-*H*), 7.11 (1H, td, *J* = 7.9, 1.5 Hz, Ar-*H*), 6.95 (1H, td, *J* = 7.9, 1.5 Hz, Ar-*H*), 6.65 (1H, app. d, Ar-*H*), 5.83 (1H, s, O*H*), 3.36 (3H, s, O-*Me*), 2.32 (4H, t, *J* = 7.1 Hz, CH_2), 1.61 (4H, sxt, *J* = 7.1 Hz, CH_2), 1.03 (6H, t, *J* = 7.1 Hz, CH_3). δ_c 151.59 ($_q$C), 140.74 ($_q$C), 136.17 ($_q$C), 132.77 (CH), 131.10 (CH), 129.98 (CH), 127.99 (CH), 126.89 (CH), 125.80 (CH), 125.41 (CH), 121.07 (CH), 110.74 (CH), 87.17 ($_q$C), 80.88 ($_q$C), 66.15 ($_q$C), 55.31 (CH), 21.88 (CH_3), 21.74 (CH_2), 20.95 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3435 w (OH), 3253 w (NH), 2963 m (Ar-H), 2934 m (CH_2, CH_3), 2872 w (CH_2, CH_3), 2242 w (C≡C), 1600 m (C=C), 1497 s (CH_2), 1382 m (CH_3), 1333 s (SO_2), 1156 s (R-OH), 1110 s (SO_2).

2-[3-Hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-(2-methoxyphenyl)benzenesulfonamide (2.23De)



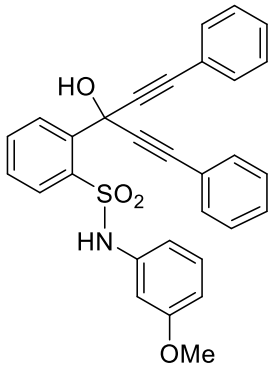
From (trimethylsilyl)acetylene (17.3 mmol) and 2-(2-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (6.91 mmol) to give the title compound as a brown solid (2.08 g, 62%)

m.p. 138 – 139 °C; HRMS found $[M+Na]^+$ = 508.1404; $C_{24}H_{31}NO_4SSi_2Na$ $[M+Na]^+$ requires = 508.1404.

δ_H ($CDCl_3$) 8.34 (1H, app. d, 2-*H*), 8.02 (1H, s, N*H*), 7.57 – 7.50 (2H, m, 3-*H,* Ar-*H*), 7.42 (1H, app. d, 5-*H*), 7.22 – 7.15 (2H, m, 4-*H,* Ar-*H*), 7.01 – 6.97 (1H, m, Ar-*H*), 6.68 – 6.65 (1H, m, Ar-*H*), 6.12 (1H, s, O*H*), 3.31 (3H, s, O-*Me*), 0.25 (18H, s, Si-Me_3). δ_c 152.27 ($_q$C), 138.92 ($_q$C), 136.39 ($_q$C), 132.81 (CH), 131.26 (CH), 129.87 (CH), 128.24 (CH), 127.63 (CH), 127.49 (CH), 124.87 ($_q$C), 121.03 (CH), 104.00 ($_q$C), 91.87 ($_q$C), 66.32 ($_q$C), 54.99 (CH_3), -0.50 (Si-Me_3).

ν_{max}/cm^{-1}: 3424 w (OH), 3219 b (NH), 2961 m (CH_3), 1598 s (C=C), 1325 m (SO_2), 1157 s (R-OH), 1059 m (SO_2).

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(3-methoxyphenyl)benzenesulfonamide (2.23Ea)

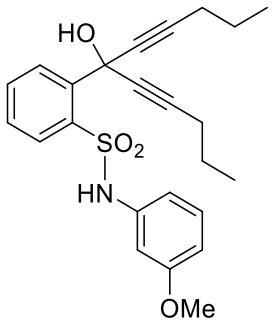


From phenylacetylene (13.0 mmol) and 2-(3-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5.18 mmol) to give the title compound as a beige powder (2.16 g, 84%) m.p. 150 – 152 °C; HRMS found $[M+Na]^+$ = 516.1244; $C_{30}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 516.1245.

δ_H ($CDCl_3$) 8.43 (1H, dd, *J* = 7.9, 1.0 Hz, 2-*H*), 7.91 (1H, app. d, 5-*H*), 7.63 (1H, s, N*H*), 7.61 – 7.56 (5H, m, 3-*H,* Ph-*H*), 7.40 – 7.30 (7H, m, 4-*H*, Ar-*H*), 7.04 (1H, app. t, Ar-*H*), 6.66 – 6.62 (2H, m, Ar-*H*), 6.56 (1H, dd, *J* = 8.0, 1.1 Hz, Ar-*H*), 5.96 (1H, s, O*H*), 3.67 (3H, s, O-*Me*). δ_c 160.16 ($_q$C), 139.43 ($_q$C), 137.16 ($_q$C), 133.44 (CH), 132.27 (CH), 131.92 (CH), 130.40 (CH), 129.84 (CH), 129.40 (CH), 128.94 (CH), 128.71 ($_q$C), 128.55 (CH), 128.29 (CH), 121.30 ($_q$C), 115.34 (CH), 112.16 (CH), 109.02 (CH), 88.78 ($_q$C), 86.90 ($_q$C), 67.08 ($_q$C), 55.30 (CH_3).

ν_{max}/cm^{-1}: 3404 b (OH), 3271 w (NH), 2229 w (C≡C), 1606 w (C=C), 1488 m (CH_3), 1392 s (SO_2), 1149 s (R-OH), 1049 w (SO_2), 730 s (Ph-H), 688 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(3-methoxyphenyl)benzenesulfonamide (2.23Eb)



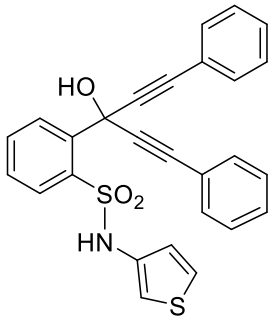
From 1-pentyne (13.0 mmol) and 2-(3-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (5.18 mmol) to give the title compound as an orange powder (1.63 g, 74%) m.p. 84 – 85 °C; HRMS found $[M+Na]^+$ = 448.1555; $C_{24}H_{27}NO_4SNa$ $[M+Na]^+$ requires = 448.1558.

δ_H ($CDCl_3$) 8.29 (1H, dd, *J* = 1.0, 7.9 Hz, 2-*H*), 7.98 (1H, s, N*H*), 7.69 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.52 (1H, td, *J* = 7.9, 1.0 Hz, 3-*H*), 7.26* (1H, td, *J* = 7.9, 1.0 Hz, 4-*H*), 7.10 – 7.05 (1H, m, Ar-*H*), 6.69 – 6.68 (2H, m, Ar-*H*), 6.56 (1H, app. d, Ar-*H*), 5.69 (1H, s, O*H*), 3.73 (3H, s, O-*Me*), 2.33 (4H, t, *J* = 7.1 Hz, CH_2), 1.62 (4H, sxt, *J* = 7.1 Hz, CH_2), 1.03 (6H, t, *J* = 7.1 Hz, CH_3). δ_c 160.15 ($_q$C), 140.20 ($_q$C), 137.34 ($_q$C), 135.08 ($_q$C), 133.16 (CH), 131.90 (CH), 130.46 (CH), 129.79 (CH), 128.48 (CH), 115.75 (CH), 112.13 (CH), 109.56 (CH), 87.62 ($_q$C), 81.43 ($_q$C), 66.33 ($_q$C), 55.33 (CH), 21.70 (CH_2), 20.90 (CH_2), 13.57 (CH_3).

ν_{max}/cm^{-1}: 3402 b (OH), 3254 m (NH), 2963 m (Ar-H), 2932 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 2235 w (C≡C), 1606 m (C=C), 1491 s (CH_2), 1394 m (CH_3), 1327 s (SO_2), 1169 s (R-OH), 1109 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(thiophen-3-yl)benzenesulfonamide (2.23Ga)

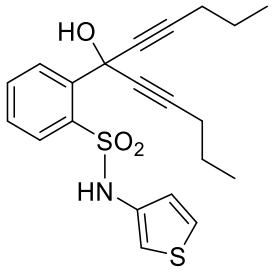


From phenylacetylene (18.9 mmol) and 2-(thiophen-3-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (7.54 mmol) to give the title compound as a brown solid (1.49 g, 42%) m.p. 107 °C decomp; HRMS found $[M+Na]^+$ = 492.0699; $C_{27}H_{19}NO_3S_2Na$ $[M+Na]^+$ requires = 492.0698.

δ_H ($CDCl_3$) 8.43 (1H, dd, *J* = 8.0, 1.2 Hz, 2-*H*), 7.80 (1H, app. d, 5-*H*), 7.72 (1H, s, N*H*), 7.61 (1H, td, *J* = 8.0, 1.2 Hz, 3-*H*), 7.59 – 7.55 (2H, m, Ph-*H*), 7.50 – 7.47 (3H, m, Ph-*H*), 7.41 – 7.30 (6H, m, Ph-*H,* 4-*H*), 7.12 – 7.10 (1H, m, Ar-*H*), 6.83 (1H, dd, *J* = 3.0, 1.3 Hz, Ar-*H*), 6.74 (1H, dd, *J* = 5.0, 1.3 Hz, Ar-*H*), 5.95 (1H, s, O*H*). δ_c 139.42 ($_q$C), 135.33 ($_q$C), 133.87 ($_q$C), 133.53 (CH), 132.35 (CH), 131.90 (CH), 130.42 ($_q$C), 128.98 (CH), 128.73 (CH), 128.58 (CH), 128.30 (CH), 125.56 (CH), 123.94 (CH), 115.74 (CH), 88.66 ($_q$C), 86.87 ($_q$C), 67.05 ($_q$C).

ν_{max}/cm^{-1}: 3415 w (OH), 3275 w (NH), 2235 w (C≡C), 1597 w (C=C), 1488 s (R-OH), 1277 m (SO_2), 1155 w (SO_2), 776 s (Ph-H), 670 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(thiophen-3-yl)benzenesulfonamide (2.23Gb)

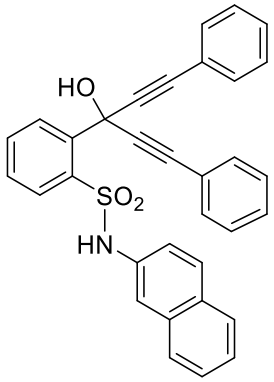


From 1-pentyne (18.9 mmol) and 2-(thiophen-3-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (7.54 mmol) to give the title compound as a light brown solid (2.19 g, 69%) m.p. 87 – 88 °C; HRMS found $[M+Na]^+$ = 424.1016; $C_{21}H_{23}NO_3S_2Na$ $[M+Na]^+$ requires = 424.1011.

δ_H ($CDCl_3$) 8.30 (1H, dd, *J* = 7.9, 1.1 Hz, 2-*H*), 7.86 (1H, s, N*H*), 7.72 (1H, dd, *J* = 7.9, 1.1 Hz, 5-*H*), 7.55 (1H, td, *J* = 8.0, 1.2 Hz, 3-*H*), 7.29 (1H, td, *J* = 8.0, 1.2 Hz, 4-*H*), 7.15 – 7.13 (1H, m, Ar-*H*), 6.85 (1H, dd, *J* = 4.0, 1.3 Hz, Ar-*H*), 6.80 (1H, dd, *J* = 4.0, 1.3 Hz, Ar-*H*), 5.65 (1H, s, O*H*), 2.32 (4H, t, *J* = 7.3 Hz, CH_2), 1.61 (4H, sxt, *J* = 7.3 Hz, CH_2), 1.02 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 140.21 ($_q$C), 134.94 ($_q$C), 134.10 ($_q$C), 133.25 (CH), 131.97 (CH), 130.49 (CH), 128.51 (CH), 125.50 (CH), 124.22 (CH), 116.19 (CH), 87.57 ($_q$C), 81.30 ($_q$C), 66.31 ($_q$C), 21.71 (CH_2), 20.88 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3393 b (OH), 3234 m (NH), 2963 m (Ar-H), 2904 w (CH_2, CH_3), 2869 w (CH_2, CH_3), 2222 w (C≡C), 1452 w (CH_2), 1362 m (CH_3), 1336 s (SO_2), 1163 s (R-OH), 1107 s (SO_2).

2-(3-Hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (2.23Ha)

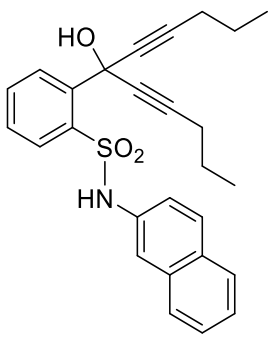


From phenylacetylene (24.3 mmol) and 2-(naphthalen-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (9.70 mmol) to give a beige powder which was recrystallised (EtOAc – pentane) to give the title compound as a beige powder (4.88 g, 98%) m.p. 166 – 168 °C; HRMS found $[M+Na]^+$ = 536.1301; $C_{33}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 536.1300.

δ_H ($CDCl_3$) 8.43 (1H, dd, *J* = 8.0, 1.2 Hz, 2-*H*), 7.86 (1H, s, N*H*), 7.74 – 7.72 (2H, m, Ar-*H*, 5-*H*), 7.65 – 7.53 (7H, m, Ar-*H*, 3-*H*), 7.47 (1H, d, *J* = 2.1 Hz, Ar-*H*), 7.44 – 7.33 (8H, m, Ar-*H*), 7.23 (1H, td, *J* = 8.0, 1.2 Hz, 4-*H*), 7.17 (1H, dd, *J* = 8.7, 2.1 Hz, Ar-*H*), 5.99 (1H, s, O*H*). δ_c 139.46 ($_q$C), 135.54 ($_q$C), 133.51 ($_q$C), 133.45 (CH), 133.43 ($_q$C), 132.21 (CH), 131.94 (CH), 131.58 ($_q$C), 130.45 (CH), 129.42 (CH), 129.20 (CH), 129.00 (CH), 128.57 (CH), 127.63 (CH), 127.60 (CH), 126.61 (CH), 125.88 (CH), 122.43 (CH), 121.32 ($_q$C), 121.06 (CH), 88.85($_q$C), 86.96 ($_q$C), 67.16 ($_q$C).

ν_{max}/cm^{-1}: 3387 b (OH), 3270 m (NH), 3055 w (Ar-H), 2226 s (C≡C), 1598 w (C=C), 1373 m (SO_2), 1162 s (R-OH), 1032 s (SO_2), 752 s (Ph-H), 721 s (Ph-H).

2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (2.23Hb)

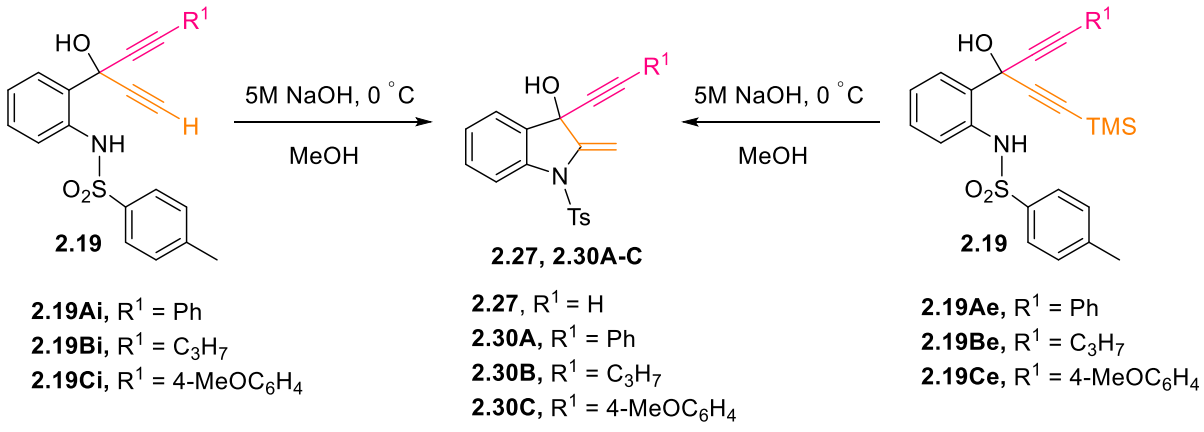


From 1-pentyne (24.3 mmol) and 2-(naphthalen-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (9.70 mmol) to give the title compound as yellow flakes (3.85 g, 89%) m.p. 127 – 128 °C; HRMS found $[M+Na]^+$ = 468.1601; $C_{27}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 468.1610.

δ_H ($CDCl_3$) 8.30 (1H, dd, *J* = 7.9, 1.1 Hz, 2-*H*), 7.99 (1H, s, N*H*), 7.77 – 7.75 (1H, m, Ar-*H*), 7.71 – 7.67 (2H, m, Ar-*H*), 7.64 (1H, dd, *J* = 7.9, 1.1 Hz, 5-*H*), 7.50 – 7.41 (4H, m, Ar-*H*), 7.21 – 7.14 (2H, m, Ar-*H,* 4-*H*), 5.72 (1H, s, O*H*), 2.35 (4H, t, *J* = 7.3 Hz, CH_2), 1.64 (4H, sxt, *J* = 7.3 Hz, CH_2), 1.04 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 140.21 ($_q$C), 135.13 ($_q$C), 133.67 ($_q$C), 133.47 ($_q$C), 133.16 (CH), 131.85 (CH), 131.68 ($_q$C), 130.52 (CH), 129.16 (CH), 128.54 (CH), 127.65 (CH), 127.63 (CH), 126.62 (CH), 125.93 (CH), 122.79 (CH), 121.48 (CH), 87.68 ($_q$C), 81.40 ($_q$C), 66.40 ($_q$C), 21.70 (CH_2), 20.94 (CH_2), 13.59 (CH_3).

ν_{max}/cm^{-1}: 3405 b (OH), 3261 m (NH), 2961 m (Ar-H), 2933 w (CH_2, CH_3), 2870 w (CH_2, CH_3), 2219 w (C≡C), 1602 w (Ar-H), 1453 w (CH_2), 1353 m (CH_3), 1322 s (SO_2), 1162 s (R-OH), 1110 s (SO_2).

6.2.7 General Method for Synthesis of 3-Alkynyl-2-methylene-1-tosylindolin-3-ols



2.19Ai, R^1 = Ph
2.19Bi, R^1 = C_3H_7
2.19Ci, R^1 = 4-$MeOC_6H_4$

2.27, R^1 = H
2.30A, R^1 = Ph
2.30B, R^1 = C_3H_7
2.30C, R^1 = 4-$MeOC_6H_4$

2.19Ae, R^1 = Ph
2.19Be, R^1 = C_3H_7
2.19Ce, R^1 = 4-$MeOC_6H_4$

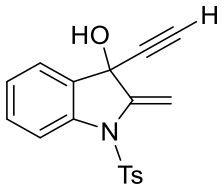
Scheme 6.1

To a cold (0 °C) solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (X mmol, 1 equiv.) in MeOH (10 – 80 mL) was added 5M NaOH (Y equiv.) dropwise. The mixture was brought to r.t. and stirred for 0.5 – 24 h (Table 5.1). After this time, the reaction mixture was diluted with water and EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated. The following were synthesised by this method.

Entry	R^1	Dialkynol	Time (h)	Base equiv.	Product	Yield (%)
1	TMS	**2.5e**	0.25	28.3	**2.27**	100
2	Ph	**2.19Ae**	24	11.2	**2.30A**	76
3	Ph	**2.19Ai**	1	59.5	**2.30A**	70*
4	C_3H_7	**2.19Be**	24	10.1	**2.30B**	62
5	C_3H_7	**2.19Bi**	0.5	5.0	**2.30B**	91
6	4-$MeOC_6H_4$	**2.19Ce**	24	22.9	**2.30C**	40
7	4-$MeOC_6H_4$	**2.19Ci**	24	60.4	**2.30C**	77

Table 6.1 Base mediated cyclisation to **2.27** and **2.30.** *By ^{1}H NMR

3-Ethynyl-2-methylene-1-tosylindolin-3-ol (2.27)

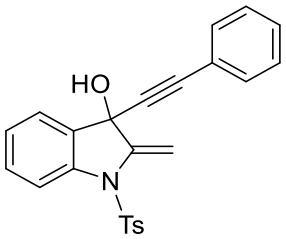


Entry 1 (Table 6.1) to give the title compound as a brown oil; HRMS found $[M+Na]^+$ = 348.0661; $C_{18}H_{15}NO_3SNa$ $[M+Na]^+$ requires = 348.0665.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 4-*H*), 7.57 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.45 (1H, app. d, 7-*H*), 7.42 – 7.37 (1H, m, 5-*H*), 7.20 – 7.15 (3H, m, 6-*H*, *m*-Ar-*H*), 5.90 (1H, d, *J* = 2.0 Hz, C*H*), 5.46 (1H, d, *J* = 2.0 Hz, C*H*), 2.55 (1H, s, C*H*), 2.32 (3H, s, Ar-*Me*), 2.21 (1H, s, O*H*). δ_c 149.73 ($_q$C), 144.82 ($_q$C), 140.81 ($_q$C), 133.64 ($_q$C), 132.20 ($_q$C), 130.98 (CH), 129.49 (CH), 127.427 (CH), 125.66 (CH), 124.44 (CH), 116.89 (CH), 102.41 (CH_2), 82.21 ($_q$C), 74.68 (CH), 72.13 ($_q$C), 21.59 (CH_3).

ν_{max}/cm^{-1}: 3498 s (OH), 3284 w (C≡C-H),1658 w (C=C), 1597 s (C=C), 1353 s (SO_2), 1164 s (R-OH), 1089 w (SO_2), 1018 m (C=CH_2), 936 m (C=CH_2).

2-Methylene-3-(phenylethynyl)-1-tosylindolin-3-ol (2.30A)

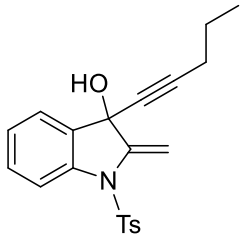


From entries 2 or 3 (Table 6.1) to give the title compound as an orange oil; HRMS found $[M+Na]^+$ = 424.0979; $C_{24}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 424.0978.

δ_H [$(CD_3)_2CO$] 7.78 (1H, app. d, 4-*H*), 7.61 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.47 (1H, dd, *J* = 7.8, 0.9 Hz, 7-*H*), 7.40 – 7.36 (1H, m, 5-*H*), 7.32 – 7.29 (3H, m, Ph-*H*), 7.23 – 7.16 (5H, m, Ph-*H*, 6-*H*, *m*-Ar-*H*), 5.78 (1H, d, *J* = 1.7 Hz, C*H*), 5.65 (1H, s, O*H*), 5.41 (1H, d, *J* = 1.7 Hz, C*H*), 2.17 (3H, s, Ar-*Me*). δ_c 151.30 ($_q$C), 144.96 ($_q$C), 140.45 ($_q$C), 134.16 ($_q$C), 133.96 ($_q$C), 131.53 ($_q$C), 131.44 (CH), 130.21 (CH), 129.51 (CH), 128.71 (CH), 128.45 (CH), 127.45 (CH), 125.39 (CH), 124.71 (CH), 115.95 (CH), 99.70 (CH_2), 89.36 ($_q$C), 85.24 (CH), 72.16 ($_q$C), 20.47 (CH_3).

ν_{max}/cm^{-1}: 3387 s (OH), 2222 w (C≡C), 1658 w (C=C), 1597 s (C=C), 1355 s (SO_2), 1167 s (R-OH), 1089 w (SO_2), 1020 m (C=CH_2), 938 m (C=CH_2).

2-Methylene-3-(pent-1-yn-1-yl)-1-tosylindolin-3-ol (2.30B)

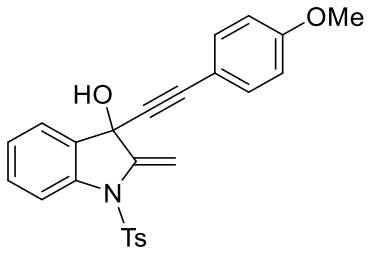


From entries 4 or 5 (Table 6.1) to give the title compound as a red oil; HRMS found $[M-H_2O+H]^+$ = 350.1213; $C_{21}H_{20}NO_2S$ $[M-H_2O+H]^+$ requires = 350.1205.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 4-*H*), 7.58 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.44 (1H, dd, *J* = 7.5, 0.9 Hz, 7-*H*), 7.37 (1H, app. t, 5-*H*), 7.19 – 7.14 (3H, m, 6-*H, m*-Ar-*H*), 5.86 (1H, d, *J* = 1.9 Hz, C*H*), 5.44 (1H, d, *J* = 1.9 Hz, C*H*), 2.32 (3H, s, Ar-*Me*), 2.11 (2H, t, *J* = 7.2 Hz, CH_2), 1.99 (1H, s, O*H*), 1.46 (2H, sxt, *J* = 7.1 Hz, CH_2), 0.91 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 150.49 ($_q$C), 144.65 ($_q$C), 140.65 ($_q$C), 133.78 ($_q$C), 133.19 ($_q$C), 130.62 (CH), 129.42 (CH), 127.48 (CH), 125.54 (CH), 124.36 (CH), 116.80 (CH), 101.77 (CH_2), 87.56 ($_q$C), 78.99 ($_q$C), 72.49 ($_q$C), 21.76 (CH_2), 21.58 (CH_3), 20.65 (CH_2), 13.41 (CH_3).

ν_{max}/cm^{-1}: 3481 s (OH), 2961 w (Ar-H), 2929 w (CH_2, CH_3), 2871 w (CH_2, CH3), 2236 w (C≡C), 1716 w (C=C), 1598 m (C=C), 1463 s (CH_2, CH_3), 1355 s (SO_2), 1168 s (R-OH), 1089 s (SO_2), 1025 m (C=CH_2), 942 m (C=CH_2).

3-[(4-Methoxyphenyl)ethynyl]-2-methylene-1-tosylindolin-3-ol (2.30C)



From entries 6 or 7 (Table 6.1) to give the title compound as an orange oil; HRMS found $[M+Na]^+$ = 454.1081; $C_{25}H_{21}NO_4SNa$ $[M+Na]^+$ requires = 454.1089.

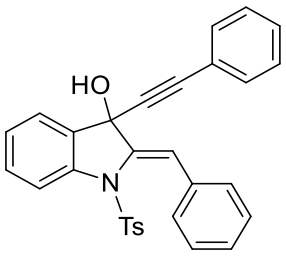
δ_H ($CDCl_3$) 7.87 (1H, app. d, 4-*H*), 7.59 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.51 (1H, app. d, 7-*H*), 7.40 – 7.40 (1H, app. t, 5-*H*), 7.24* (2H, d, *J* = 8.8 Hz, Ar-*H*), 7.19 (1H, app. t, 6-*H*), 7.11 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 6.80 (2H, d, *J* = 8.8 Hz, Ar-*H*), 5.92 (1H, d, *J* = 1.9 Hz, C*H*), 3.79 (3H, s, O-*Me*), 2.22 (3H, s, Ar-*Me*), 2.13 (1H, s, O*H*). δ_c 159.99 ($_q$C), 150.40 ($_q$C), 144.74 ($_q$C), 140.70 ($_q$C), 133.72 ($_q$C), 133.24 (CH), 133.05 ($_q$C), 130.72 (CH), 129.42 (CH), 127.48 (CH), 125.64 (CH), 124.47 (CH), 116.93 (CH), 113.90 ($_q$C), 113.87 (CH), 102.07 (CH_2), 86.48 ($_q$C), 86.11 (CH), 72.88 ($_q$C), 55.32 (CH_3), 21.48 (CH_3).

ν_{max}/cm^{-1}: 2359 w (C≡C), 1604 w (C=C), 1509 m (C=C), 1355 m (SO_2), 1168 s (R-OH), 1069 m (SO_2), 1031 w (C=CH_2), 943 w (C=CH_2).

*Overlapping with $CDCl_3$ signal

6.2.8 Silver(I) Catalysed Cyclisations of *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

(*Z*)-2-Benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol (2.33a)



To a solution of *N*-[2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (1.00g, 2.09 mmol, 1 equiv.) in MeCN (38.3 mL/mmol) was added $AgNO_3$ on silica (5 mol %, 10 % w/w) and the mixture stirred at reflux overnight. After

this time the reaction mixture was allowed to cool, filtered through Celite and evaporated to give the title compound as a brown oil (1.00 g, 100%); HRMS found $[M+Na]^+$ = 500.1293; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H [$(CD_3)_2CO$] 7.82 – 7.79 (3H, m, Ph-*H*, 4-*H*), 7.52 (1H, dd, *J* = 7.6, 0.8 Hz, 7-*H*), 7.48 – 7.44 (3H, m, 5-*H*, *o*-Ar-*H*), 7.39 – 7.34 (7H, m, Ph-*H*), 7.28 – 7.24 (2H, m, Ph-*H,* 6-*H*), 7.00 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 6.94 (1H, s, C*H*), 5.51 (1H, s, O*H*), 2.05* (3H, s, Ar-*Me*). δ_c 144.44 ($_qC$), 143.13 ($_qC$), 141.43 ($_qC$), 136.60 ($_qC$), 136.13 ($_qC$), 133.76 ($_qC$), 131.64 (CH), 129.83 (CH), 129.73 (CH), 128.94 (CH), 128.73 (CH), 128.71 ($_qC$), 128.48 (CH), 127.75 (CH), 127.47 (CH), 126.44 (CH), 124.46 (CH), 122.49 ($_qC$), 121.74 (CH), 118.570 (CH), 89.04 ($_qC$), 85.70 ($_qC$), 73.41 ($_qC$), 20.39 (CH_3).

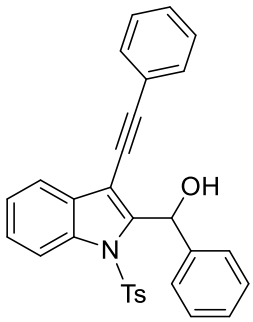
ν_{max}/cm^{-1}: 3526 w (OH), 1595 m (C=C), 1355 s (SO_2), 1162 s (R-OH), 1087 w (SO_2), 770 s (Ph-H), 690 s (Ph-H).

*Overlapping with $(CD_3)_2CO$ signal

General Method for the AgOAc-Mediated Cyclisation of *N*-[2-(3-Hydroxy-penta-1,4-diyn-3-yl)phenyl]benzenesulfonamides

To a solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added AgOAc (5 mol %) and the mixture stirred at reflux overnight. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated. The residue was purified by flash column chromatography. The following were synthesised by this method.

Phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methanol (2.32a)

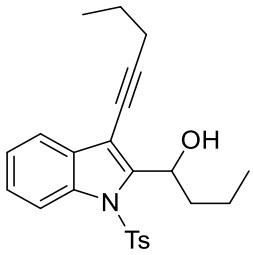


From *N*-[2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (2.09 mmol) to give the title compound as a brown oil (1.00 g, 100%); HRMS found $[M+Na]^+$ = 500.1298; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H [$(CD_3)_2CO$] 8.20 (1H, app. d, 4-*H*), 7.73 – 7.71 (3H, m, 7-*H*, *o*-Ar-*H*), 7.57 – 7.55 (2H, m, Ph-*H*), 7.49 – 7.42 (3H, m, Ph-*H,* 6-*H*), 7.39 – 7.33 (6H, m, Ph-*H,* 5-*H*), 7.29 – 7.26 (3H, m, *m*-Ar-*H,* Ph-*H*), 6.95 (1H, d, *J* = 7.1 Hz, C*H*), 5.19 (1H, d, *J* = 7.1 Hz, O*H*), 2.32 (3H, s, Ar-*Me*). δ_c 145.79 ($_q$C), 145.63 ($_q$C), 142.45 ($_q$C), 135.81 ($_q$C), 135.08 ($_q$C), 131.43 (CH), 130.07 ($_q$C), 129.97 (CH), 128.48 (CH), 128.44 (CH), 128.07 (CH), 127.22 (CH), 126.96 (CH), 126.53 (CH), 126.00 (CH), 124.52 (CH), 123.17 ($_q$C), 120.00 (CH), 115.18 (CH), 106.70 ($_q$C), 97.26 ($_q$C), 80.52 ($_q$C), 68.38 (CH), 20.58 (CH_3).

ν_{max}/cm^{-1}: 3519 w (OH), 3062 w (Ar-H), 2922 w (CH_3), 1709 s (C=C), 1596 m (C=C), 1362 s (SO_2), 1168 s (R-OH), 1087 s (SO_2), 749 s (Ph-H), 690 s (Ph-H).

1-[3-(Pent-1-yn-1-yl)-1-tosyl-1*H*-indol-2-yl]butan-1-ol (2.32b)



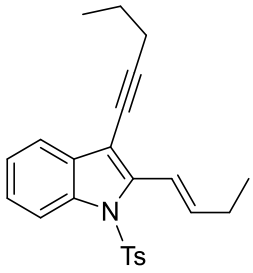
From *N*-[2-(6-hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an orange oil (0.62 g, 62%); HRMS found $[M+Na]^+$ = 500.1298; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H ($CDCl_3$) 8.06 (1H, app. d, 4-*H*), 7.71 (2H, d, *J* = 8.4 Hz, *o*-Ar-*H*), 7.55 (1H, app. d, 7-*H*), 7.32 – 7.23* (2H, m, 6-*H,* 5-*H*), 7.13 (2H, d, *J* = 8.4 Hz, *m*-Ar-*H*), 5.51 (1H, dt, *J* = 10.8, 7.1 Hz, C*H*), 3.72 (1H, d, *J* = 10.8 Hz, O*H*), 2.49 (2H, t, *J* = 7.2 Hz, CH_2), 2.26 (3H, s, Ar-*Me*), 2.16 – 2.10 (2H, m, CH_2), 1.68 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.08 (3H, t, *J* = 7.2 Hz, CH_3), 0.98 – 0.86 (5H, m, CH_3, CH_2). δ_c 145.25 ($_q$C), 145.16 ($_q$C), 136.06 ($_q$C), 135.02 ($_q$C), 130.21 ($_q$C), 129.87 (CH), 126.59 (CH), 125.63 (CH), 124.15 (CH), 120.11 (CH), 114.99 (CH), 107.07 ($_q$C), 99.27 ($_q$C), 71.52 ($_q$C), 68.74 (CH), 39.75 (CH_2), 22.19 (CH_2), 21.76 (CH_2), 21.52 (CH_3), 19.35 (CH_2), 13.85 (CH_3), 13.62 (CH_3).

ν_{max}/cm^{-1}: 3544 w (OH), 2959 w (Ar-H), 2932 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 1597 w (C=C), 1451 s (CH_2, CH_3), 1364 s (SO_2), 1172 s (R-OH), 1088 s (SO_2).

*Overlapping with $CDCl_3$ signal

(*E*)-2-(But-1-en-1-yl)-3-(pent-1-yn-1-yl)-1-tosyl-1*H*-indole (2.39)



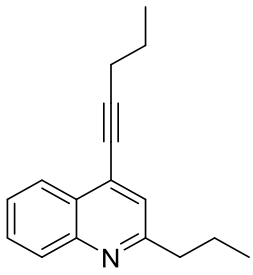
From *N*-[2-(6-hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a brown oil (0.16 g, 17%); HRMS found $[M+Na]^+$ = 414.1497; $C_{24}H_{25}NO_2SNa$ $[M+Na]^+$ requires = 414.1498.

δ_H ($CDCl_3$) 8.19 (1H, app. d, 4-*H*), 7.60 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.53 (1H, app. d, 7-*H*), 7.32 – 7.24* (2H, m, 5-*H,* 6-*H*), 7.13 (2H, d, *J* = 8.4 Hz, *m*-Ar-*H*), 6.99 (1H, d, *J* = 15.8 Hz, C*H*), 6.79 (1H, dt, *J* = 15.8, 6.5 Hz, C*H*), 2.47 (2H, t, *J* = 7.2 Hz, CH_2), 2.41 – 2.33 (2H, m, CH_2), 2.30 (3H, s, Ar-*Me*), 1.65 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.18 (3H, t, *J* = 7.4 Hz, CH_3), 1.08 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 144.85 ($_q$C), 140.69 (CH), 140.03 ($_q$C), 135.69 ($_q$C), 135.43 ($_q$C), 131.27 ($_q$C), 129.59 (CH), 126.73 (CH), 125.15 (CH), 124.06 (CH), 119.77 (CH), 118.24 (CH), 115.14 (CH), 104.29 ($_q$C), 97.02 ($_q$C), 73.35 ($_q$C), 26.69 (CH_2), 22.26 (CH_2), 21.86 (CH_2), 21.56 (CH_3), 13.64 (CH_3), 13.40 (CH_3).

ν_{max}/cm^{-1}: 2962 w (Ar-H), 2931 w (CH_2, CH_3), 2872 w (CH_2, CH_3), 1682 w (C=C), 1597 w (C=C), 1450 s (CH_2, CH_3), 1370 s (SO_2), 1171 s (R-OH), 1088 s (SO_2), 965 w (trans CH=CH).

*Overlapping with $CDCl_3$ signal

4-(Pent-1-yn-1-yl)-2-propylquinoline (2.35b)

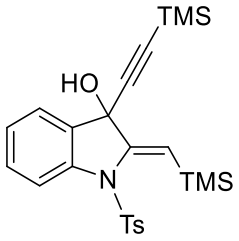


From *N*-[2-(6-hydroxyundeca-4,7-diyn-6-yl)phenyl]-4-methylbenzenesulfonamide (2.44 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an orange oil (0.04 g, 8%); HRMS found $[M+H]^+$ = 238.1604; $C_{17}H_{20}N$ $[M+H]^+$ requires = 238.1590.

δ_H ($CDCl_3$) 8.22 (1H, app. d, 5-*H*), 8.04 (1H, app. d, 8-*H*), 7.70 – 7.66 (1H, m, 7-*H*), 7.54 – 7.50 (1H, m, 6-*H*), 7.36 (1H, s, C*H*), 2.93 – 2.89 (2H, m, CH_2), 2.56 (2H, t, *J* = 7.3 Hz, CH_2), 1.89 – 1.70 (4H, m, CH_2), 1.13 (3H, t, *J* = 7.3 Hz, CH_3), 1.01 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 162.30 ($_q$C), 147.67 ($_q$C), 130.78 ($_q$C), 129.63 (CH), 129.01 (CH), 126.63 ($_q$C), 126.05 (CH), 125.80 (CH), 123.95 (CH), 99.83 [2 X C ($_q$C)], 41.01 (CH_2), 23.24 (CH_2), 22.10 (CH_2), 21.76 (CH_2), 14.01 (CH_3), 13.69 (CH_3).

ν_{max}/cm^{-1}: 2960 m (Ar-H), 2931 m (CH_2, CH_3), 2871 m (CH_2, CH_3), 1597 s (C=C), 1453 m (CH_2, CH_3).

(*Z*)-1-Tosyl-3-[(trimethylsilyl)ethynyl]-2-[(trimethylsilyl)methylene]indolin-3-ol (2.33e)



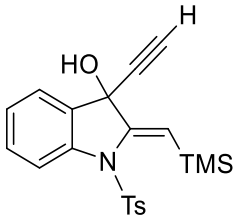
From *N*-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a white powder (0.22 g, 11%) m.p. 164 – 165 °C; HRMS found $[M+H]^+$ = 470.1635; $C_{24}H_{32}NO_3SSi_2$ $[M+H]^+$ requires = 470.1636.

δ_H ($CDCl_3$) 7.79 (1H, app. d, 4-*H*), 7.42 – 7.38 (4H, m, *o*-Ar-*H,* 7-*H*, 5-*H*), 7.20 (1H, app. t, 6-*H*), 7.09 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 6.14 (1H, s, C*H*), 2.29 (3H, s, Ar-*Me*), 1.08 (1H, s, O*H*), 0.33 (9H,

s, Si-*Me*$_3$), 0.15 (9H, s, Si-*Me*$_3$). δ_c 153.22 ($_q$C), 144.67 ($_q$C), 141.71 ($_q$C), 134.25 ($_q$C), 133.37 ($_q$C), 130.55 (CH), 129.27 (CH), 128.12 (CH), 126.43 (CH), 124.61 (CH), 124.43 (CH), 119.14 (CH), 103.48 ($_q$C), 91.76 ($_q$C), 74.15 ($_q$C), 21.57 (CH_3), 0.29 (Si-Me_3).

ν_{max}/cm^{-1}: 3438 m (OH), 2951 w (Ar-H), 2898 w (CH_3), 1644 s (C=C), 1599 s (C=C), 1340 s (SO_2), 1166 s (R-OH), 1092 s (SO_2).

(*Z*)-3-Ethynyl-1-tosyl-2-[(trimethylsilyl)methylene]indolin-3-ol (2.33e')

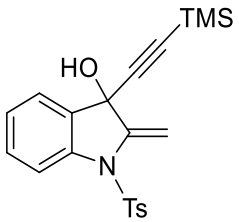


From *N*-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as a brown powder (0.88 g, 64%) m.p. 64 – 65 °C; HRMS found $[M+H]^+$ = 398.1239; $C_{21}H_{24}NO_3SSi$ $[M+H]^+$ requires = 398.1241.

δ_H ($CDCl_3$) 7.75 (1H, app. d, 4-*H*), 7.40 – 7.34 (4H, m, *o*-Ar-*H,* 7-*H*, 5-*H*), 7.16 (1H, app. t, 6-*H*), 7.05 (2H, d, *J* = 8.2 Hz, *m*-Ar-*H*), 6.05 (1H, s, C*H*), 2.43 (1H, s, O*H*), 2.26 (3H, s, Ar-*Me*), 0.32 (9H, s, Si-*Me*$_3$). δ_c 153.69 ($_q$C), 144.56 ($_q$C), 141.38 ($_q$C), 134.44 ($_q$C), 133.49 ($_q$C), 130.46 (CH), 129.24 (CH), 128.31 (CH), 126.47 (CH), 124.40 (CH), 122.95 (CH), 119.04 (CH), 82.45 ($_q$C), 74.57 (CH), 73.40 ($_q$C), 21.56 (CH_3), 0.11 (Si-Me_3).

ν_{max}/cm^{-1}: 3561 w (OH), 3286 w (C≡C-H), 2951 w (Ar-H), 1640 s (C=C), 1598 s (C=C), 1359 s (SO_2), 1166 s (R-OH), 1068 s (SO_2).

2-Methylene-1-tosyl-3-[(trimethylsilyl)ethynyl]indolin-3-ol (2.27')

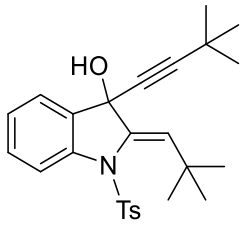


From *N*-{2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]phenyl}-4-methylbenzenesulfonamide (4.26 mmol). From flash column chromatography (5% EtOAc –

hexane) to give the title compound as a brown oil (0.01 g, 1%); HRMS found $[M+H]^+$ = 398.1243; $C_{21}H_{24}NO_3SSi$ $[M+H]^+$ requires = 398.1241.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 4-*H*), 7.58 (2H, d, *J* = 8.3 Hz, *o*-Ar-*H*), 7.45 (1H, app. d, 7-*H*), 7.41 – 7.37 (1H, m, 5-*H*), 7.20 – 7.15 (3H, m, 6-*H*, *m*-Ar-*H*), 5.89 (1H, d, *J* = 2.0 Hz, C*H*), 5.47 (1H, d, *J* = 2.0 Hz, C*H*), 2.32 (3H, s, Ar-*Me*), 0.13 (9H, s, Si-*Me*$_3$). δ_c 149.93 ($_q$C), 144.75 ($_q$C), 140.88 ($_q$C), 133.74 ($_q$C), 132.48 ($_q$C), 130.84 (CH), 129.47 (CH), 127.45 (CH), 125.57 (CH), 124.56 (CH), 116.74 (CH), 103.05 (CH_2), 102.29 ($_q$C), 91.56 ($_q$C), 72.54 ($_q$C), 21.61 (CH_3), -0.33 (Si-Me_3).

(*Z*)-3-(3,3-Dimethylbut-1-yn-1-yl)-2-(2,2-dimethylpropylidene)-1-tosylindolin-3-ol (2.33j)

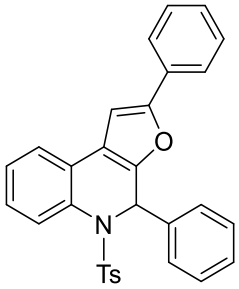


From *N*-[2-(5-hydroxy-2,2,8,8-tetramethylnona-3,6-diyn-5-yl)phenyl]-4-methylbenzenesulfonamide (2.29 mmol). From flash column chromatography (5% EtOAc – hexane) to give the title compound as an off white solid (0.54 g, 54%) m.p. 125 – 126 °C; HRMS found $[M+H]^+$ = 438.2102; $C_{26}H_{32}NO_3S$ $[M+H]^+$ requires = 438.2098.

δ_H ($CDCl_3$) 7.67 (1H, app. d, 4-*H*), 7.43 – 7.36 (4H, m, *o*-Ar-*H,* 7-*H*, 5-*H*), 7.20 (1H, app. t, 6-*H*), 7.09 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 6.08 (1H, s, C*H*), 2.29 (3H, s, Ar-*Me*), 1.36 (9H, s, *Me*$_3$), 1.20 (9H, s, *Me*$_3$). δ_c 144.65 ($_q$C), 142.42 ($_q$C), 138.95 ($_q$C), 138.58 (CH), 136.61 ($_q$C), 133.40 ($_q$C), 130.04 (CH), 129.16 (CH), 128.66 (CH), 126.71 (CH), 124.27 (CH), 119.77 (CH), 95.79 ($_q$C), 77.54 ($_q$C), 74.46 ($_q$C), 34.37 ($_q$C), 30.73 (Me_3), 29.44 (Me_3), 27.43 ($_q$C), 21.57 (CH_3).

ν_{max}/cm^{-1}: 3490 w (OH), 2963 m (Ar-H), 2868 w (CH_3), 1598 m (C=C), 1461 s (CH_3), 1354 s (SO_2), 1166 s (R-OH), 1088 s (SO_2).

6.2.9 Synthesis of 2,4-Diphenyl-5-tosyl-4,5-dihydrofuro[2,3-*c*]quinoline (2.53)

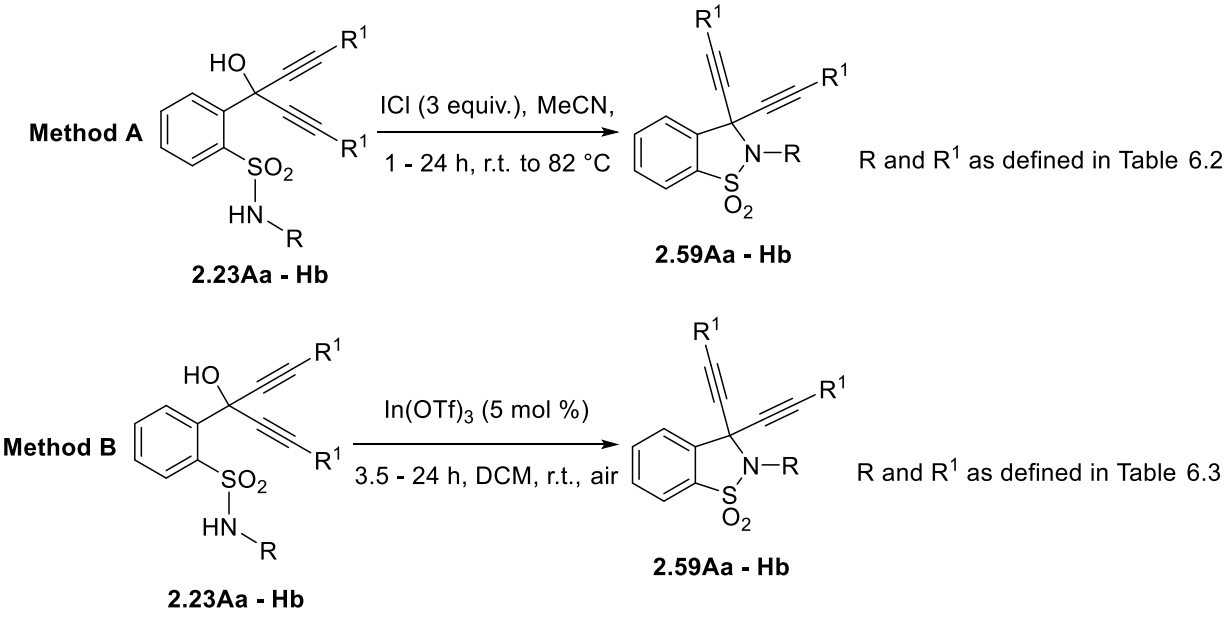


To a solution of *N*-[2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)phenyl]-4-methylbenzenesulfonamide (1.00 g, 2.09 mmol, 1 equiv.) in DCM (38.3 mL/mmol) was added indium(III) trifluoromethanesulfonate (5 mol %), the mixture stirred at r.t. for 18 h. After this time the reaction mixture was filtered through Celite. The residue was purified by flash column chromatography (10% EtOAc – hexane) and recrystallised with EtOAc – hexane to give the title compound as a beige powder (0.22 g, 22%) m.p. 130 – 131 °C; HRMS found $[M+H]^+$ = 478.1477; $C_{30}H_{24}NO_3S$ $[M+H]^+$ requires = 478.1472.

δ_H [$(CD_3)_2CO$] 7.75 – 7.73 (2H, m, Ph-*H*), 7.70 (1H, dd, *J* = 7.8, 1.2 Hz, 9-*H*), 7.49 – 7.45 (2H, m, Ph-*H*), 7.41 (1H, dd, *J* = 7.8, 1.2 Hz, 6-*H*), 7.38 – 7.22 (10H, m, Ph-*H*, 8-*H*, 7-*H*, *o*-Ar-*H*), 7.02 (2H, d, *J* = 8.0 Hz, *m*-Ar-*H*), 6.95 (1H, s, Ar-*H*), 6.73 (1H, s, 1-*H*), 2.15 (3H, s, Ar-*Me*). δ_c 154.72 ($_q$C), 147.80 ($_q$C), 143.91 ($_q$C), 137.73 ($_q$C), 134.43 ($_q$C), 131.24 ($_q$C), 130.28 ($_q$C), 129.20 (CH), 129.00 (CH), 128.85 (CH), 128.65 (CH), 128.21 (CH), 127.83 (CH), 127.70 (CH), 126.83 ($_q$C), 126.77 (CH), 126.69 (CH), 126.65 (CH), 123.67 (CH), 123.06 (CH), 118.53 ($_q$C), 100.91 (CH), 56.49 (CH), 20.36 (CH_3).

ν_{max}/cm^{-1}: 1599 w (C=C), 1450 s (CH_3), 1353 s (SO_2), 1164 s (SO_2), 750 s (Ph-H), 685 s (Ph-H).

6.2.10 General Method for the Synthesis of 3,3-Di(alkynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides



Scheme 6.2

Method **A**: To a solution of 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3.0 equiv.), the mixture was stirred at the temperature for the time indicated in Table 5.2. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography or by recrystallisation.

Entry	R	R^1	Dialkynol	Time (h)	Temp (°C)	1,2-Benzisothiazole 1,1-dioxide	Yield (%)
1*	Me	Ph	**2.23Aa**	3.5	82	**2.59Aa**	48
2	Tolyl	Ph	**2.23Ba**	24	82	**2.59Ba**	45
3	Tolyl	C_3H_7	**2.23Bb**	3.5	r.t.	**2.59Bb**	36
4	Tolyl	CH_2OMe	**2.23Bf**	1	82	**2.59Bf**	40
5	3-MeC_6H_4	Ph	**2.23Ca**	4.5	82	**2.59Ca**	47
6	3-MeC_6H_4	C_3H_7	**2.23Cb**	1.5	82	**2.59Cb**	75
7	3-$MeOC_6H_4$	C_3H_7	**2.23Eb**	21	82	**2.59Eb**	54

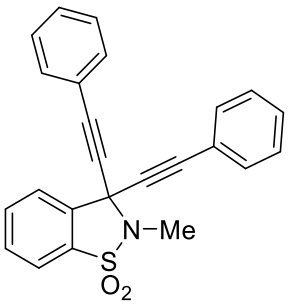
Table 6.2 Cyclisation of dialkynols **2.23Aa – Eb** with ICl to **2.59Aa – Eb** results. * 2 equiv. of ICl used

Method **B**: To a solution of 3-[2-(sulfamoyl)phenyl]penta-1,4-diyn-3-ols derivative (1.0 equiv.) in DCM (38.3 mL/mmol) was added indium(III) trifluoromethanesulfonate (5 mol %), the mixture stirred at r.t. for the time indicated in Table 5.3. After this time the reaction mixture was filtered through Celite and evaporated to give the title compound. The residue was purified by column chromatography or by recrystallisation.

Entry	Dialkynol	R	R^1	1,2-Benzisothiazole 1,1-dioxide	Time (h)	Yield (%)
1	**2.23Aa**	Me	Ph	**2.59Aa**	24	100
2	**2.23Ab**	Me	C_3H_7	**2.59Ab**	5	92
3	**2.23Ba**	Tolyl	Ph	**2.59Ba**	24	100
4	**2.23Bb**	Tolyl	C_3H_7	**2.59Bb**	24	98
5	**2.23Bc**	Tolyl	4-$MeOC_6H_4$	**2.59Bc**	23	99
6	**2.23Be**	Tolyl	TMS	**2.59Be**	24	27
7	**2.23Ca**	3-MeC_6H_4	Ph	**2.59Ca**	24	53
8	**2.23Cb**	3-MeC_6H_4	C_3H_7	**2.59Cb**	24	82
9	**2.23Da**	2-$MeOC_6H_4$	Ph	**2.59Da**	22	37
10	**2.23Db**	2-$MeOC_6H_4$	C_3H_7	**2.59Db**	3	63
11	**2.23Eb**	3-$MeOC_6H_4$	C_3H_7	**2.59Eb**	24	100
12	**2.23Gb**	3-thienyl	C_3H_7	**2.59Gb**	24	49
13	**2.23Ha**	2-naphthyl	Ph	**2.59Ha**	24	43
14	**2.23Hb**	2-naphthyl	C_3H_7	**2.59Hb**	7.3	45

Table 6.3 Yields of $In(OTf)_3$ promoted cyclisation of **2.23Aa – Hb** to **2.59Aa – Hb**

2-Methyl-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Aa)

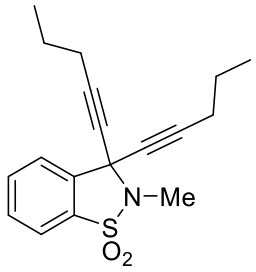


From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-methylbenzenesulfonamide (Method **A**: 1.74 mmol, Method **B**: 1.25 mmol). Method **A** – From column chromatography (10% EtOAc – pet ether) to give the title compound as a brown oil (Method **A**: 0.32 g, 48%, Method **B**: 0.48 g, 100%); HRMS found $[M+H]^+$ = 384.1047; $C_{24}H_{18}NO_2S$ $[M+H]^+$ requires = 384.1053.

δ_H ($CDCl_3$) 7.90 (1H, app. d, 4-*H*), 7.84 (1H, app. d, 7-*H*), 7.73 (1H, app. t, 6-*H*), 7.62 (1H, app. t, 5-*H*), 7.49 – 7.46 (4H, m, Ph-*H*), 7.38 – 7.28 (6H, m, Ph-*H*), 3.16 (3H, s, *Me*). δ_c 137.80 ($_qC$), 133.84 (CH), 133.02 ($_qC$), 132.11 (CH), 130.43 (CH), 129.37 (CH), 128.39 (CH), 124.96 (CH), 121.36 (CH), 121.16 ($_qC$), 85.95 ($_qC$), 83.29 ($_qC$), 57.01 ($_qC$), 25.56 (CH_3).

ν_{max}/cm^{-1}: 3056 w (Ar-H), 2229 w (C≡C), 1597 w (C=C), 1490 s (CH_3), 1309 s (SO_2), 1158 s (SO_2), 752 s (Ph-H), 688 s (Ph-H).

2-Methyl-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ab)

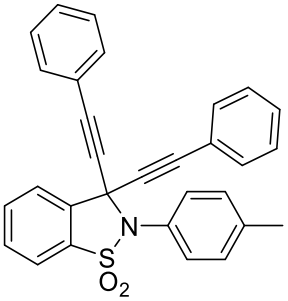


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **B**: 3.00 mmol) to give the title compound as an orange oil (Method **B**: 0.87 g, 92%); HRMS found $[M+H]^+$ = 316.1368; $C_{18}H_{22}NO_2S$ $[M+H]^+$ requires = 316.1375.

δ_H ($CDCl_3$) 7.77 (1H, app. d, 7-*H*), 7.73 (1H, app. d, 4-*H*), 7.68 (1H, app. t, 5-*H*), 7.56 (1H, app. t, 6-*H*), 3.00 (3H, s, *Me*), 2.20 (4H, t, *J* = 7.0 Hz, CH_2), 1.53 (4H, sxt, *J* = 7.3 Hz, CH_2), 0.96 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 138.91 ($_qC$), 133.45 (CH), 132.84 ($_qC$), 129.90 (CH), 124.65 (CH), 121.09 (CH), 86.59 ($_qC$), 75.58 ($_qC$), 56.31 ($_qC$), 25.08 (CH_3), 21.70 (CH_2), 20.63 (CH_2), 13.37 (CH_3).

ν_{max}/cm^{-1}: 2964 m (Ar-H), 2934 m (CH_2, CH_3), 2873 w (CH_2, CH_3), 2241 w (C≡C), 1455 s (CH_2), 1380 w (CH_3), 1306 s (SO_2), 1158 s (SO_2).

3,3-Bis(phenylethynyl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ba)

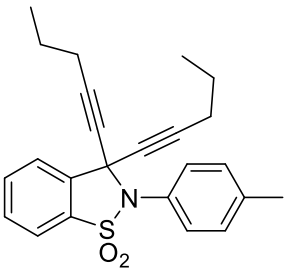


From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **A**: 2.09 mmol, Method **B**: 1.47 mmol). Method **A** – From column chromatography (12% EtOAc – pet ether) to give the title compound as a brown powder (Method **A**: 0.43 g, 45%, Method **B**: 0.68 g, 100%) m.p. 130 – 131 °C; HRMS found $[M+H]^+$ = 460.1371; $C_{30}H_{22}NO_2S$ $[M+H]^+$ requires = 460.1366.

δ_H ($CDCl_3$) 7.96 – 7.92 (2H, m, 4-*H,* 7-*H*), 7.78 (1H, app. t, 5-*H*), 7.73 (2H, d, *J* = 8.2 Hz, *o*-Ar-*H*), 7.68 (1H, app. t, 6-*H*), 7.42 – 7.40 (4H, m, Ph-*H*), 7.35 – 7.28 (6H, m, Ph-*H, m*-Ar-*H*), 2.43 (3H, s, *Me*). δ_c 140.03 ($_qC$), 137.53 ($_qC$), 133.67 (CH), 133.42 ($_qC$), 132.10 (CH), 131.93 (CH), 130.44 (CH), 130.02 (CH), 129.25 (CH), 128.91 ($_qC$), 128.34 (CH), 125.18 (CH), 121.50 (CH), 121.32 ($_qC$), 86.19 ($_qC$), 84.71 ($_qC$), 58.58 ($_qC$), 21.41 (CH_3).

ν_{max}/cm^{-1}: 3056 w (Ar-H), 2229 w (C≡C), 1597 w (C=C), 1490 s (CH_3), 1311 s (SO_2), 1173 s (SO_2), 754 s (Ph-H), 688 s (Ph-H).

3,3-Di(pent-1-yn-1-yl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Bb)

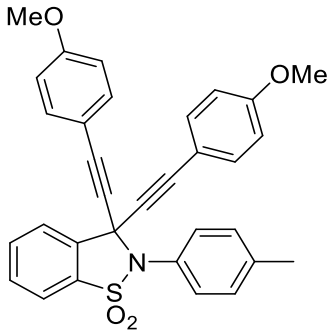


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **B**: 1.71 mmol) to give the title compound as a brown powder (Method **B**: 0.66 g, 98%) m.p. 131 – 133 °C; HRMS found $[M+Na]^+$ = 414.1518; $C_{24}H_{25}NO_2SNa$ $[M+Na]^+$ requires = 414.1498.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 7-*H*), 7.77 (1H, app. d, 4-*H*), 7.71 (1H, app. t, 5-*H*), 7.62 – 7.58 (3H, m, *o*-Ar-*H*, 6-*H*), 7.28 (1H, d, *J* = 5.2 Hz, *m*-Ar-*H*), 2.42 (3H, s, Ar-*Me*), 2.15 (4H, t, *J* = 7.3 Hz, CH_2), 1.48 (4H, sxt, *J* = 7.3 Hz, CH_2), 0.90 (6H, t, *J* = 7.3 Hz, CH_3). δ_c 139.58 ($_q$C), 138.72 ($_q$C), 133.35 (CH), 133.16 ($_q$C), 131.87 (CH), 129.94 (CH), 129.78 (CH), 129.06 ($_q$C), 124.90 (CH), 121.19 (CH), 87.00 ($_q$C), 76.88 ($_q$C), 57.93 ($_q$C), 21.60 (CH_2), 21.38 (CH_3), 20.70 (CH_2), 13.46 (CH_3).

ν_{max}/cm^{-1}: 2965 m (Ar-H), 2935 m (CH_2, CH_3), 2873 w (CH_2, CH_3), 2235 w (C≡C), 1508 s (C=C), 1455 s (CH_2), 1380 w (CH_3), 1299 s (SO_2), 1024 s (SO_2).

3,3-Bis[(4-methoxyphenyl)ethynyl]-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Bc)

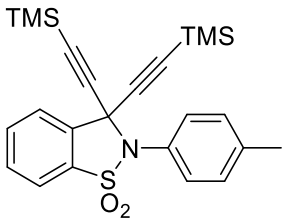


From 2-[3-hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (Method **B**: 1.86 mmol) to give the title compound as a brown powder (Method **B**: 0.95 g, 99%) m.p. 140 – 141 °C; HRMS found $[M+Na]^+$ = 542.1403; $C_{32}H_{25}NO_4SNa$ $[M+Na]^+$ requires = 542.1402.

δ_H ($CDCl_3$) 7.96 – 7.90 (2H, m, 4-*H,* 7-*H*), 7.78 – 7.64 (4H, m, 5-*H, o*-Ar-*H,* 6-*H*), 7.42 – 7.40 (4H, m, Ph-*H*), 7.35 – 7.30 (6H, m, Ar-*H, m*-Ar-*H*), 6.82 (2H, d, *J* = 8.8 Hz, Ar-*H*), 3.80 (6H, s, O-*Me*), 2.42 (3H, s, Ar-*Me*). δ_c 160.25 ($_q$C), 139.88 ($_q$C), 137.96 ($_q$C), 133.59 (CH), 133.48 [2 X C (CH)], 133.37 ($_q$C), 132.13 (CH), 130.27 (CH), 129.96 (CH), 129.01 ($_q$C), 125.21 (CH), 121.41 (CH), 113.94 (CH), 113.40 ($_q$C), 86.16 ($_q$C), 83.64 ($_q$C), 55.33 ($_q$C), 21.41 (CH_3).

ν_{max}/cm^{-1}: 2952 w (Ar-H), 2840 w (CH_3), 2224 w (C≡C), 1605 s (C=C), 1508 s (C=C), 1294 s (SO_2), 1174 s (SO_2).

2-(*p*-Tolyl)-3,3-bis[(trimethylsilyl)ethynyl]-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Be)

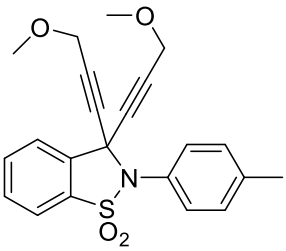


From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (Method **B**: 2.13 mmol) to give the title compound as white crystals (Method **B**: 0.26 g, 27%) m.p. 183 °C; HRMS found $[M+H]^+$ = 452.1335; $C_{24}H_{30}NO_2SSi_2$ $[M+H]^+$ requires = 452.1538.

δ_H ($CDCl_3$) 7.72 (1H, app. d, 7-*H*), 7.66 (1H, app. d, 4-*H*), 7.59 (1H, td, *J* = 1.1, 7.4 Hz, 5-*H*), 7.51 – 7.44 (4H, m, 6-*H*, *o*-Ar-*H*), 7.15 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 2.30 (3H, s, Ar-*Me*), 0.00 (18H, s, Si-*Me*$_3$). δ_c 139.98 ($_q$C), 137.18 ($_q$C), 133.56 (CH), 133.22 ($_q$C), 132.36 (CH), 130.29 (CH), 129.74 (CH), 128.67 ($_q$C), 125.11 (CH), 121.33 (CH), 99.79 ($_q$C), 91.59 ($_q$C), 58.28 ($_q$C), 21.42 (CH_3), -0.54 (Si-Me_3).

ν_{max}/cm^{-1}: 2960 m (Ar-H), 1508 m (C=C), 1310 s (SO_2), 1173 s (SO_2).

3,3-Bis(3-methoxyprop-1-yn-1-yl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Bf)



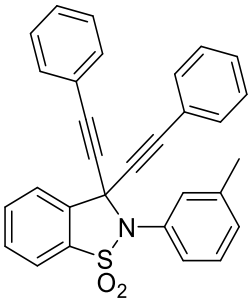
From 2-(4-hydroxy-1,7-dimethoxyhepta-2,5-diyn-4-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **A**: 1.21 mmol). Flash column chromatography (10% EtOAc – hexane) to give the title compound as a brown powder (Method **A**: 0.19 g, 40%) m.p. 115 °C decomp; HRMS found $[M+Na]^+$ = 418.1092; $C_{22}H_{21}NO_4SNa$ $[M+Na]^+$ requires = 418.1083.

δ_H ($CDCl_3$) 7.87 (1H, app. d, 7-*H*), 7.82 (1H, app. d, 4-*H*), 7.74 (1H, td, *J* = 7.4, 1.1 Hz, 5-*H*), 7.67 – 7.61 (3H, m, *o*-Ar-*H*, 6-*H*), 7.29 (1H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 4.10 (4H, s, CH_2), 3.29 (6H, s, CH_3), 2.42 (3H, s, Ar-*Me*). δ_c 140.02 ($_q$C), 136.98 ($_q$C), 133.67 (CH), 133.28 ($_q$C), 131.71 (CH),

130.54 (CH), 130.03 (CH), 128.69 ($_q$C), 124.95 (CH), 121.44 (CH), 82.54 ($_q$C), 81.83 ($_q$C), 59.66 (CH_2), 57.84 (CH_3), 21.38 (CH_3).

ν_{max}/cm^{-1}: 2942 m (CH_2, CH_3), 1507 s (C=C), 1453 s (CH_2), 1373 w (CH_3), 1312 s (SO_2), 1178 s (SO_2).

3,3-Bis(phenylethynyl)-2-(*m*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ca)

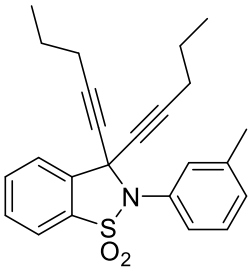


From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*m*-tolyl)benzenesulfonamide (Method **A**: 2.09 mmol, Method **B**: 0.45 mmol). Method **A** and **B** – The residue was recrystallised from EtOH – H_2O to give the title compound as a white solid (Method **A**: 0.45 g, 47%, Method **B**: 0.15 g, purity 75%, 53%) m.p. 140 °C decomp; HRMS found $[M+Na]^+$ = 482.1187; $C_{30}H_{21}NO_2SNa$ $[M+Na]^+$ requires = 482.1191.

δ_H ($CDCl_3$) 7.97 – 7.91 (2H, m, 4-*H*, 7-*H*), 7.78 (1H, td, *J* = 7.5, 1.1 Hz, 5-*H*), 7.69 – 7.64 (3H, m, 6-*H,* Ar-*H*), 7.42 – 7.38 (5H, m, Ar-*H*), 7.36 – 7.27 (7H, m, Ar-*H*), 2.41 (3H, s, Ar-*Me*) δ_c 139.15 ($_q$C), 137.50 ($_q$C), 133.67 (CH), 133.46 ($_q$C), 132.67 (CH), 131.89 (CH), 131.71 ($_q$C), 130.57 (CH), 130.44 (CH), 129.25 (CH), 129.05 (CH), 129.00 (CH), 128.33 (CH), 125.17 (CH), 121.48 (CH), 121.33 ($_q$C), 86.34 ($_q$C), 84.75 ($_q$C), 58.54 ($_q$C), 21.42 (CH_3).

ν_{max}/cm^{-1}: 2233 m (C≡C), 1604 w (C=C), 1488 m (CH_3), 1311 s (SO_2), 1171 s (SO_2), 784 s (Ph-H), 690 s (Ph-H).

3,3-Di(pent-1-yn-1-yl)-2-(*m*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Cb)



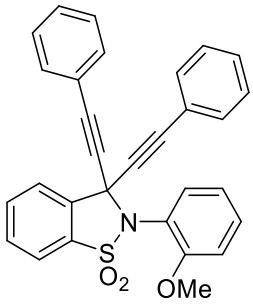
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*m*-tolyl)benzenesulfonamide (Method **A**: 2.44 mmol, Method **B**: 0.49 mmol). Method **A** - The residue was recrystallised from EtOH – H_2O, the liquor was subject to flash column chromatography (20% Ether – pet ether) to give the title compound as beige crystals (Method **A**: 0.26 g, 75%, Method **B**: 0.16 g, 82%) m.p. 100 – 101 °C; HRMS found $[M+H]^+$ = 392.1681; $C_{24}H_{26}NO_2S$ $[M+H]^+$ requires = 392.1686.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 7-*H*), 7.78 (1H, app. d, 4-*H*), 7.71 (1H, td, *J* = 7.4, 1.1 Hz, 5-*H*), 7.60 (1H, td, *J* = 7.4, 1.1 Hz, 6-*H*), 7.56 – 7.53 (2H, m, Ar-*H*), 7.36 (1H, app. t, Ar-*H*), 7.29 – 7.27 (1H, m, Ar-*H*), 2.41 (3H, s, Ar-*Me*), 2.16 (4H, t, *J* = 7.2 Hz, CH_2), 1.49 (4H, sxt, *J* = 7.2 Hz, CH_2), 0.90 (6H, t, *J* = 7.2 Hz, CH_3). δ_c 138.56 ($_q$C), 138.71 ($_q$C), 133.35 (CH), 133.19 ($_q$C), 132.32 (CH), 131.85 ($_q$C), 130.15 (CH), 129.94 (CH), 128.77 (CH), 128.75 (CH), 124.89 (CH), 121.17 (CH), 87.06 ($_q$C), 76.93* ($_q$C), 57.86 ($_q$C), 21.59 (CH_2), 21.34 (CH_3), 20.70 (CH_2), 13.41 (CH_3).

ν_{max}/cm^{-1}: 2964 m (Ar-H), 2935 m (CH_2, CH_3), 2872 w (CH_2, CH_3), 2235 w (C≡C), 1604 w (C=C), 1454 m (CH_2), 1296 s (SO_2), 1176 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-(2-Methoxyphenyl)-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Da)



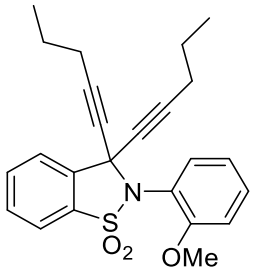
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (Method **B**: 1.01 mmol). Flash column chromatography (10% EtOAc – hexane) to give the title compound as a white solid (Method **B**: 0.18 g, 37%) m.p. 165 – 166 °C; HRMS found $[M+Na]^+$ = 498.1135; $C_{30}H_{21}NO_3SNa$ $[M+Na]^+$ requires = 498.1132.

δ_H ($CDCl_3$)(600 MHz) 7.94 (1H, app. d, 4-*H*), 7.92 – 7.90 (2H, m, 7-*H,* Ar-*H*), 7.76 (1H, td, *J* = 7.8, 1.1 Hz, 5-*H*), 7.65 (1H, td, *J* = 7.8, 1.1 Hz, 6-*H*), 7.49 – 7.46 (1H, m, Ar-*H*), 7.41 – 7.39 (4H, m, Ph-*H*), 7.34 – 7.27 (6H, m, Ph-*H*), 7.09 – 7.05 (1H, m, Ar-*H*), 3.76 (3H, s, O-*Me*) δ_c (150

MHz) 160.05 ($_q$C), 137.93 ($_q$C), 134.99 (CH), 133.52 (CH), 131.89 (CH), 131.70 [2 X C (CH) ($_q$C)], 130.25 (CH), 129.08 (CH), 128.27 (CH), 125.13 (CH), 121.58 ($_q$C), 121.49 (CH), 120.51 (CH), 119.56 ($_q$C), 112.65 (CH), 85.53 ($_q$C), 84.96 ($_q$C), 58.31 ($_q$C), 56.15 (CH_3).

ν_{max}/cm^{-1}: 1496 m (C=C), 1443 m (CH_3), 1314 s (SO_2), 1020 s (SO_2).

2-(2-Methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Db)



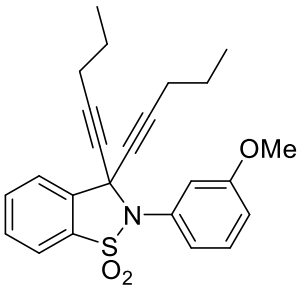
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (Method **B**: 0.94 mmol). Trituration with acetone to give the title compound as a white crystalline solid (Method **B**: 0.24 g, 63%) m.p. 200 °C; HRMS found $[M+Na]^+$ = 430.1449; $C_{24}H_{25}NO_3SNa$ $[M+Na]^+$ requires = 430.1453.

δ_H ($CDCl_3$) 7.84 – 7.76 (3H, m, 7-*H,* Ar-*H,* 4-*H*), 7.69 (1H, app. t, 5-*H*), 7.58 (1H, app. t, 6-*H*), 7.45 (1H, app. t, Ar-*H*), 7.05 – 7.02 (2H, m, Ar-*H*), 3.82 (3H, s, O-*Me*), 2.15 (4H, t, *J* = 7.2 Hz, CH_2), 1.47 (4H, sxt, *J* = 7.2 Hz, CH_2), 0.89 (6H, t, *J* = 7.2 Hz, CH_3). δ_c 159.98 ($_q$C), 139.20 ($_q$C), 134.92 (CH), 133.36 ($_q$C), 133.17 (CH), 131.39 (CH), 129.74 (CH), 124.84 (CH), 121.23 ($_q$C), 120.34 (CH), 119.75 ($_q$C), 112.53 (CH), 86.33 ($_q$C), 76.80* ($_q$C), 55.94 (CH_3), 21.63 (CH_2), 20.77 (CH_2), 13.44 (CH_3).

ν_{max}/cm^{-1}: 2966 m (Ar-H), 2936 m (CH_2, CH_3), 2874 w (CH_2, CH_3), 2235 w (C≡C), 1592 m (C=C), 1498 s (CH_2), 1298 s (SO_2), 1176 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-(3-Methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Eb)



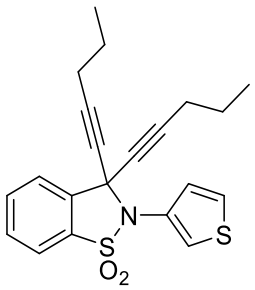
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(3-methoxyphenyl)benzenesulfonamide (Method **A** and **B**: 1.17 mmol). Method **A** – From column chromatography (20% EtOAc – pet ether) to give the title compound as a black solid (Method **A**: 0.26 g, 54%, Method **B**: 0.48 g, 100%) m.p. 98 – 100 °C; HRMS found $[M+H]^+$ = 408.1634; $C_{24}H_{26}NO_3S$ $[M+H]^+$ requires = 408.1635.

δ_H ($CDCl_3$) 7.84 (1H, app. d, 7-*H*), 7.78 (1H, app. d, 4-*H*), 7.72 (1H, td, *J* = 7.4, 1.1 Hz, 5-*H*), 7.9 (1H, app. t, 6-*H*), 7.38 – 7.35 (2H, m, Ar-*H*), 7.32 – 7.31 (1H, m, Ar-*H*), 7.04 – 7.00 (1H, m, Ar-*H*), 3.82 (3H, s, O-*Me*), 2.16 (4H, t, *J* = 7.2 Hz, C*H*$_2$), 1.48 (4H, sxt, *J* = 7.2 Hz, C*H*$_2$), 0.90 (6H, t, *J* = 7.2 Hz, C*H*$_3$). δ_c 159.96 ($_q$C), 138.68 ($_q$C), 133.45 (CH), 133.20 ($_q$C), 133.06 ($_q$C), 130.00 (CH), 129.50 (CH), 124.87 (CH), 123.48 (CH), 121.14 (CH), 116.55 (CH), 115.38 (CH), 87.17 ($_q$C), 76.88* ($_q$C), 57.77 ($_q$C), 55.38 (CH_3), 21.59 (CH_2), 20.71 (CH_2), 13.43 (CH_3).

ν_{max}/cm^{-1}: 2965 m (Ar-H), 2934 w (CH_2, CH_3), 2872 w (CH_2, CH_3), 2237 w (C≡C), 1597 s (C=C), 1486 s (CH_2), 1303 s (SO_2), 1038 s (SO_2).

*Overlapping with the $CDCl_3$ signal

3,3-Di(pent-1-yn-1-yl)-2-(thiophen-3-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Gb)



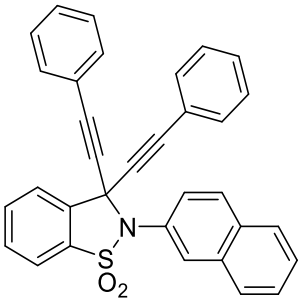
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(thiophen-3-yl)benzenesulfonamide (Method **B**: 2.49 mmol). Flash column chromatography (10% EtOAc – pet ether) to give the title compound as red oil (Method **B**: 0.47 g, 49%); HRMS found $[M+H]^+$ = 384.1090; $C_{21}H_{22}NO_2S_2$ $[M+H]^+$ requires = 384.1096.

δ_H ($CDCl_3$) 7.83 (1H, app. d, 7-*H*), 7.78 (1H, app. d, 4-*H*), 7.73 – 7.69 (2H, m, 5-*H,* Ar-*H*), 7.60 (1H, td, *J* = 7.8, 1.1 Hz, 6-*H*), 7.46 – 7.44 (1H, m, Ar-*H*), 7.39 – 7.37 (1H, m, Ar-*H*), 2.16 (4H, t, *J* = 7.2 Hz, C*H*$_2$), 1.48 (4H, sxt, *J* = 7.2 Hz, C*H*$_2$), 0.90 (6H, t, *J* = 7.2 Hz, C*H*$_3$). δ_c 138.44 ($_q$C), 133.60 (CH), 132.70 ($_q$C), 130.05 (CH), 129.93 ($_q$C), 127.22 (CH), 124.88 (CH), 124.68 (CH), 123.71 (CH), 121.19 (CH), 86.98 ($_q$C), 76.76* ($_q$C), 57.58 ($_q$C), 21.59 (CH_2), 20.67 (CH_2), 13.41 (CH_3).

ν_{max}/cm^{-1}: 2962 w (Ar-H), 2932 w (CH_2, CH_3), 2872 w (CH_2, CH_3), 1453 w (CH_2), 1306 s (SO_2), 1174 s (SO_2).

*Overlapping with $CDCl_3$ signal

2-(Naphthalen-2-yl)-3,3-bis(phenylethynyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Ha)



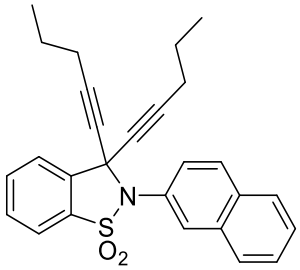
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (Method **B**: 1.95 mmol). Flash column chromatography (toluene) to give the title compound as a brown foam (Method **B**: 0.41 g, 43%) m.p. 82 – 83 °C; HRMS found $[M+Na]^+$ = 518.1178; $C_{33}H_{21}NO_2SNa$ $[M+Na]^+$ requires = 518.1191.

δ_H [$(CD_3)_2CO$] 8.51 (1H, d, *J* = 1.9 Hz, Ar-*H*), 8.22 (1H, app. d, 7-*H*), 8.16 (1H, app. d, 4-*H*), 8.11 – 8.09 (2H, m, Ar-*H*), 8.06 – 7.99 (3H, m, Ar-*H,* 5-*H,* 6-*H*), 7.92 (1H, td, *J* = 7.6, 1.0 Hz, Ar-*H*), 7.68 – 7.61 (2H, m, Ar-*H*), 7.51 – 7.48 (4H, m, Ph-H, Ar-*H*), 7.47 – 7.38 (6H, m, Ph-*H*). δ_c 137.06 ($_q$C), 134.38 (CH), 133.67 ($_q$C), 133.62 ($_q$C), 133.55 ($_q$C), 131.69 (CH), 131.29 (CH), 131.23 (CH), 129.99 ($_q$C), 129.61 (CH), 129.02 (CH), 128.78 (CH), 128.68 (CH), 128.23 (CH),

127.82 (CH), 127.36 (CH), 126.80 (CH), 125.52 (CH), 121.32 (CH), 120.97 ($_q$C), 86.37 ($_q$C), 84.71 ($_q$C), 58.54 ($_q$C).

ν_{max}/cm^{-1}: 2228 m (C≡C), 1595 w (C=C), 1309 s (SO_2), 1174 s (SO_2), 752 s (Ph-H), 688 s (Ph-H).

2-(Naphthalen-2-yl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (2.59Hb)

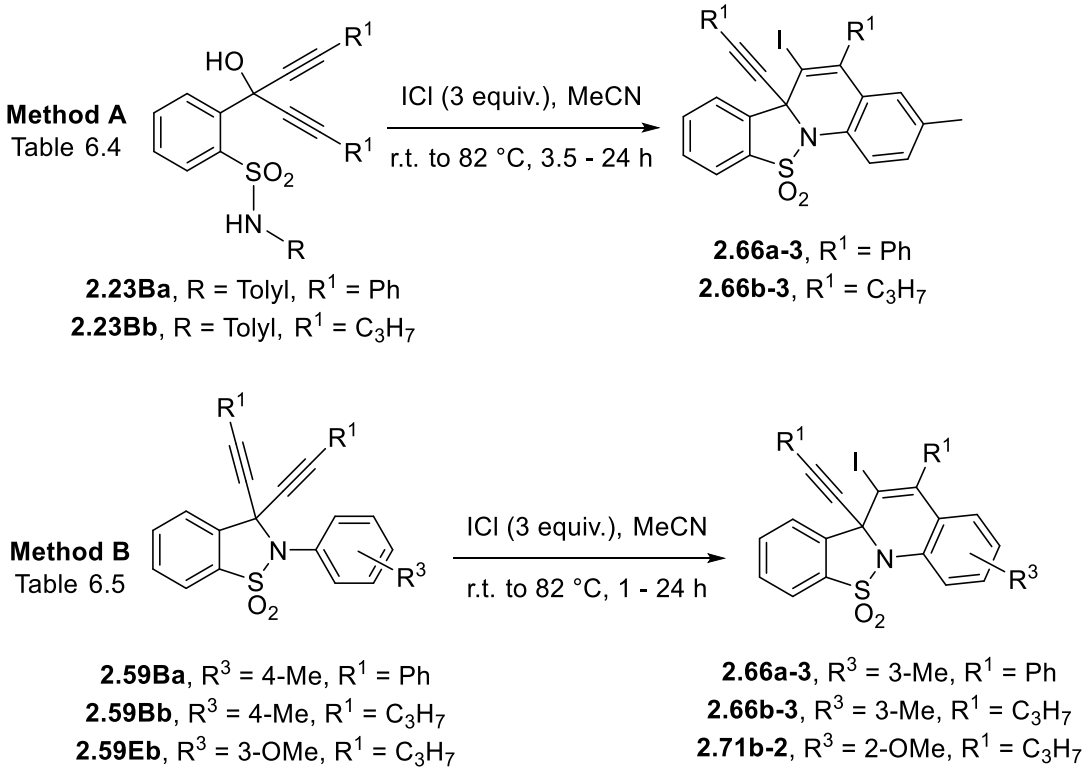


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (Method **B**: 2.24 mmol). Flash column chromatography (toluene) to give the title compound as a grey powder (Method **B**: 0.43 g, 45%) m.p. 93 – 94 °C; HRMS found $[M+H]^+$ = 428.1678; $C_{27}H_{26}NO_2S$ $[M+H]^+$ requires = 428.1686.

δ_H (CD_2Cl_2) 8.33 (1H, app. s, Ar-*H*), 7.98 – 7.92 (3H, m, 4-*H,* Ar-*H*), 7.85 – 7.74 (4H, m, Ar-*H,* 7-*H*, 5-*H*), 7.65 (1H, td, *J* = 7.7, 1.0 Hz, 6-*H*), 7.60 – 7.53 (2H, m, Ar-*H*), 2.17 (4H, t, *J* = 7.2 Hz, CH_2), 1.48 (4H, sxt, *J* = 7.2 Hz, CH_2), 0.89 (6H, t, *J* = 7.2 Hz, CH_3). δ_c 138.53 ($_q$C), 133.65 (CH), 133.41 ($_q$C), 133.35 ($_q$C), 133.11 ($_q$C), 130.84 (CH), 130.26 (CH), 129.76 ($_q$C), 128.71 (CH), 128.56 (CH), 128.26 (CH), 127.66 (CH), 127.04 (CH), 126.45 (CH), 125.05 (CH), 120.94 (CH), 87.53 ($_q$C), 76.80 ($_q$C), 58.03 ($_q$C), 21.77 (CH_2), 20.54 (CH_2), 13.18 (CH_3).

ν_{max}/cm^{-1}: 2961 w (Ar-H), 2932 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 1511 w (Ar-H), 1463 w (CH_2), 1311 s (SO_2), 1164 s (SO_2).

6.2.11 General Method for the Synthesis of 1,2-Benzisothiazolo[2,3-*a*]quinoline 11,11-dioxides



2.23Ba, R = Tolyl, R^1 = Ph
2.23Bb, R = Tolyl, R^1 = C_3H_7

2.66a-3, R^1 = Ph
2.66b-3, R^1 = C_3H_7

2.59Ba, R^3 = 4-Me, R^1 = Ph
2.59Bb, R^3 = 4-Me, R^1 = C_3H_7
2.59Eb, R^3 = 3-OMe, R^1 = C_3H_7

2.66a-3, R^3 = 3-Me, R^1 = Ph
2.66b-3, R^3 = 3-Me, R^1 = C_3H_7
2.71b-2, R^3 = 2-OMe, R^1 = C_3H_7

Scheme 6.3

Method **A**: To a solution of 3-[2-(aminosulfamoyl)phenyl]penta-1,4-diyn-3-ols derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3 equiv.) and the mixture stirred at the temperature and time indicated in Table 6.4. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography.

Entry	R	R^1	Dialkynol	Time (h)	Temp (°C)	Tetracycle	Yield (%)
1	Tolyl	Ph	**2.23Ba**	24	82	**2.66a-3**	35
2	Tolyl	C_3H_7	**2.23Bb**	3.5	r.t.	**2.66b-3**	33

Table 6.4 Cyclisation of dialkynols **2.23Ba – Bb** with ICl

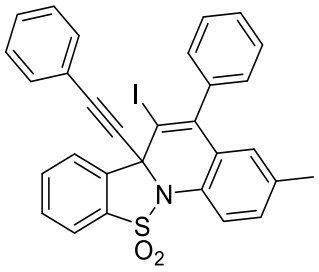
Method **B**: To a solution of 3,3-di(alkynyl)-*N*-(substituted)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (3 equiv.) and the mixture stirred at the temperature and time indicated in Table 5.5. After this time the reaction

mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography.

Entry	R^1	R^3	1,2-Benzisothiazole	Time (h)	Temp (°C)	Tetracycle	Yield (%)
1	Ph	4-Me	**2.59Ba**	24	82	**2.66a-3**	91
2	C_3H_7	4-Me	**2.59Bb**	3.5	r.t.	**2.66b-3**	40
3	C_3H_7	3-OMe	**2.59Eb**	1	82	**2.71b-2**	41

Table 6.5 Results of iodocyclisation of 3,3-di(alkynyl)-1,2-benzisothiazole 1,1-dioxide **2.59Ba – Eb**

6-Iodo-3-methyl-5-phenyl-6*a*-(phenylethynyl)-6*a*H-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide (2.66a-3)



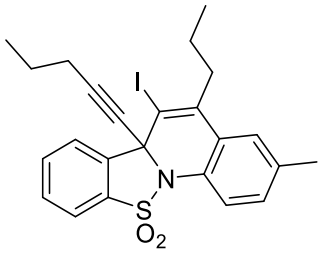
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **A**: 1.26 mmol, entry 1, Table 5.4) from flash column chromatography (12% EtOAc – pet ether). From 3,3-bis(phenylethynyl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzoisothiazole 1,1-dioxide (Method **B**: 0.44 mmol, entry 1, Table 5.5). To give the title compound as a beige powder m.p. 96 – 98 °C; HRMS found $[M+H]^+$ = 586.0328; $C_{30}H_{21}INO_2S$ $[M+H]^+$ requires = 586.0330.

δ_H ($CDCl_3$) 8.23 (1H, app. d, 7-*H*), 7.90 (1H, app. d, 10-*H*), 7.77 (1H, app. t, 8-*H*), 7.68 – 7.61 (2H, m, 9-*H*, Ar-*H*), 7.54 – 7.50 (1H, m, Ar-*H*), 7.45 – 7.24* (9H, m, Ar-*H*), 7.08 – 7.06 (1H, m, Ar-*H*), 6.68 (1H, app. s, Ar-*H*), 2.25 (3H, s, Ar-*Me*). δ_c 144.92 ($_q$C), 142.13 ($_q$C), 138.06 ($_q$C), 137.86 ($_q$C), 133.94 ($_q$C), 132.12 (CH), 130.50 (CH), 130.37 (CH), 130.14 (CH), 130.05 ($_q$C), 129.57 (CH), 129.24 (CH), 128.99 (CH), 128.80 (CH), 128.77 (CH), 128.37 (CH), 128.32 (CH), 128.17 (CH), 127.06 ($_q$C), 125.35 (CH), 121.48 ($_q$C), 121.20 (CH), 101.43 ($_q$C), 86.82 ($_q$C), 83.99 ($_q$C), 64.97 ($_q$C), 21.35 (CH_3).

ν_{max}/cm^{-1}: 2980 s (C-H), 2224 w (C≡C), 1486 s (CH_3), 1319 s (SO_2), 1173 s (SO_2), 755 s (Ph-H), 690 s (Ph-H), 573 s (C-I).

*Overlapping with $CDCl_3$ signal

6-Iodo-3-methyl-6*a*-(pent-1-yn-1-yl)-5-propyl-6*a*H-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide (2.66b-3)

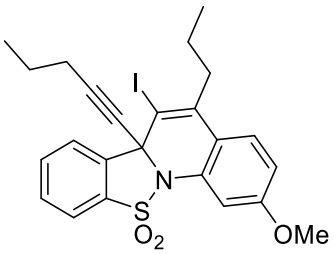


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide (Method **A**: 2.56 mmol, entry 2, Table 5.4) from flash column chromatography (20% ether – pet ether). From 3,3-di(pent-1-yn-1-yl)-2-(*p*-tolyl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (Method **B**: 1.53 mmol, entry 2, Table 5.5). To give the title compound as an orange oil; HRMS found $[M+H]^+$ = 518.0644; $C_{24}H_{25}INO_2S$ $[M+H]^+$ requires = 518.0652.

δ_H ($CDCl_3$) 8.12 (1H, app. d, 7-*H*), 7.81 (1H, app. d, 10-*H*), 7.77 (1H, td, *J* = 7.7, 1.1 Hz, 8-*H*), 7.61 (1H, td, *J* = 7.7, 1.1 Hz, 9-*H*), 7.54 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.35 (1H, app. s, Ar-*H*), 7.24 (1H, d, *J* = 8.0 Hz, Ar-*H*), 2.79 (2H, t, *J* = 7.5 Hz, C*H*$_2$), 2.44 (3H, s, Ar-*Me*), 2.09 (2H, t, *J* = 7.0 Hz, C*H*$_2$), 1.67 – 1.49 (2H, m, C*H*$_2$), 1.42 (2H, sxt, *J* = 7.5 Hz, C*H*$_2$), 0.99 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 0.85 (3H, t, *J* = 7.0 Hz, C*H*$_3$). δ_c 140.95 ($_q$C), 138.90 ($_q$C), 137.65 ($_q$C), 133.98 ($_q$C), 131.78 (CH), 130.18 (CH), 130.04 [2 X C (CH)], 127.56 ($_q$C), 128.62 ($_q$C), 125.82 (CH), 125.74 (CH), 120.99 (CH), 101.75 ($_q$C), 87.91 ($_q$C), 75.60 ($_q$C), 64.72 ($_q$C), 40.09 (CH_2), 21.66 (CH_2), 21.64 (CH_3), 21.33 (CH_2), 20.75 (CH_2), 13.84 (CH_3), 13.25 (CH_3).

ν_{max}/cm^{-1}: 2960 m (Ar-H), 2930 m (CH_2, CH_3), 2871 m (CH_2, CH_3), 2260 w (C≡C), 1489 s (C=C), 1453 w (CH_3), 1316 s (SO_2), 1175 s (SO_2), 572 (C-I).

6-Iodo-2-methoxy-6*a*-(pent-1-yn-1-yl)-5-propyl-6*a*H-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide (2.71b-2)



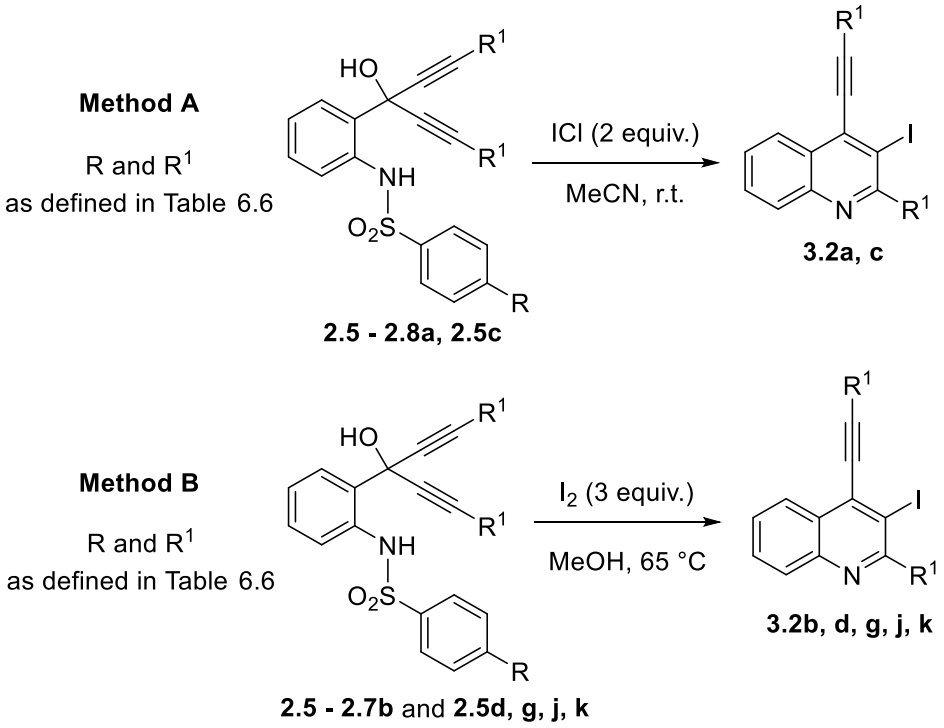
From 2-(3-methoxyphenyl)-3,3-di(pent-1-yn-1-yl)-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (Method **B**: 0.58 mmol, entry 3, Table 5.5) from flash column chromatography (15% EtOAc – pet ether) to give the title compound as a white powder; HRMS found $[M+H]^+$ = 534.0595; $C_{24}H_{25}INO_3S$ $[M+H]^+$ requires = 534.0602.

δ_H ($CDCl_3$) 8.13 (1H, app. d, 7-*H*), 7.82 (1H, app. d, 10-*H*), 7.74 (1H, app. t, 8-*H*), 7.62 (1H, app. t, 9-*H*), 7.47 (1H, d, *J* = 8.8 Hz, Ar-*H*), 7.20 (1H, d, *J* = 2.6 Hz, Ar-*H*), 6.91 (1H, dd, *J* = 8.8, 2.6 Hz, Ar-*H*), 3.89 (3H, s, O-*Me*), 2.76 (2H, t, *J* = 7.7 Hz, C*H*$_2$), 2.10 (2H, t, *J* = 7.0 Hz, C*H*$_2$), 1.64 – 1.39 (4H, m, C*H*$_2$), 0.97 (3H, t, *J* = 7.3 Hz, C*H*$_3$), 0.85 (3H, t, *J* = 7.0 Hz, C*H*$_3$). δ_c 160.17 ($_q$C), 140.71 [2 X C ($_q$C)], 138.79 ($_q$C), 133.89 ($_q$C), 131.83 (CH), 130.18 (CH), 130.04 (CH), 126.54 (CH), 121.90 ($_q$C), 120.93 (CH), 114.16 (CH), 110.34 (CH), 97.83 ($_q$C), 87.65 ($_q$C), 75.83 ($_q$C), 64.71 ($_q$C), 55.66 (CH_3), 40.14 (CH_2), 21.66 (CH_2), 21.34 (CH_2), 20.74 (CH_2), 13.78 (CH_3), 13.23 (CH_3).

ν_{max}/cm^{-1}: 2959 m (Ar-H), 2929 m (CH_2, CH_3), 2870 m (CH_2, CH_3), 1586 s (C=C), 1462 s (CH_2, CH_3), 1316 s (SO_2), 1174 s (SO_2), 557 (C-I).

6.3 Chapter 3 Experimental

6.3.1 General Method for the Synthesis of 4-Alkynyl-3-iodo-quinolines



Scheme 6.4

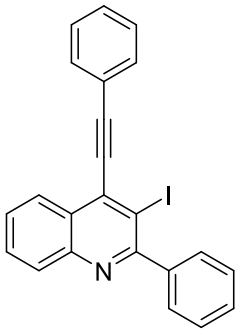
Method **A**: To a solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeCN (38.3 mL/mmol) was added ICl (2.0 equiv.) in MeCN and the mixture stirred at r.t. for the time indicated in Table 6.6. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography or washed with cold hexane.

Method **B**: To a solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1.0 equiv.) in MeOH (38.3 mL/mmol) was added I_2 (3.0 equiv.) and stirred at 65 °C for the time indicated in Table 5.6. After this time the reaction mixture was concentrated and diluted with EtOAc and quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography.

Entry	R	R^1	Dialkynol	Method	Time (h)	Product	Yield (%)
1	Me	Ph	**2.5a**	A	1.0	**3.2a**	60
2	Me	C_3H_7	**2.5b**	B	1.0	**3.2b**	46
3	Me	4-$OMeC_6H_4$	**2.5c**	A	1.0	**3.2c**	40
4	Me	C_4H_9	**2.5d**	B	1.5	**3.2d**	63
5	Me	Me	**2.5g**	B	2.25	**3.2g**	26
8	OMe	Ph	**2.6a**	A	1.0	**3.2a**	63
9	OMe	C_3H_7	**2.6b**	B	0.83	**3.2b**	50
10[a]	NO_2	Ph	**2.7a**	A	1.0	**3.2a**	32
11	NO_2	C_3H_7	**2.7b**	B	19.0	**3.2b**	12
12	H	Ph	**2.8a**	A	2.0	**3.2a**	41

Table 6.6 Iodocyclisations of dialkynols **2.5 – 2.8** results. a = 3,6-diiodo-2-phenyl-4-(phenylethynyl)quinoline **3.4a** also isolated

3-Iodo-2-phenyl-4-(phenylethynyl)quinoline (3.2a)

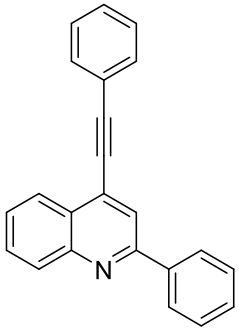


From entries; 1, 8, 10 and 12 (Table 6.6). From column chromatography (5% ether – hexane) resultant material recrystallised from EtOH – EtOAc to give the title compound as off-white needle-like crystals m.p. 149 – 150 °C; HRMS found $[M+H]^+$ = 432.0245 $C_{23}H_{15}IN$ requires $[M+H]^+$ = 432.0244.

δ_H ($CDCl_3$) 8.41 (1H, app. d, 5-*H*), 8.13 (1H, app. d, 8-*H*), 7.80 – 7.75 (3H, m, Ar-*H*), 7.66 – 7.62 (3H, m, Ar-*H*), 7.53 – 7.44 (6H, m, Ph-*H*). δ_c 161.77 ($_qC$), 146.60 ($_qC$), 143.27 ($_qC$), 137.60 ($_qC$), 132.04 (CH), 130.52 (CH), 129.82 (CH), 129.74 (CH), 129.21 (CH), 128.76 (CH), 128.66 (CH), 128.05 (CH), 127.96 (CH), 127.50 ($_qC$), 126.30 (CH), 122.17 ($_qC$), 102.29 ($_qC$), 99.21 ($_qC$), 89.70 ($_qC$).

ν_{max}/cm^{-1}: 2217 w (C≡C), 1580 s (C=C), 756 s (Ph), 690 s (Ph), 543 s (C-I).

2-Phenyl-4-(phenylethynyl)quinoline (2.35a)

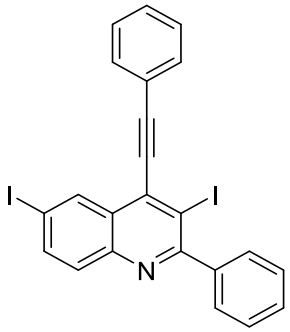


From flash column chromatography (5% ether – hexane) to give the title compound as a pale yellow solid (0.04 g, 6%) m.p. 100 °C; HRMS found $[M+H]^+$ = 306.1285; $C_{23}H_{16}N$ $[M+H]^+$ requires = 306.1204.

δ_H ($CDCl_3$) 8.37 (1H, dd, *J* = 8.3, 0.9 Hz, 5-*H*), 8.21 – 8.17 (3H, m, Ar-*H*), 8.08 (1H, s, 3-*H*), 7.79 – 7.75 (1H, m, 7-*H*), 7.72 – 7.69 (2H, m, Ph-*H*), 7.66 – 7.60 (1H, m, 6-*H*), 7.57 – 7.43 (6H, m, Ph-*H*). δ_c 156.91 ($_q$C), 148.23 ($_q$C), 139.20 ($_q$C), 132.00 (CH), 130.41 ($_q$C), 130.13 (CH), 130.11 (CH), 129.54 (CH), 129.35 (CH), 128.91 (CH), 128.62 (CH), 127.53 (CH), 126.91 (CH), 126.62 ($_q$C), 125.76 (CH), 122.34 ($_q$C), 121.69 (CH), 98.16 ($_q$C), 85.48 ($_q$C).

ν_{max}/cm^{-1}: 3055 w (Ar-H), 2216 m (C≡C), 1597 s (C=C), 756 s (Ph-H), 690 s (Ph-H).

3,6-Diiodo-2-phenyl-4-(phenylethynyl)quinoline (3.4a)



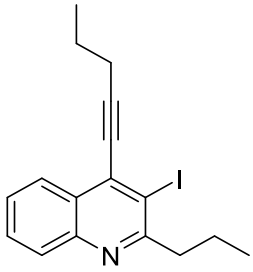
From entry 10 (Table 6.6). From flash column chromatography (5% EtOAc – hexane) to give the title compound as white needles (0.05 g, 18%) m.p. 245 – 246 °C; HRMS found $[M+H]^+$ = 557.9207; $C_{23}H_{14}I_2N$ $[M+H]^+$ requires = 557.9210.

δ_H ($CDCl_3$) 8.75 (1H, d, *J* = 1.9 Hz, 5-*H*), 8.00 (1H, dd, *J* = 8.8, 1.9 Hz, 7-*H*), 7.82 (1H, d, *J* = 8.8 Hz, 8-*H*), 7.78 – 7.75 (2H, m, Ph-*H*), 7.63 – 7.60 (2H, m, Ph-*H*), 7.53 – 7.45 (6H, m, Ph-*H*). δ_c 162.36 ($_q$C), 145.57 ($_q$C), 142.93 ($_q$C), 139.33 (CH), 136.48 ($_q$C), 135.17 (CH), 132.11 (CH),

131.39 (CH), 129.96 (CH), 129.11 (CH), 128.94 (CH), 128.80 ($_q$C), 128.71 (CH), 128.08 (CH), 121.86 ($_q$C), 102.90 ($_q$C), 100.03 ($_q$C), 94.01 ($_q$C), 89.23 ($_q$C).

ν_{max}/cm^{-1}: 3061 w (Ar-H), 2205 m (C≡C), 1590 w (C=C), 759 s (Ph), 687 s (Ph), 534 m (C-I), 528 m (C-I).

3-Iodo-4-(pent-1-yn-1-yl)-2-propylquinoline (3.2b)

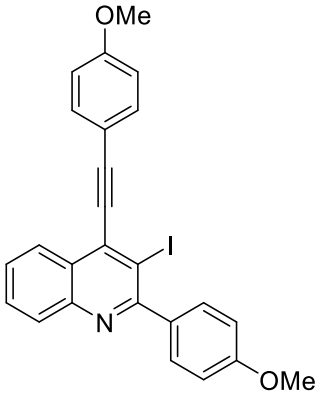


From entries; 2, 9 and 11 (Table 6.6). Flash column chromatography (6% EtOAc – hexane) to give the title compound as a yellow oil; HRMS found $[M+H]^+$ = 364.0565; $C_{17}H_{19}IN$ $[M+H]^+$ requires = 364.0557.

δ_H ($CDCl_3$) 8.21 (1H, app. d, 5-*H*), 7.98 (1H, app. d, 8-*H*), 7.69 (1H, app. t, 7-*H*), 7.51 (1H, app. t, 6-*H*), 3.21 – 3.17 (2H, m, C*H*$_2$), 2.65 (2H, t, *J* = 7.3 Hz, C*H*$_2$), 1.92 – 1.76 (4H, m, C*H*$_2$), 1.18 (3H, t, *J* = 7.3 Hz, CH_3), 1.08 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 162.53 ($_q$C), 146.48 ($_q$C), 137.76 ($_q$C), 129.97 (CH), 128.93 (CH), 127.53 ($_q$C), 126.90 (CH), 126.42 (CH), 104.76 ($_q$C), 100.69 ($_q$C), 81.27 ($_q$C), 44.98 (CH_2), 22.51 (CH_2), 22.07 (CH_2), 21.94 (CH_2), 14.09 (CH_3), 13.87 (CH_3).

ν_{max}/cm^{-1}: 3058 w (Ar-H), 2957 m (CH_2, CH_3), 2927 m (CH_2, CH_3), 2869 m (CH_2, CH_3), 2217 w (C≡C), 1582 w (C=C), 602 w (C-I).

3-Iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (3.2c)

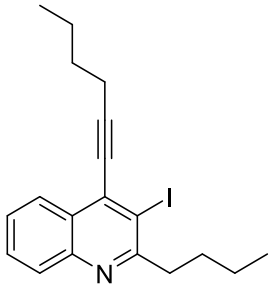


From entry 3 (Table 6.6). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as yellow needles m.p. 163 – 165 °C; HRMS found $[M+H]^+$ = 492.0448; $C_{25}H_{19}INO_2$ $[M+H]^+$ requires = 492.0455.

δ_H ($CDCl_3$) 8.38 (1H, dd, *J* = 7.6, 0.7 Hz, 5-*H*), 8.10 (1H, app. d, 8-*H*), 7.78 – 7.34 (1H, m, 7-*H*), 7.72 – 7.68 (2H, m, *o*-Ar-*H*), 7.63 – 7.59 (3H, m, Ar-*H,* 6-*H*), 7.04 – 7.01 (2H, m, Ar-*H*), 6.98 – 6.95 (2H, m, Ar-*H*), 3.89 (3H, s, O-*Me*), 3.88 (3H, s, O-*Me*). δ_c 160.81 ($_q$C), 159.96 ($_q$C), 146.65 ($_q$C), 137.95 ($_q$C), 135.98 ($_q$C), 133.68 (CH), 130.77 (CH), 130.36 (CH), 129.69 (CH), 127.63 (CH), 127.27 ($_q$C), 126.36 (CH), 114.33 (CH), 113.35 (CH), 102.76 ($_q$C), 99.21 ($_q$C), 89.06 ($_q$C), 55.45 (CH_3), 55.39 (CH_3).

ν_{max}/cm^{-1}: 3058 w (Ar-H), 2833 s (CH_3), 2209 s (C≡C), 1605 s (C=C), 1339 s (CH_3).

2-Butyl-4-(hex-1-yn-1-yl)-3-iodoquinoline (3.2d)

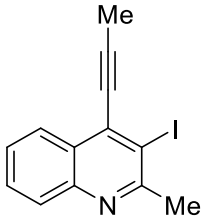


From entry 4 (Table 6.6). From flash column chromatography (2% ether – hexane) to give the title compound as a brown oil; HRMS found $[M+H]^+$ = 392.0882; $C_{19}H_{23}IN$ $[M+H]^+$ requires = 392.0870.

δ_H ($CDCl_3$) 8.20 (1H, app. d, 5-*H*), 7.97 (1H, app. d, 8-*H*), 7.69 (1H, app. t, 7-*H*), 7.51 (1H, app. t, 6-*H*), 3.26 – 3.19 (2H, m, CH_2), 2.67 (2H, t, *J* = 7.0 Hz, CH_2), 1.83 – 1.72 (4H, m, CH_2), 1.66 – 1.45 (6H, m, CH_2), 1.10 – 0.96 (6H, m, CH_3). δ_c 162.75 ($_q$C), 146.56 ($_q$C), 137.74 ($_q$C), 129.93 (CH), 128.95 (CH), 127.51 ($_q$C), 126.85 (CH), 126.41 (CH), 104.84 ($_q$C), 100.65 ($_q$C), 81.13 ($_q$C), 42.89 (CH_2), 31.24 (CH_2), 30.44 (CH_2), 22.76 (CH_2), 22.20 (CH_2), 19.76 (CH_2), 14.02 (CH_3), 13.67 (CH_3).

ν_{max}/cm^{-1}: 2954 m (CH_2, CH_3), 2926 m (CH_2, CH_3), 2870 w (CH_2, CH_3), 1562 w (C=C), 627 m (C-I).

3-Iodo-2-methyl-4-(prop-1-yn-1-yl)quinoline (3.2g)



From entry 5 (Table 6.6). Flash column chromatography (5% EtOAc – hexane) to give the title compound as a yellow solid m.p. 90 °C decomp; HRMS found $[M+H]^+$ = 307.9938; $C_{13}H_{11}IN$ $[M+H]^+$ requires = 307.9931.

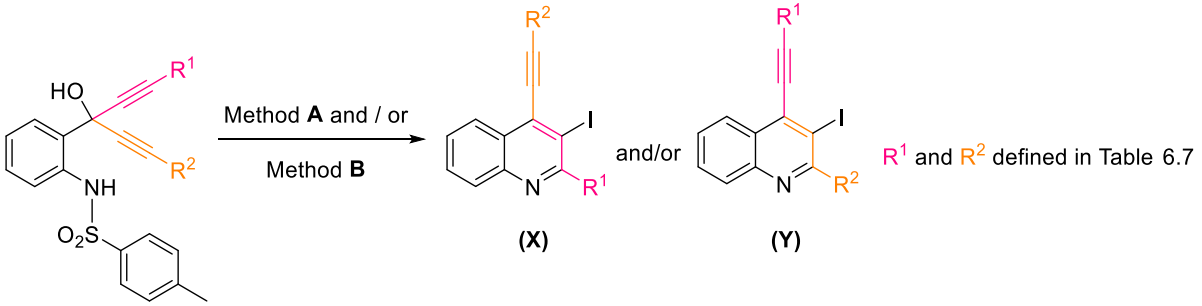
δ_H ($CDCl_3$) 8.23 – 8.20 (1H, m, 5-*H*), 7.96 (1H, app. d, 8-*H*), 7.72 – 7.67 (1H, m, 7-*H*), 7.54 – 7.49 (1H, m, 6-*H*), 2.97 (3H, s, *Me*), 2.32 (3H, s, *Me*). δ_c 159.73 ($_qC$), 146.43 ($_qC$), 137.47 ($_qC$), 130.05 ($_qC$), 128.76 (CH), 127.45 (CH), 126.91 (CH), 126.39 (CH), 100.64 ($_qC$), 100.41 ($_qC$), 80.03 ($_qC$), 31.33 (CH_3), 5.14 (CH_3).

ν_{max}/cm^{-1}: 2981 s (Ar-H), 2911 m (CH_3), 2217 w (C≡C), 1564 w (C=C), 1484 s (CH_3), 640 s (C-I).

6.3.2 General Method for the Synthesis of 4-Alkynyl-3-iodo-quinolines from Unsymmetrical Dialkynols

Method **A**: To a solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added ICl (2 equiv.) in MeCN and the mixture stirred at r.t. for the time indicated in Table 6.7. After this time the reaction mixture was quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography or washed with cold hexane.

Method **B**: To a solution of *N*-[2-(3-hydroxy-1,5-disubstituted-1,4-diyn-3-yl)phenyl]-4-benzenesulfonamide derivative (1 equiv.) in MeOH (38.3 mL/mmol) was added I_2 (3 equiv.) and stirred at 65 °C for the times indicated in Table 6.7. After this time the reaction mixture was concentrated, diluted with EtOAc and quenched with aqueous sodium thiosulfate. The organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography.



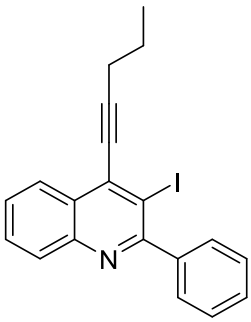
Method A: ICl (2 equiv.), MeCN, r.t.
Method B: I_2 (3 equiv.), MeOH, 65 °C

Scheme 6.5

Entry	R^1	R^2	Dialkynol	Method	Time (h)	Quinoline	Product -X yield	Quinoline	Product -Y yield
1	Ph	C_3H_7	**2.20Ab**	A	4.3	**3.5Ab-X**	14	**3.5Ab-Y**	31
2	Ph	C_3H_7	**2.20Ab**	B	1	**3.5Ab-X**	0	**3.5Ab-Y**	15
3	Ph	4-$MeOC_6H_4$	**2.20Ac**	A	0.75	**3.5Ac-X**	0	**3.5Ac-Y**	32
4	Ph	Me	**2.20Ag**	B	1.5	**3.5Ag-X**	8	**3.5Ag-Y**	17
5	Ph	*t*-Bu	**2.20Aj**	A	0.75	**3.5Aj-X**	19	**3.5Aj-Y**	0
6	4-$MeOC_6H_4$	C_3H_7	**2.20Cb**	B	1.25	**3.5Cb-X**	28	**3.5Cb-Y**	0

Table 6.7 Results of iodocyclisations of unsymmetrical dialkynols **2.20**

3-Iodo-4-(pent-1-yn-1-yl)-2-phenylquinoline (3.5Ab-X)

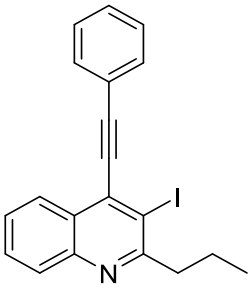


From entries; 1 and 2 (Table 6.7). From flash column chromatography (5% ether – hexane) to give the title compound as an orange paste; HRMS found $[M+H]^+$ = 398.0400; $C_{20}H_{17}IN$ $[M+H]^+$ requires = 398.0407.

δ_H ($CDCl_3$) 8.30 (1H, dd, *J* = 8.3, 0.9 Hz, 5-*H*), 8.09 (1H, app. d, 8-*H*), 7.76 – 7.72 (1H, m, 6-*H*), 7.61 – 7.57 (3H, m, Ph-*H*), 7.51 – 7.45 (3H, m, Ph-*H*, 7-*H*), 2.67 (2H, t, *J* = 7.1 Hz, C*H*$_2$), 1.81 (2H, sxt, *J* = 7.1 Hz C*H*$_2$), 1.18 (3H, t, *J* = 7.1 Hz, C*H*$_3$). δ_c 161.73 ($_q$C), 146.50 ($_q$C), 143.44 ($_q$C), 138.44 ($_q$C), 130.33 (CH), 129.67 (CH), 129.15 (CH), 128.65 (CH), 127.99 (CH), 127.93 ($_q$C), 127.73 (CH), 126.48 (CH), 105.19 ($_q$C), 99.05 ($_q$C), 81.39 ($_q$C), 22.11 (CH_2), 21.92 (CH_2), 13.83 (CH_3).

ν_{max}/cm^{-1}: 3056 w (Ar-H), 2956 m (CH_2, CH_3), 2928 m (CH_2, CH_3), 2869 m (CH_2, CH_3), 2210 m (C≡C), 1596 w (C=C), 756 s (Ph-H), 688 s (Ph-H), 584 w (C-I).

3-Iodo-4-(phenylethynyl)-2-propylquinoline (3.5Ab-Y)



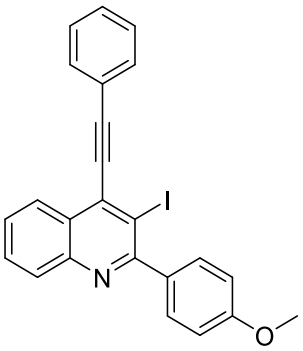
From entries; 1 and 2 (Table 6.7). From flash column chromatography (5% Ether – hexane) to give the title compound as a yellow solid. m.p. 107 – 108 °C; HRMS found $[M+H]^+$ = 398.0406; $C_{20}H_{17}IN$ $[M+H]^+$ requires = 398.0400.

δ_H ($CDCl_3$) 8.33 (1H, app. d, 5-*H*), 8.04 (1H, app. d, 8-*H*), 7.78 – 7.73 (3H, m, Ph-*H,* 6-*H*), 7.58 (1H, app. t, 7-*H*), 7.48 – 7.47 (3H, m, Ph-*H*), 3.27 – 3.23 (2H, m, C*H*$_2$), 1.90 (2H, sxt, *J* = 7.3 Hz

C*H*$_2$), 1.12 (3H, t, *J* = 7.3 Hz, C*H*$_3$). δ_c 162.60 ($_q$C), 146.60 ($_q$C), 136.87 ($_q$C), 131.96 (CH), 130.14 (CH), 130.62 (CH), 129.11 (CH), 128.63 (CH), 127.12 (CH), 126.23 (CH), 122.26 ($_q$C), 102.93 ($_q$C), 100.85 ($_q$C), 89.57 ($_q$C), 44.91 (CH_2), 22.51 (CH_2), 14.09 (CH_3).

ν_{max}/cm^{-1}: 2955 m (CH_2, CH_3), 2869 w (CH_2, CH_3), 2210 m (C≡C), 1595 w (C=C), 781 s (Ph-H), 688 s (Ph-H), 603 m (C-I).

3-Iodo-2-(4-methoxyphenyl)-4-(phenylethynyl)quinoline (3.5Ac-Y)

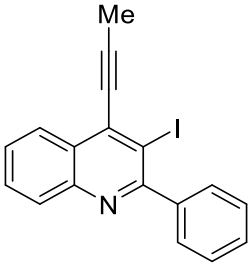


From entry 3 (Table 6.7). From washing the precipitate, obtained in the crude product, with cold hexane, to give the title compound as yellow needles (0.29 g, 32%) m.p. 125 – 126 °C; HRMS found $[M+H]^+$ = 462.0356; $C_{25}H_{19}INO_2$ $[M+H]^+$ requires = 462.0349.

δ_H ($CDCl_3$) 8.38 (1H, app. d, 5-*H*), 8.10 (1H, app. d, 8-*H*), 7.77 – 7.75 (3H, m, 7-*H,* Ph-*H*), 7.62 – 7.60 (3H, m, *o*-Ar-*H,* 6-*H*), 7.45 – 7.44 (3H, m, Ph-*H*), 7.02 (2H, d, *J* = 8.5 Hz, *m*-Ar-*H*), 3.89 (3H, s, O-*Me*). δ_c 161.31 ($_q$C), 159.99 ($_q$C), 146.65 ($_q$C), 137.56 ($_q$C), 135.77 ($_q$C), 131.98 (CH), 130.75 (CH), 130.39 (CH), 129.72 (CH), 129.66 (CH), 128.61 (CH), 127.73 (CH), 127.32 ($_q$C), 126.24 (CH), 122.19 ($_q$C), 113.34 (CH), 102.10 ($_q$C), 99.56 ($_q$C), 89.78 ($_q$C), 55.36 (CH_3).

ν_{max}/cm^{-1}: 3061 w (Ar-H), 2980 w (Ar-H), 2840 w (CH_3), 2206 m (C≡C), 1607 s (C=C), 752 s (Ph-H), 708 s (Ph-H), 521 s (C-I).

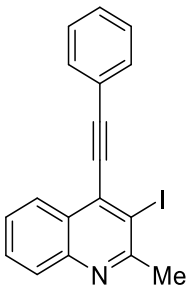
3-Iodo-2-phenyl-4-(prop-1-yn-1-yl)quinoline (3.5Ag-X)



From entry 4 (Table 5.7). From using Biotage Isolera 4 (SNAP Ultra 10g cartridge, EtOAc – pet ether 10% → 100%) to give the title compound as a beige solid (0.007 g, 8%); HRMS found $[M+H]^+$ = 370.0098; $C_{18}H_{13}IN$ $[M+H]^+$ requires = 370.0087.

δ_H ($CDCl_3$) 8.33 (1H, dd, *J* = 8.2, 0.8 Hz, 5-*H*), 8.11 (1H, app. d, 8-*H*), 7.79 – 7.75 (1H, m, 7-*H*), 7.63 – 7.59 (3H, m, Ph-*H*), 7.53 – 7.46 (3H, m, 6-*H*, Ph-*H*), 2.36 (3H, s, *Me*). δ_c 161.72 ($_qC$), 146.51 ($_qC$), 143.41 ($_qC$), 138.39 ($_qC$), 131.99 ($_qC$), 130.35 (CH), 129.88 ($_qC$), 129.67 (CH), 129.14 (CH), 128.66 (CH), 127.99 (CH), 127.73 (CH), 126.48 (CH), 100.70 ($_qC$), 98.97 ($_qC$), 80.43 ($_qC$), 5.18 (CH_3).

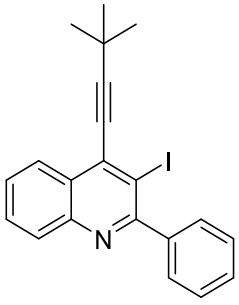
3-Iodo-2-methyl-4-(phenylethynyl)quinoline (3.5Ag-Y)



From entry 4 (Table 6.7). From using Biotage Isolera 4 (SNAP Ultra 10g cartridge, EtOAc – pet ether 10% → 100%) to give the title compound as a beige solid (0.015 g, 17%); HRMS found $[M+H]^+$ = 370.0095; $C_{18}H_{13}IN$ $[M+H]^+$ requires = 370.0087.

δ_H ($CDCl_3$) 8.33 (1H, dd, *J* = 8.3, 0.8 Hz, 5-*H*), 8.02 (1H, app. d, 8-*H*), 7.78 – 7.74 (3H, m, Ph-*H*, 7-*H*), 7.61 – 7.57 (1H, m, 6-*H*), 7.49 – 7.45 (3H, m, Ph-*H*), 3.03 (3H, s, *Me*). δ_c 159.83 ($_qC$), 146.46 ($_qC$), 136.72 ($_qC$), 131.99 (CH), 130.24 (CH), 129.68 (CH), 128.87 (CH), 128.64 (CH), 127.17 (CH), 126.99 ($_qC$), 126.22 (CH), 122.19 ($_qC$), 102.13 ($_qC$), 100.90 ($_qC$), 89.29 ($_qC$), 31.20 (CH_3).

4-(3,3-Dimethylbut-1-yn-1-yl)-3-iodo-2-phenylquinoline (3.5Aj-X)

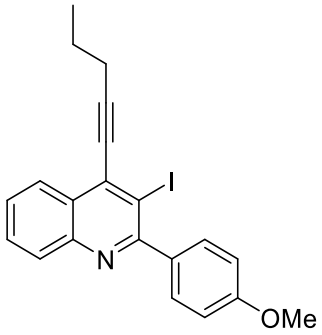


From entry 5 (Table 6.7). From flash column chromatography (5% EtOAc – pet ether) to give the title compound as an orange paste (0.12 g, at 60% purity, 19%); HRMS found $[M+H]^+$ = 412.0558; $C_{21}H_{13}IN$ $[M+H]^+$ requires = 412.0564.

δ_H ($CDCl_3$) 8.26 (1H, dd, *J* = 8.3, 0.8 Hz, 5-*H*), 8.08 (1H, app. d, 8-*H*), 7.76 – 7.72 (1H, m, 6-*H*), 7.61 – 7.45 (6H, m, Ph-*H*, 7-*H*), 1.49 (9H, s, *Me*$_3$). δ_c 161.71 ($_q$C), 146.49 ($_q$C), 143.47 ($_q$C), 138.28 ($_q$C), 130.31 (CH), 129.63 (CH), 129.14 (CH), 128.93 ($_q$C), 128.64 (CH), 127.99 (CH), 127.72 (CH), 127.69 ($_q$C), 126.45 (CH), 112.93 ($_q$C), 99.30 ($_q$C), 80.17 ($_q$C), 30.66 (CH_3).

ν_{max}/cm^{-1}: 3057 w (Ar-H), 2923 s (CH_3), 2224 m (C≡C), 1361 m (CH_3), 771 s (Ph-H), 695 s (Ph-H), 583 m (C-I)

3-Iodo-2-(4-methoxyphenyl)-4-(pent-1-yn-1-yl)quinoline (3.5Cb-X)

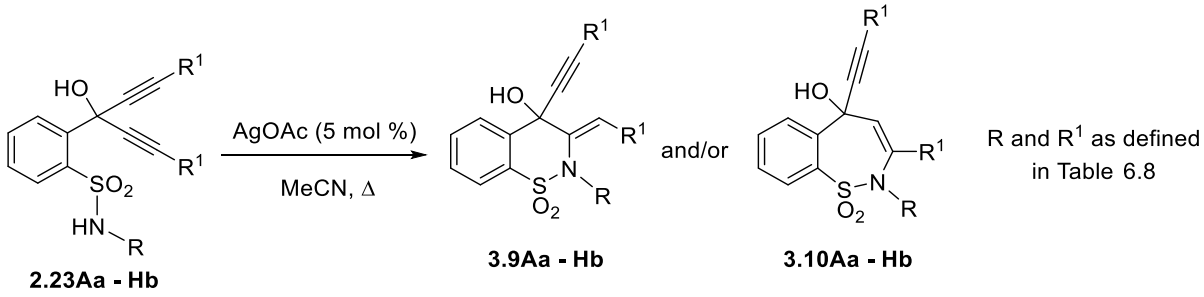


From entry 6 (Table 6.7). From using Biotage Isolera 4 (SNAP Ultra 25g cartridge, EtOAc – pet ether 1% → 20%) to give the title compound as a brown oil (0.20 g, 28%); HRMS found $[M+H]^+$ = 428.0512; $C_{21}H_{19}INO$ $[M+H]^+$ requires = 428.0506.

δ_H ($CDCl_3$) 8.28 (1H, dd, *J* = 8.4, 1.0 Hz, 5-*H*), 8.07 (1H, app. d, 8-*H*), 7.75 – 7.71 (1H, m, 7-*H*), 7.59 – 7.55 (3H, m, *o*-Ar-*H*, 6-*H*), 7.03 – 6.99 (2H, m, *m*-Ar-*H*), 3.88 (3H, s, O-*Me*) 2.67 (2H, t, *J* = 7.3 Hz, C*H*$_2$), 1.81 (2H, sxt, *J* = 7.3 Hz, C*H*$_2$), 1.18 (3H, t, *J* = 7.3 Hz, C*H*$_3$). δ_c 161.30, 159.92 ($_q$C), 146.58 ($_q$C), 138.43 ($_q$C), 135.99 ($_q$C), 130.72 (CH), 130.25 (CH), 129.60 (CH), 127.78 ($_q$C), 127.54 (CH), 126.45 (CH), 113.31 (CH), 105.03 ($_q$C), 99.46 ($_q$C), 81.49 ($_q$C), 55.38 (CH_3) 22.11 (CH_2), 21.92 (CH_2), 13.86 (CH_3).

ν_{max}/cm^{-1}: 2959 w (Ar-H), 2930 w (CH_2, CH_3), 2970 w (CH_2, CH_3), 2833 w (CH_2, CH_3), 2217 m (C≡C), 1606 s (C=C), 825 s (An-H), 578 m (C-I)

6.3.3 General Method for the Synthesis of 1,2-Benzothiazine 1,1-dioxides and 1,2-Benzothiazepine 1,1-dioxides



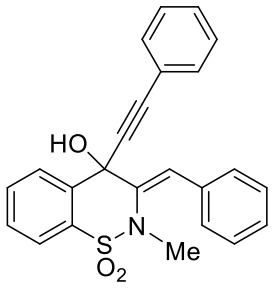
Scheme 6.6

To a solution of 2-(3-hydroxypenta-1,4-diyn-3-yl)-*N*-(substituted)benzenesulfonamide derivative (1 equiv.) in MeCN (38.3 mL/mmol) was added AgOAc (5 mol %) and the mixture stirred at reflux for the time indicated in Table 5.8. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated. The residue was purified by flash column chromatography unless otherwise stated. The following were synthesised by this method.

Entry	R	R^1	Dialkynol	Time (h)	Product	1,2- Benzothiazine Yield (%)	Product	1,2-Benzothiazepine Yield (%)
1	Me	Ph	**2.23Aa**	24	**3.9Aa**	48	**3.10Aa**	0
2[ab]	Me	C_3H_7	**2.23Ab**	20	**3.9Ab**	12[b]	**3.10Ab**	7
3	Tolyl	Ph	**2.23Ba**	3	**3.9Ba**	78	**3.10Ba**	0
4	Tolyl	C_3H_7	**2.23Bb**	1	**3.9Bb**	82	**3.10Bb**	0
5	Tolyl	4-$MeOC_6H_4$	**2.23Bc**	23	**3.9Bc**	62	**3.10Bc**	0
6[c]	Tolyl	TMS	**2.23Be**	2	**3.9Be**	61	**3.10Be**	0
7	Tolyl	CH_2OMe	**2.23Bf**	20	**3.9Bf**	86	**3.10Bf**	0
8	3-MeC_6H_4	Ph	**2.23Ca**	4	**3.9Ca**	72	**3.10Ca**	0
9	3-MeC_6H_4	C_3H_7	**2.23Cb**	1.5	**3.9Cb**	59	**3.10Cb**	0
10	2-$MeOC_6H_4$	Ph	**2.23Da**	2	**3.9Da**	86	**3.10Da**	0
11	2-$MeOC_6H_4$	C_3H_7	**2.23Db**	2	**3.9Db**	61	**3.10Db**	0
12	3-$MeOC_6H_4$	Ph	**2.23Ea**	3	**3.9Ea**	96	**3.10Ea**	0
13	3-$MeOC_6H_4$	C_3H_7	**2.23Eb**	3	**3.9Eb**	80	**3.10Eb**	0
14	3-thienyl	C_3H_7	**2.23Gb**	3.7	**3.9Gb**	70	**3.10Gb**	11
15	2-naphthyl	Ph	**2.23Ha**	3	**3.9Ha**	75	**3.10Ha**	0
16	2-naphthyl	C_3H_7	**2.23Hb**	3	**3.9Hb**	84	**3.10Hb**	0

Table 6.8 Yields from the AgOAc cyclisation of reversed sulfonamides **2.23Aa – Hb.** a = 3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2*H*-1,2-benzothiazine 1,1-dioxide **3.11Ab** also obtained from this reaction. b = yield from ^{1}H NMR spectrum c = 4-Hydroxy-3-methylene-2-(*p*-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide **3.9Be'** also obtained from the reaction

(*Z*)-3-Benzylidene-4-hydroxy-2-methyl-4-(phenylethynyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Aa)

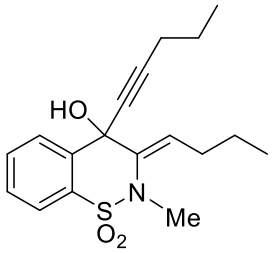


From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-methylbenzenesulfonamide (2.02 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as a yellow powder (0.39 g, 48%) m.p. 79 – 80 °C; HRMS found $[M+Na]^+$ = 424.0980; $C_{24}H_{19}NO_3SNa$ $[M+Na]^+$ requires = 424.0978.

δ_H ($CDCl_3$)(600MHz) 8.10 (1H, dd, *J* = 8.0, 1.1 Hz, 5-*H*), 7.87 (1H, dd, *J* = 8.0, 1.1 Hz, 8-*H*), 7.82 – 7.81 (2H, m, Ph-*H*), 7.65 (1H, td, *J* = 8.0, 1.1 Hz, 6-*H*), 7.52 (1H, td, *J* = 8.0, 1.1 Hz, 7-*H*), 7.49 (1H, s, C*H*), 7.48 – 7.46 (2H, m, Ph-*H*), 7.42 – 7.32 (6H, m, Ph-*H*), 3.42 (1H, s, O*H*), 3.12 (3H, s, N-*Me*). δ_c (150 MHz) 139.17 ($_q$C), 138.22 ($_q$C), 133.98 ($_q$C), 133.24 ($_q$C), 133.22 (CH), 131.67 (CH), 131.03 (CH), 129.55 (CH), 129.52 (CH), 129.17 (CH), 129.11 (CH), 129.03 (CH), 128.65 (CH), 128.42 (CH), 124.03 (CH), 121.49 ($_q$C), 89.12 ($_q$C), 87.89 ($_q$C), 68.32 ($_q$C), 38.38 (CH_3).

ν_{max}/cm^{-1}: 3433 b (OH), 1490 w (C=C), 1443 s (CH_3), 1327 s (SO_2), 1165 s (R-OH), 1132 m (SO_2), 755 s (Ph-H), 690 s (Ph-H), 661 w (C=CH).

(*Z*)-3-Butylidene-4-hydroxy-2-methyl-4-(pent-1-yn-1-yl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Ab)

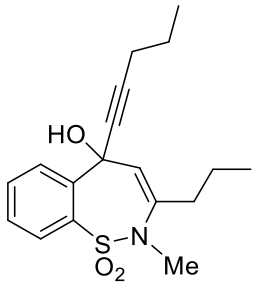


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as a yellow

oil (0.31 g, at 40% purity by NMR, 12%); LC-MS found $[M+H]^+$ = 333.1391; $C_{18}H_{23}NO_3S$ $[M+H]^+$ requires = 333.1400.

δ_H ($CDCl_3$) 7.94 (1H, dd, *J* = 8.0, 1.0 Hz, 5-*H*), 7.77 (1H, dd, *J* = 8.0, 1.0 Hz, 8-*H*), 7.60 – 7.56 (1H, m, 6-*H*), 7.48 – 7.44 (1H, m, 7-*H*), 6.64 (1H, t, *J* = 7.3 Hz, C*H*), 3.15 (3H, s, *Me*), 3.03 (1H, s, O*H*), 2.34 – 2.32 (2H, m, CH_2), 2.26 – 2.23 (2H, m, CH_2), 1.58 – 1.47 (4H, m, CH_2), 0.99 – 0.94 (6H, m, CH_3). δ_c 138.93 ($_q$C), 138.92 ($_q$C), 136.19 (CH), 135.06 ($_q$C), 134.22 ($_q$C), 132.74 (CH), 131.87 (CH), 130.67 (CH), 129.28 (CH), 129.05 (CH), 123.96 (CH), 88.87 ($_q$C), 81.06 ($_q$C), 67.72 ($_q$C), 39.68 (CH_3), 28.91 (CH_2), 21.77 (CH_2), 20.76 (CH_2), 14.00 (CH_3), 13.52 (CH_3).

5-Hydroxy-2-methyl-5-(pent-1-yn-1-yl)-3-propyl-2,5-dihydrobenzo[*f*][1,2]thiazepine 1,1-dioxide (3.10Ab)

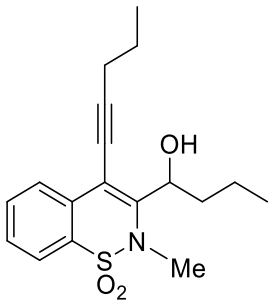


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as an orange oil (0.065 g, 7%); HRMS found $[M+H]^+$ = 334.1463; $C_{18}H_{24}NO_3S$ $[M+H]^+$ requires = 334.1479.

δ_H ($CDCl_3$) 8.41 (1H, app. d, 6-*H*), 7.96 (1H, dd, *J* = 7.7, 1.2 Hz, 9-*H*), 7.67 (1H, td, *J* = 7.7, 1.2 Hz, 7-*H*), 7.53 (1H, td, *J* = 7.7, 1.2 Hz, 8-*H*), 5.78 (1H, s, 4-*H*), 5.36 (1H, s, O*H*), 2.78 (3H, s, *Me*), 2.37 (2H, t, *J* = 7.3 Hz, CH_2), 1.69 – 1.60 (4H, m, CH_2), 1.26 (2H, t, *J* = 7.3 Hz, CH_2), 1.06 (3H, t, *J* = 7.3 Hz, CH_3), 1.01 (3H, t, *J* = 7.3 Hz, CH_3).

ν_{max}/cm^{-1}: 3339 b (OH), 2964 m (Ar-H), 2932 m (CH_2, CH_3), 2874 w (CH_2, CH_3), 1463 m (CH_2), 1337 s (SO_2), 1162 s (R-OH), 1127 m (SO_2).

3-(1-Hydroxybutyl)-2-methyl-4-(pent-1-yn-1-yl)-2*H*-1,2-benzothiazine 1,1-dioxide (3.11Ab)

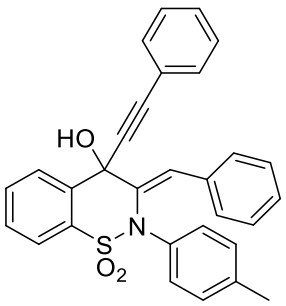


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-methylbenzenesulfonamide (3.00 mmol). From flash column chromatography (10% EtOAc – pet ether) to give the title compound as an orange oil (0.15 g, 15%); HRMS found $[M+Na]^+$ = 356.1294; $C_{18}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 356.1297.

δ_H ($CDCl_3$) 7.88 (1H, app. d, 5-*H*), 7.82 (1H, dd, *J* = 7.6, 1.1 Hz, 8-*H*), 7.63 (1H, td, *J* = 7.6, 1.1 Hz, 6-*H*), 7.51 (1H, td, *J* = 7.6, 1.1 Hz, 7-*H*), 5.18 (1H, m, C*H*), 3.28 (3H, s, *Me*), 2.69 (1H, d, *J* = 5.2 Hz, O*H*), 2.48 (2H, t, *J* = 7.2 Hz, CH_2), 1.61 – 1.84 (2H, m, CH_2), 1.72 – 1.55 (4H, m, CH_2), 1.07 (3H, t, *J* = 7.2 Hz, CH_3), 1.00 (3H, t, *J* = 7.4 Hz, CH_3). δ_c 149.20 ($_q$C), 132.56 ($_q$C), 132.07 (CH), 131.39 ($_q$C), 128.59 (CH), 127.23 (CH), 122.03 (CH), 108.54 ($_q$C), 100.61 ($_q$C), 74.18 ($_q$C), 72.23 (CH), 37.63 (CH_2), 35.53 (CH_3), 22.14 (CH_2), (CH_2), 21.69 (CH_2), 19.22 (CH_2), 13.85 (CH_3), 13.70 (CH_3).

ν_{max}/cm^{-1}: 3442 b (OH), 2960 m (Ar-H), 2933 m (CH_2, CH_3), 2872 w (CH_2, CH_3), 1580 w (C=C), 1470 m (CH_2), 1336 s (SO_2), 1180 s (R-OH), 1127 m (SO_2).

(*Z*)-3-Benzylidene-4-hydroxy-4-(phenylethynyl)-2-(*p*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Ba)



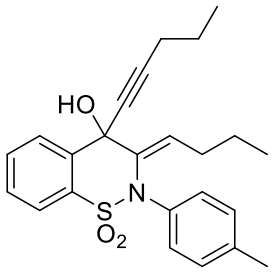
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.09 mmol). From flash column chromatography (20% ether – pet ether) to give the title

compound as an orange oil (0.78 g, 78%); HRMS found $[M+Na]^+$ = 500.1294; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1291.

δ_H ($CDCl_3$) 8.24 (1H, app. d, 5-*H*), 7.79 (1H, app. d, 8-*H*), 7.68 – 7.64 (3H, m, 6-*H*, Ph-*H*), 7.57 (1H, s, C*H*), 7.50 – 7.43 (3H, m, Ph-*H,* 7-*H*)*,* 7.38 – 7.31 (2H, m, Ph-*H*), 7.28 – 7.18 (3H, m, Ph-*H*), 7.12 (2H, d, *J* = 8.5 Hz, *o*-Ar-*H*), 6.86 (2H, d, *J* = 8.5 Hz, *m*-Ar-*H*), 4.16 (1H, s, O*H*), 2.12 (3H, s, Ar-*Me*). δ_c 141.16 ($_q$C), 138.80 ($_q$C), 137.11 ($_q$C), 136.44 ($_q$C), 134.67 ($_q$C), 133.65 (CH), 133.25 (CH), 131.85 (CH), 129.74 (CH), 129.42 (CH), 129.25 (CH), 129.23 (CH), 129.20 (CH), 128.79 (CH), 128.63 ($_q$C), 128.50 (CH), 128.25 (CH), 125.04 (CH), 124.29 (CH), 121.70 ($_q$C), 89.31 ($_q$C), 88.06 ($_q$C), 69.24 ($_q$C), 20.85 (CH_3).

ν_{max}/cm^{-1}: 3432 b (OH), 2920 w (Ar-H), 1700 m (C=C), 1597 w (C=C), 1443 s (CH_3), 1347 s (SO_2), 1172 s (R-OH), 1127 s (SO_2), 755 s (Ph-H), 733 s (C=CH), 690 s (Ph-H).

(*Z*)-3-Butylidene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(*p*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Bb)



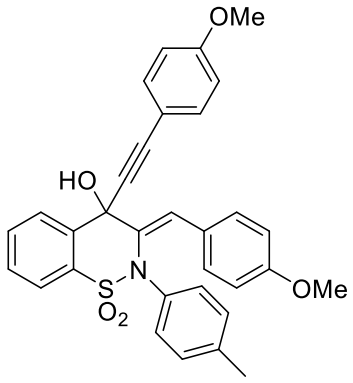
From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.44 mmol). From flash column chromatography (10% EtOAc – hexane) to give the title compound as an orange oil (0.82 g, 82%); HRMS found $[M+Na]^+$ = 432.1612; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 432.1610.

δ_H ($CDCl_3$) 8.13 (1H, app. d, 5-*H*), 7.77 (1H, dd, *J* = 7.8, 1.1 Hz, 8-*H*), 7.64 (1H, td, *J* = 7.8, 1.1 Hz, 6-*H*), 7.46 (1H, td, *J* = 7.8, 1.1 Hz, 7-*H*)*,* 7.19 (2H, d, *J* = 8.4 Hz, *o*-Ar-*H*), 7.05 (2H, d, *J* = 8.4 Hz, *m*-Ar-*H*), 6.62 (1H, t, *J* = 7.3 Hz, C*H*), 3.52 (1H, s, O*H*), 2.35 (2H, t, *J* = 7.1 Hz, CH_2), 2.28 (3H, s, Ar-*Me*), 2.16 – 1.98 (2H, m, CH_2), 1.62 (2H, sxt, *J* = 7.1 Hz, CH_2), 1.28 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.02 (3H, t, *J* = 7.1 Hz, CH_3), 0.79 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 141.29 ($_q$C), 139.24 ($_q$C), 138.16 ($_q$C), 136.29 ($_q$C), 135.17 ($_q$C), 135.00 (CH), 133.17 (CH), 129.48 (CH), 129.11 (CH),

128.91 (CH), 125.01 (CH), 124.15 (CH), 89.14 ($_q$C), 80.61 ($_q$C), 68.76 ($_q$C), 29.32 (CH_2), 21.85 (CH_2), 21.32 (CH_2), 20.93 (CH_3), 20.87 (CH_2), 13.79 (CH_3), 13.62 (CH_3).

ν_{max}/cm^{-1}: 3466 b (OH), 2960 w (Ar-H), 2931 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 1509 w (C=C), 1463 w (CH_2), 1323 s (SO_2), 1164 s (R-OH), 1127 s (SO_2), 734 s (C=CH).

(*Z*)-4-Hydroxy-3-(4-methoxybenzylidene)-4-[(4-methoxyphenyl)ethynyl]-2-(*p*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Bc)

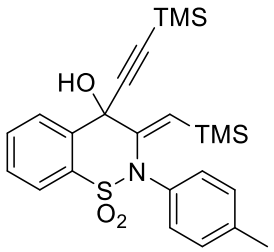


From 2-[3-hydroxy-1,5-bis(4-methoxyphenyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (1.86 mmol). From flash column chromatography (20% EtOAc – pet ether) to give the title compound as an orange oil (0.62 g, 62%); HRMS found $[M+Na]^+$ = 560.1509; $C_{32}H_{27}NO_5SNa$ $[M+Na]^+$ requires = 560.1508.

δ_H ($CDCl_3$) 8.22 (1H, app. d, 5-*H*), 7.79 (1H, app. d, 8-*H*), 7.68 – 7.63 (3H, m, Ar-*H,* 6-*H*), 7.51 (1H, s, C*H*), 7.47 – 7.40 (3H, m, 7-*H,* Ar-*H*), 7.19 (2H, d, *J* = 8.4 Hz, *o*-Ar-*H*), 6.89 (2H, d, *J* = 8.4 Hz, *m*-Ar-*H*), 6.85 (2H, d, *J* = 8.8 Hz, Ar-*H*), 6.79 (2H, d, *J* = 8.8 Hz, Ar-*H*), 3.79 (3H, s, O-*Me*), 3.75 (3H, s, O-*Me*), 2.60 (1H, s, O*H*), 2.14 (3H, s, Ar-*Me*). δ_c 160.17 ($_q$C), 159.94 ($_q$C), 139.26 ($_q$C), 138.72 ($_q$C), 137.30 ($_q$C), 136.17 ($_q$C), 134.65 ($_q$C), 133.51 (CH), 133.32 (CH), 131.43 [2 x C (CH)], 129.25 [2 X C (CH)], 129.20 (CH), 125.88 ($_q$C), 124.71 (CH), 124.15 (CH), 114.05 (CH), 113.80 (CH), 113.68 ($_q$C), 88.30 ($_q$C), 87.88 ($_q$C), 69.22 ($_q$C), 55.35 (CH_3), 55.22 (CH_3), 20.82 (CH_3).

ν_{max}/cm^{-1}: 3432 b (OH), 2969 w (Ar-H), 2837 w (CH_3), 1700 m (C=C), 1604 s (C=C), 1508 s (CH_3), 1350 s (SO_2), 1246 s (R-OH), 1172 s (SO_2), 764 m (C=CH).

(*Z*)-4-Hydroxy-2-(*p*-tolyl)-4-[(trimethylsilyl)ethynyl]-3-[(trimethylsilyl)methylene]-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Be)

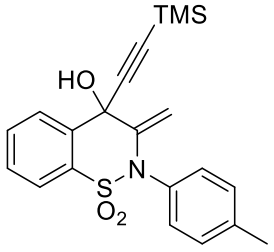


From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (2.13 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a straw coloured oil (0.61 g, 61%); HRMS found $[M+Na]^+$ = 492.1459; $C_{24}H_{31}NO_3SSi_2Na$ $[M+Na]^+$ requires = 492.1461.

δ_H ($CDCl_3$) 8.16 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.73 (1H, dd, *J* = 7.9, 1.0 Hz, 8-*H*), 7.65 (1H, td, *J* = 7.9, 1.0 Hz, 6-*H*), 7.44 (1H, td, *J* = 7.9, 1.0 Hz, 7-*H*), 7.27 – 7.24 (2H, m, *o*-Ar-*H*), 7.05 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 6.91 (1H, s, C*H*), 3.94 (1H, s, O*H*), 2.28 (3H, s, Ar-*Me*), 0.29 (9H, s, Si-*Me*$_3$), 0.00 (9H, s, Si-*Me*$_3$). δ_c 154.96 ($_q$C), 138.78 ($_q$C), 138.60 ($_q$C), 136.14 ($_q$C), 134.71 (CH), 133.97 ($_q$C), 133.49 (CH), 129.30 (CH), 129.28 (CH), 129.20 (CH), 124.65 (CH), 124.26 (CH), 105.68 ($_q$C), 93.21 ($_q$C), 69.74 ($_q$C), 20.84 (CH_3), -0.35 (CH_3), -1.35 (CH_3).

ν_{max}/cm^{-1}: 3456 b (OH), 2958 s (CH_3), 1509 s (C=C), 1356 w (SO_2), 1159 m (R-OH), 1116 s (SO_2), 723 w (CH=CH).

4-Hydroxy-3-methylene-2-(*p*-tolyl)-4-[(trimethylsilyl)ethynyl]-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Be')

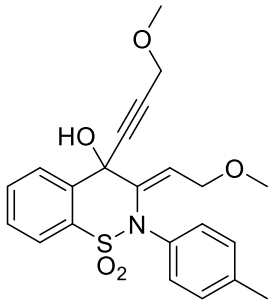


From 2-[3-hydroxy-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-yl]-*N*-(*p*-tolyl)benzenesulfonamide (2.13 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a straw coloured oil (0.02 g, 2%); HRMS found $[M+H]^+$ = 398.1251; $C_{21}H_{24}NO_3SSi$ $[M+H]^+$ requires = 398.1248.

δ_H ($CDCl_3$) 8.14 (1H, dd, *J* = 8.0, 1.0 Hz, 5-*H*), 7.90 (1H, dd, *J* = 8.0, 1.0 Hz, 8-*H*), 7.70 (1H, td, *J* = 8.0, 1.0 Hz, 6-*H*), 7.57 (1H, td, *J* = 8.0, 1.0 Hz, 7-*H*), 7.34 – 7.31 (2H, m, *o*-Ar-*H*), 7.23 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 5.82 (1H, d, *J* = 1.8 Hz, C*H*), 4.76 (1H, d, *J* = 1.8 Hz, C*H*), 2.38 (3H, s, Ar-*Me*), 0.25 (9H, s, Si-*Me*$_3$). δ_C 148.96 ($_q$C), 138.87 ($_q$C), 136.87 ($_q$C), 136.82 ($_q$C), 135.86 ($_q$C), 134.42 ($_q$C), 133.36 (CH), 130.44 (CH), 129.56 (CH), 128.50 (CH), 128.41 (CH), 123.30 (CH), 107.86 (CH2), 102.94 ($_q$C), 94.10 ($_q$C), 69.54 ($_q$C), 21.21 (CH_3), -0.36 (CH_3).

ν_{max}/cm^{-1}: 3285 w (OH), 2959 m (CH_2, CH_3), 1509 m (C=C), 1338 w (SO_2), 1165 s (R-OH), 1138 w (SO_2), 992 w (CH=CH), 842 s (CH=CH).

(*Z*)-4-Hydroxy-3-(2-methoxyethylidene)-4-(3-methoxyprop-1-yn-1-yl)-2-(*p*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Bf)

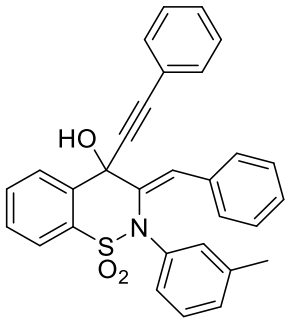


From 2-(4-hydroxy-1,7-dimethoxyhepta-2,5-diyn-4-yl)-*N*-(*p*-tolyl)benzenesulfonamide (2.42 mmol) to give the title compound as a brown oil (0.86 g, 86%); HRMS found $[M+Na]^+$ = 436.1190; $C_{22}H_{23}NO_5SNa$ $[M+Na]^+$ requires = 436.1195.

δ_H ($CDCl_3$) 8.14 (1H, dd, *J* = 7.9, 0.9 Hz, 5-*H*), 7.79 (1H, dd, *J* = 7.9, 0.9 Hz, 8-*H*), 7.66 (1H, td, *J* = 7.9, 0.9 Hz, 6-*H*), 7.49 (1H, td, *J* = 7.9, 0.9 Hz, 7-*H*), 7.18 (2H, d, *J* = 8.5 Hz, *o*-Ar-*H*), 7.07 (2H, d, *J* = 8.5 Hz, *m*-Ar-*H*), 6.67 (1H, t, *J* = 5.6 Hz, C*H*), 4.22 (2H, s, CH_2), 4.04 (1H, dd, *J* = 14.1, 5.8 Hz, CH_aCH$_b$), 3.99 (1H, s, O*H*), 3.92 (1H, dd, *J* = 14.1, 5.8 Hz, CH$_a$CH_b), 3.39 (3H, s, O-*Me*), 3.20 (3H, s, O-*Me*), 3.28 (3H, s, Ar-*Me*). δ_c 141.99 ($_q$C), 138.14 ($_q$C), 137.45 ($_q$C), 136.88 ($_q$C), 135.02 ($_q$C), 133.48 (CH), 131.43 (CH), 129.77 (CH), 129.47 (CH), 128.83 (CH), 125.07 (CH), 124.24 (CH), 86.09 ($_q$C), 84.26 ($_q$C), 68.09 (CH_2), 68.07 ($_q$C), 59.89 (CH_2), 58.47 (CH_3), 58.00 (CH_3), 20.95 (CH_3).

ν_{max}/cm^{-1}: 3346 b (OH), 2924 s (CH_3), 1611 s (C=C), 1508 s (CH_3), 1347 s (SO_2), 1168 s (R-OH), 1097 s (SO_2) 733 s (C=CH).

(*Z*)-3-Benzylidene-4-hydroxy-4-(phenylethynyl)-2-(*m*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Ca)



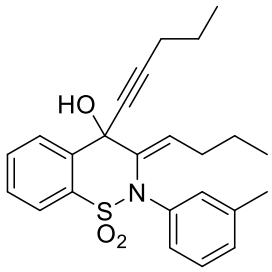
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(*m*-tolyl)benzenesulfonamide (2.09 mmol). From flash column chromatography (20% EtOAc – hexane) and resultant solid recrystalised from ether – hexane to give the title compound as a white powder (0.72 g, 72%) m.p. 160 – 161 °C; HRMS found $[M+Na]^+$ = 500.1291; $C_{30}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 500.1297.

δ_H ($CDCl_3$) 8.26 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.84 (1H, dd, *J* = 7.9, 1.0 Hz, 8-*H*), 7.71 (1H, td, *J* = 7.9, 1.0 Hz, 6-*H*), 7.63 – 7.61 (2H, m, Ar-*H*), 7.59 (1H, s, C*H*), 7.56 – 7.50 (3H, m, Ar-*H,* 7-*H*), 7.42 – 7.34 (3H, m, Ar-*H*), 7.28 – 7.19* (2H, m, Ar-*H*), 7.04 (2H, m, Ar-*H*), 6.98 (1H, t, *J* = 7.6 Hz, Ar-*H*), 6.82 (1H, m, Ar-*H*), 3.74 (1H, s, O*H*), 2.13 (3H, s, Ar-*Me*). δ_c 141.11 ($_q$C), 139.38 ($_q$C), 138.65 ($_q$C), 138.39 ($_q$C), 134.81 ($_q$C), 133.62 (CH), 133.19 ($_q$C), 131.82 [2 X C (CH)], 129.65 (CH), 129.48 (CH), 129.25 (CH), 129.09 (CH), 128.69 (CH), 128.49 (CH), 128.31 (CH), 128.14 (CH), 127.30 (CH), 125.92 (CH), 124.31 (CH), 121.98 (CH), 121.64 ($_q$C), 89.04 ($_q$C), 88.25 ($_q$C), 69.52 ($_q$C), 21.27 (CH_3).

ν_{max}/cm^{-1}: 3470 b (OH), 1489 m (C=C), 1349 s (SO_2), 1180 s (R-OH), 1137 s (SO_2), 757 s (C=CH).

*Overlapping with $CDCl_3$ signal

(*Z*)-3-Butylidene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(*m*-tolyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Cb)

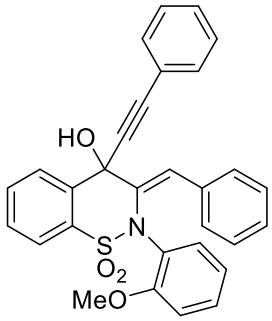


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(*m*-tolyl)benzenesulfonamide (2.44 mmol). From flash column chromatography (15% EtOAc – pet ether) to give the title compound as a yellow glass-like solid (0.59 g, 59%); HRMS found $[M+Na]^+$ = 432.1611; $C_{24}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 432.1610.

δ_H ($CDCl_3$) 8.11 (1H, dd, *J* = 7.9, 1.2 Hz, 5-*H*), 7.79 (1H, dd, *J* = 7.9, 1.2 Hz, 8-*H*), 7.64 (1H, td, *J* = 7.8, 1.2 Hz, 6-*H*), 7.47 (1H, td, *J* = 7.8, 1.2 Hz, 7-*H*), 7.21 – 7.21 (1H, m, Ar-*H*), 7.15 – 7.13 (2H, m, Ar-*H*), 6.99 – 6.96 (1H, m, Ar-*H*), 6.62 (1H, t, *J* = 7.3 Hz, C*H*), 3.40 (1H, s, O*H*), 2.35 (2H, t, *J* = 7.1 Hz, CH_2), 2.29 (3H, s, Ar-*Me*), 2.16 – 1.99 (2H, m, CH_2), 1.62 (2H, sxt, *J* = 7.1 Hz, CH_2), 1.32 – 1.22 (2H, m, CH_2), 1.02 (3H, t, *J* = 7.1 Hz, CH_3), 0.78 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 140.72 ($_q$C), 140.59 ($_q$C), 139.18 ($_q$C), 138.77 ($_q$C), 135.39 ($_q$C), 135.02 (CH), 133.12 (CH), 129.16 (CH), 128.79 (CH), 128.59 (CH), 127.05 (CH), 125.50 (CH), 124.05 (CH), 121.75 (CH), 89.22 ($_q$C), 80.58 ($_q$C), 68.87 ($_q$C), 29.27 (CH_2), 21.84 (CH_2), 21.41 (CH_3), 21.27 (CH_2), 20.86 (CH_2), 13.76 (CH_3), 13.69 (CH_3).

ν_{max}/cm^{-1}: 3455 b (OH), 2961 m (Ar-H), 2933 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 2233 w (C≡C), 1605 m (C=C), 1488 m (CH_2), 1319 s (SO_2), 1163 s (R-OH), 1126 s (SO_2), 734 s (C=CH).

(*Z*)-3-Benzylidene-4-hydroxy-2-(2-methoxyphenyl)-4-(phenylethynyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Da)



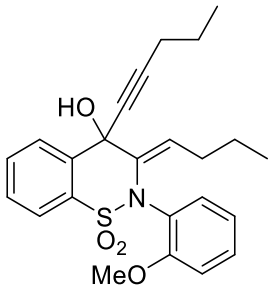
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (2.03 mmol). From flash column chromatography (20% ether – hexane) to give the title compound as a golden foam (0.86 g, 86%); HRMS found $[M+Na]^+$ = 516.1239; $C_{30}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 516.1246.

δ_H ($CDCl_3$) 8.30 (1H, dd, *J* = 8.0, 0.9 Hz, 5-*H*), 7.84 (1H, dd, *J* = 8.0, 0.9 Hz, 8-*H*), 7.70 (1H, td, *J* = 8.0, 0.9 Hz, 6-*H*), 7.64 (1H, s, C*H*), 7.57 – 7.54 (2H, m, Ar-*H*), 7.52 – 7.48 (3H, m, 7-*H*, Ar-*H*), 7.38 – 7.34 (3H, m, Ar-*H*), 7.28 – 7.19* (3H, m, Ar-*H*), 7.06 – 7.01 (1H, m, Ar-*H*), 6.95 (1H, dd, *J* = 9.0, 1.6 Hz, Ar-*H*), 6.68 (1H, dd, *J* = 9.0, 1.6 Hz, Ar-*H*), 6.59 (1H, td, *J* = 9.0, 1.6 Hz, Ar-*H*), 5.04 (1H, s, O*H*), 3.46 (3H, s, Ar-*Me*). δ_c 153.90 ($_qC$), 139.63 ($_qC$), 135.63 ($_qC$), 134.04 ($_qC$), 133.04 (CH), 131.81 (CH), 131.57 (CH), 130.21 (CH), 129.07 (CH), 129.02 (CH), 128.94 [2 X C (CH)], 128.87 [2 X C (CH)], 128.68 (CH), 128.45 (CH), 128.03 (CH), 127.43 ($_qC$), 123.22 (CH), 122.00 ($_qC$), 120.73 (CH), 112.30 (CH), 89.23 ($_qC$), 87.50 ($_qC$), 70.06 ($_qC$), 55.44 (CH_3).

ν_{max}/cm^{-1}: 3399 b (OH), 1595 m (C=C), 1341 s (SO_2), 1172 s (R-OH), 1131 m (SO_2), 751 s (Ph-H), 691 s (C=CH), 690 s (Ph-H).

*Overlapping with $CDCl_3$ signal

(*Z*)-3-Butylidene-4-hydroxy-2-(2-methoxyphenyl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Db)



From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(2-methoxyphenyl)benzenesulfonamide (2.56 mmol). From flash column chromatography (20% EtOAc – pet ether) to give the title compound as a pink oil (0.67 g, 61%); HRMS found $[M+Na]^+$ = 448.1550; $C_{24}H_{27}NO_4SNa$ $[M+Na]^+$ requires = 448.1559.

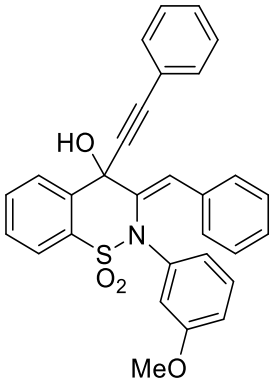
δ_H ($CDCl_3$) 8.15 (1H, dd, *J* = 8.0, 1.0 Hz, 5-*H*), 7.77 (1H, dd, *J* = 8.0, 1.0 Hz, 8-*H*), 7.63 (1H, td, *J* = 8.0, 1.0 Hz, 6-*H*), 7.54 (1H, dd, *J* = 7.9, 1.6 Hz, Ar-*H*), 7.43 (1H, td, *J* = 8.0, 1.0 Hz, 7-*H*), 7.26 – 7.22* (1H, m, Ar-*H*), 6.96 (1H, td, *J* = 7.9, 1.6 Hz, Ar-*H*), 6.86 (1H, dd, *J* = 7.9, 1.6 Hz, Ar-*H*),

6.62 (1H, t, *J* = 7.4 Hz, C*H*), 4.73 (1H, s, O*H*), 3.57 (3H, s, O-*Me*), 2.34 (2H, t, *J* = 7.2 Hz, CH_2), 2.15 – 2.08 (2H, m, CH_2), 1.62 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.24 – 1.17 (2H, m, CH_2), 1.02 (3H, t, *J* = 7.2 Hz, CH_3), 0.77 (3H, t, *J* = 7.4 Hz, CH_3). δ_c 154.48 ($_q$C), 140.68 ($_q$C), 140.08 ($_q$C), 135.77 ($_q$C), 133.69 (CH), 132.72 (CH), 130.80 (CH), 129.05 (CH), 128.84 (CH), 128.44 ($_q$C), 128.41 (CH), 123.11 (CH), 121.19 (CH), 112.63 (CH), 88.40 ($_q$C), 80.81 ($_q$C), 60.42 ($_q$C), 55.54 (CH_3), 29.22 (CH_2), 21.92 (CH_2), 21.57 (CH_2), 20.90 (CH_2), 13.72 (CH_3), 13.65 (CH_3).

ν_{max}/cm^{-1}: 3444 b (OH), 2960 w (Ar-H), 2932 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 1498 s (C=C), 1459 m (CH_2), 1334 s (SO_2), 1123 s (R-OH), 1097 w (SO_2), 742 s (C=CH).

*Overlapping with $CDCl_3$ signal

(*Z*)-3-Benzylidene-4-hydroxy-2-(3-methoxyphenyl)-4-(phenylethynyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Ea)



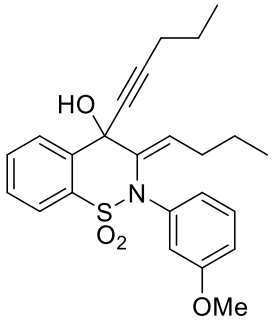
From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(3-methoxyphenyl)benzenesulfonamide (2.03 mmol). From flash column chromatography (30% ether – pet ether) to give the title compound as a yellow oil (0.96 g, 96%); HRMS found $[M+Na]^+$ = 516.1239; $C_{30}H_{23}NO_4SNa$ $[M+Na]^+$ requires = 516.1246.

δ_H ($CDCl_3$) 8.26 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.84 (1H, dd, *J* = 7.9, 1.0 Hz, 8-*H*), 7.71 (1H, td, *J* = 7.9, 1.0 Hz, 6-*H*), 7.66 – 7.63 (2H, m, Ph-*H*), 7.61 (1H, s, C*H*), 7.54 – 7.49 (3H, m, Ph-*H,* 7-*H*), 7.39 – 7.33 (3H, m, Ph-*H*), 7.30 – 7.21* (3H, m, Ph-*H*), 7.00 (1H, t, *J* = 8.2 Hz, Ar-*H*), 6.87 – 6.85 (1H, m, Ar-*H*), 6.82 – 6.81 (1H, m, Ar-*H*), 6.58 – 6.55 (1H, m, Ar-*H*), 3.87 (1H, s, O*H*), 3.57 (3H, s, O-*Me*). δ_c 159.53 ($_q$C), 140.93 ($_q$C), 140.61 ($_q$C), 138.68 ($_q$C), 134.98 ($_q$C), 133.68 (CH), 133.20 ($_q$C), 132.25 (CH), 131.83 (CH), 129.68 (CH), 129.50 (CH), 129.26 (CH), 129.12 (CH), 128.81 (CH), 128.48 (CH), 128.24 (CH), 124.31 (CH), 121.59 ($_q$C), 117.39 (CH), 112.52 (CH), 110.78 (CH), 89.09 ($_q$C), 88.17 ($_q$C), 69.36 ($_q$C), 55.18 (CH_3).

ν_{max}/cm^{-1}: 3445 b (OH), 1601 s (C=C), 1489 s (CH_3), 1347 s (SO_2), 1161 s (R-OH), 1121 m (SO_2), 755 s (Ph-H), 731 s (C=CH), 688 s (Ph-H).

*Overlapping with $CDCl_3$ signal

(*Z*)-3-Butylidene-4-hydroxy-2-(3-methoxyphenyl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Eb)

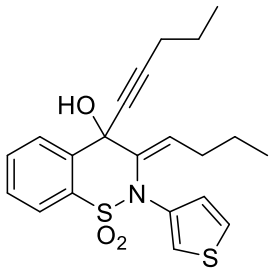


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(3-methoxyphenyl)benzenesulfonamide (1.39 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.47 g, 80%); HRMS found $[M+Na]^+$ = 448.1555; $C_{24}H_{27}NO_4SNa$ $[M+Na]^+$ requires = 448.1559.

δ_H ($CDCl_3$) 8.11 (1H, dd, *J* = 7.9, 1.0 Hz, 5-*H*), 7.78 (1H, dd, *J* = 7.9, 1.0 Hz, 8-*H*), 7.64 (1H, td, *J* = 7.9, 1.0 Hz, 6-*H*), 7.47 (1H, td, *J* = 7.9, 1.0 Hz, 7-*H*), 7.15 – 7.13 (1H, m, Ar-*H*), 6.96 – 7.93 (2H, m, Ar-*H*), 6.72 – 6.70 (1H, m, Ar-*H*), 6.64 (1H, t, *J* = 7.3 Hz, C*H*), 3.75 (3H, s, O-*Me*), 3.44 (1H, s, O*H*), 2.34 (2H, t, *J* = 7.3 Hz, CH_2), 2.18 – 2.00 (2H, m, CH_2), 1.62 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.30 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.01 (3H, t, *J* = 7.3 Hz, CH_3), 0.79 (3H, t, *J* = 7.3 Hz, CH_3).
δ_c 159.83 ($_qC$), 141.75 ($_qC$), 140.67 ($_qC$), 139.17 ($_qC$), 135.49 (CH), 135.22 ($_qC$), 133.20 (CH), 129.40 (CH), 129.20 (CH), 128.83 (CH), 124.09 (CH), 117.10 (CH), 111.96 (CH), 110.62 (CH), 89.26 ($_qC$), 80.54 ($_qC$), 68.79 ($_qC$), 55.32 (CH_3), 29.30 (CH_2), 21.84 (CH_2), 21.30 (CH_2), 20.89 (CH_2), 13.82 (CH_3), 13.62 (CH_3).

ν_{max}/cm^{-1}: 3459 b (OH), 2960 m (Ar-H), 2932 w (CH_2, CH_3), 2871 w (CH_2, CH_3), 1601 s (C=C), 1489 s (CH_2), 1318 s (SO_2), 1163 s (R-OH), 1126 s (SO_2), 733 s (C=CH).

(*Z*)-3-Butylidene-4-hydroxy-4-(pent-1-yn-1-yl)-2-(thiophen-3-yl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Gb)

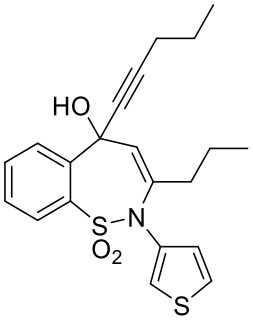


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(thiophen-3-yl)benzenesulfonamide (1.25 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.35 g, 70%); HRMS found $[M+H]^+$ = 402.1195; $C_{21}H_{24}NO_3S_2$ $[M+H]^+$ requires = 402.1199.

δ_H ($CDCl_3$) 8.07 (1H, app. d, 5-*H*), 7.80 (1H, app. d, 8-*H*), 7.63 (1H, app. t, 6-*H*), 7.48 (1H, app. t, 7-*H*), 7.18 – 7.16 (1H, m, Ar-*H*), 7.13 – 7.11 (1H, m, Ar-*H*), 7.08 (1H, dd, *J* = 5.1, 1.4 Hz, Ar-*H*), 6.67 (1H, t, *J* = 7.3 Hz, C*H*), 3.20 (1H, s, O*H*), 2.31 (2H, t, *J* = 7.3 Hz, CH_2), 2.19 – 2.17 (2H, m, CH_2), 2.16 – 1.98 (2H, m, CH_2), 1.59 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.35 (2H, sxt, *J* = 7.3 Hz, CH_2), 1.00 (3H, t, *J* = 7.3 Hz, CH_3), 0.85 (3H, t, *J* = 7.3 Hz, CH_3). δ_c 139.93 ($_q$C), 139.10 ($_q$C), 138.22 ($_q$C), 135.81 (CH), 135.12 ($_q$C), 133.16 (CH), 129.25 (CH), 128.93 (CH), 124.61 (CH), 124.22 (CH), 123.99 (CH), 115.49 (CH), 89.19 ($_q$C), 80.56 ($_q$C), 68.62 ($_q$C), 29.18 (CH_2), 21.81 (CH_2), 21.39 (CH_2), 20.83 (CH_2), 13.83 (CH_3), 13.60 (CH_3).

ν_{max}/cm^{-1}: 3407 b (OH), 2960 m (Ar-H), 2930 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 1585 m (C=C), 1468 w (CH_2), 1390 m (CH_3), 1352 s (SO_2), 1177 s (R-OH), 1068 w (SO_2) 766 (C=CH).

5-Hydroxy-5-(pent-1-yn-1-yl)-3-propyl-2-(thiophen-3-yl)-2,5-dihydrobenzo[*f*][1,2] thiazepine 1,1-dioxide (3.10Gb)

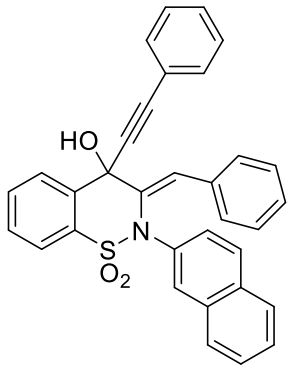


From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(thiophen-3-yl)benzenesulfonamide (1.25 mmol). From flash column chromatography (20% EtOAc – hexane) to give the title compound as an orange oil (0.05 g, 11%); HRMS found $[M+H]^+$ = 402.1199; $C_{21}H_{24}NO_3S_2$ $[M+H]^+$ requires = 402.1279.

δ_H ($CDCl_3$) 8.45 (1H, app. d, 6-*H*), 7.68 – 7.64 (2H, m, 9-*H*, 7-*H*), 7.40 (1H, app. t, 8-*H*), 7.15 – 7.12 (1H, m, Ar-*H*), 6.83 – 6.82 (1H, m, Ar-*H*), 6.72 (1H, dd, *J* = 5.0, 1.1 Hz, Ar-*H*), 5.91 (1H, s, 4-*H*), 5.43 (1H, s, O*H*), 2.41 (2H, t, *J* = 7.2 Hz, CH_2), 2.09 – 2.02 (1H, m, CH_2), 1.96 – 1.88 (1H, m, CH_2), 1.70 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.64 – 1.55 (2H, m, CH_2), 1.09 (3H, t, *J* = 7.2 Hz, CH_3), 0.97 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 137.47 ($_q$C), 137.03 ($_q$C), 135.10 ($_q$C), 134.86 ($_q$C), 133.93 (CH), 130.87 (CH), 128.80 (CH), 128.38 (CH), 126.24 (CH), 125.15 (CH), 122.19 (CH), 120.87 (CH), 89.00 ($_q$C), 82.06 ($_q$C), 72.89 ($_q$C), 37.68 (CH_2), 21.95 (CH_2), 20.99 (CH_2), 20.62 (CH_2), 13.75 (CH_3), 13.01 (CH_3).

ν_{max}/cm^{-1}: 3129 b (OH), 2962 w (Ar-H), 2927 m (CH_2, CH_3), 2871 w (CH_2, CH_3), 2207 w (C≡C) 1631 s (C=C), 1593 w (C=C), 1465 s (CH_2), 1364 m (CH_2), 1329 s (SO_2), 1157 s (R-OH), 1060 w (SO_2).

(*Z*)-3-Benzylidene-4-hydroxy-2-(naphthalen-2-yl)-4-(phenylethynyl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Ha)

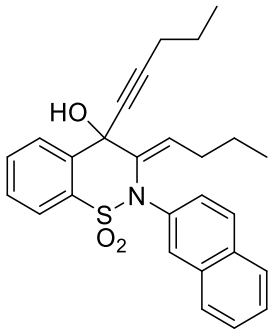


From 2-(3-hydroxy-1,5-diphenylpenta-1,4-diyn-3-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (1.95 mmol). From flash column chromatography (20% EtOAc – hexane) and resultant solid recrystalised from ether – hexane to give the title compound as a beige foam (0.75 g, 75%) m.p. 94 – 96 °C; HRMS found $[M+Na]^+$ = 536.1297; $C_{33}H_{23}NO_3SNa$ $[M+Na]^+$ requires = 536.1297.

δ_H [$(CD_3)_2CO$](600 MHz) 8.23 (1H, dd, *J* = 8.0, 0.9 Hz, 5-*H*), 7.89 (1H, app. s, Ar-*H*), 7.84 (1H, dd, *J* = 8.0, 0.9 Hz, 8-*H*), 7.77 – 7.75 (1H, m, 6-*H*), 7.66 – 7.63 (3H, m, Ar-*H*), 7.61 – 7.57 (5H, m, Ar-*H,* 7-*H*), 7.33 – 7.24 (7H, m, Ar-*H*), 7.16 – 7.13 (2H, m, Ar-*H*), 7.07 – 7.04 (1H, m, Ar-*H*), 6.66 (1H, s, O*H*). δ_c (150 MHz) 139.84 ($_q$C), 139.39 ($_q$C), 137.16 ($_q$C), 135.54 ($_q$C), 133.48 (CH), 133.33 ($_q$C), 133.06 ($_q$C), 131.52 (CH), 131.28 ($_q$C), 130.23 (CH), 129.45 (CH), 129.37 (CH), 129.05 (CH), 128.74 (CH), 128.55 (CH), 128.53 (CH), 128.03 (CH), 127.99 (CH), 127.54 (CH), 127.35 (CH), 126.36 (CH), 125.72 (CH), 123.57 (CH), 123.37 (CH), 122.43 (CH), 121.90 ($_q$C), 90.82 ($_q$C), 86.70 ($_q$C), 68.08 ($_q$C).

ν_{max}/cm^{-1}: 3454 w (OH), 1596 w (C=C), 1508 w (C=C), 1490 m (CH_3), 1342 s (SO_2), 1170 s (R-OH), 1131 s (SO_2), 753 s (Ph-H), 690 s (C=CH), 667 m (Ph-H).

(*Z*)-3-Butylidene-4-hydroxy-2-(naphthalen-2-yl)-4-(pent-1-yn-1-yl)-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (3.9Hb)



From 2-(6-hydroxyundeca-4,7-diyn-6-yl)-*N*-(naphthalen-2-yl)benzenesulfonamide (2.24 mmol). From flash column chromatography (toluene) to give the title compound as an orange oil (0.84 g, 84%); HRMS found $[M+Na]^+$ = 468.1609; $C_{27}H_{27}NO_3SNa$ $[M+Na]^+$ requires = 468.1610.

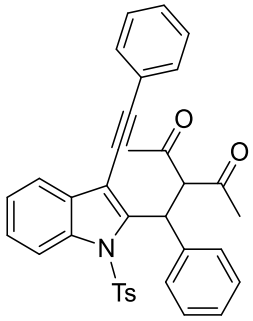
δ_H ($CDCl_3$) 8.15 (1H, dd, *J* = 8.0, 0.9 Hz, 5-*H*), 7.83 – 7.73 (5H, m, Ar-*H*), 7.65 (1H, td, *J* = 7.7, 1.3 Hz, 6-*H*), 7.52 – 7.40 (4H, m, Ar-*H*), 6.68 (1H, t, *J* = 7.2 Hz, C*H*), 3.44 (1H, s, O*H*), 2.37 (2H, t, *J* = 7.0 Hz, CH_2), 2.15 – 1.98 (2H, m, CH_2), 1.64 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.27 (2H, sxt, *J* = 7.2 Hz, CH_2), 1.03 (3H, t, *J* = 7.1 Hz, CH_3), 0.74 (3H, t, *J* = 7.2 Hz, CH_3). δ_c 140.50 ($_q$C), 139.15 ($_q$C), 138.05 ($_q$C), 135.32 (CH), 133.33 ($_q$C), 133.25 (CH), 131.50 ($_q$C), 129.27 (CH), 128.82 (CH), 128.74 (CH), 127.90 (CH), 127.54 (CH), 126.48 (CH), 125.94 (CH), 124.08 (CH), 123.42 (CH), 122.44 (CH), 89.41 ($_q$C), 80.56 ($_q$C), 68.92 ($_q$C), 29.30 (CH_2), 21.86 (CH_2), 21.31 (CH_2), 20.90 (CH_2), 13.76 (CH_3), 13.65 (CH_3).

ν_{max}/cm^{-1}: 3453 b (OH), 2959 m (Ar-H), 2929 m (CH_2, CH_3), 2870 m (CH_2, CH_3), 2231 w (C≡C), 1631 m (C=C), 1597 m (C=C), 1508 m (C=C), 1465 m (CH_2), 1317 s (SO_2), 1162 s (R-OH), 1125 s (SO_2), 732 s (C=CH).

6.4 Chapter 4 Experimental

6.4.1 Reactions with (*Z*)-2-Benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol

3-{Phenyl[3-(phenylethynyl)-1-tosyl-1*H*-indol-2-yl]methyl}pentane-2,4-dione (4.14a)



Under an argon atmosphere (*Z*)-2-benzylidene-3-(phenylethynyl)-1-tosylindolin-3-ol (0.20 g, 0.004 mmol, 1 equiv.) was dissolved in DCE (10 mL) to this 100% w/w montmorilontite K-10 (0.20 g) and acetylacetone (0.13 mL, 0.01 mmol, 3 equiv.) was added, and the mixture stirred at reflux for 2 h. After this time the reaction mixture was allowed to cool, filtered through Celite and evaporated to give the title compound as a brown oil (0.24 g, 100%); HRMS found $[M+Na]^+$ = 582.1711; $C_{35}H_{29}NO_4SNa$ $[M+Na]^+$ requires = 582.1709.

δ_H (CD_2Cl_2) 8.04 – 8.00 (1H, m, 4-*H*), 7.72 – 7.70 (3H, m, Ph-*H*), 7.63 – 7.62 (4H, m, Ar-*H*, Ph-*H*), 7.53 – 7.46 (3H, m, Ph-*H*), 7.37 – 7.29 (5H, m, Ph-*H,* 5-*H,* 6-*H, 7-H*), 7.15 (2H, d, *J* = 8.0 Hz, *m*-Ar-*H*), 6.08 (1H, d, *J* = 12.0 Hz, C*H*), 6.00 (1H, d, *J* = 12.0 Hz, C*H*), 2.33 (3H, s, Ar-*Me*), 2.23 2.22 (3H, s, *Me*), 2.06 (3H, s, *Me*). δ_c 191.30 (C=O), 145.35 ($_q$C), 144.17 ($_q$C), 139.13 ($_q$C), 135.36 ($_q$C), 135.08 ($_q$C), 131.18 (CH), 129.55 (CH), 129.40 (CH), 128.95 (CH), 128.78 (CH), 128.76 (CH), 127.45 (CH), 127.19 (CH), 125.51 (CH), 124.00 (CH), 122.78 ($_q$C), 119.63 (CH), 115.07 (CH), 97.55 ($_q$C), 82.17 ($_q$C), 72.74 (CH), 58.38 ($_q$C), 43.38 (CH), 31.32 (CH_3), 29.20 (CH_3), 21.25 (CH_3).

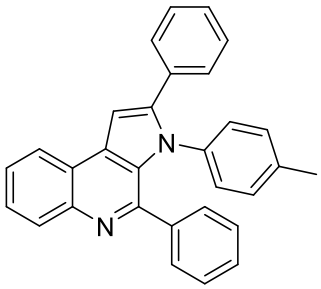
ν_{max}/cm^{-1}: 1729 s (C=O), 1699 s (C=O), 1597 m (C=C), 1377 s (CH_3), 1352 s (SO_2), 1168 s (R-OH), 1120 s (SO_2), 754 s (Ph-H), 690 s (Ph-H).

6.4.2 Reactions of 4-Alkynyl-3-iodo-quinolines

General Method for the Synthesis of Pyrrolo[2,3-*c*]quinolines and 3-Amino-4-alkynylquinolines

Under an inert (N_2) atmosphere anhydrous DMA (5 mL) was added to a mixture of 4-alkynyl-3-iodoquinoline (1 equiv.), $Pd(OAc)_2$ (8 mol %), potassium carbonate (1.38 mmol, 3 equiv.) and Xantphos (10 mol %). To this mixture was added the relevant amine (1.2 equiv.), the reaction mixture was heated to 80 °C and stirred for 16 h. After this time the mixture was cooled, diluted with EtOAc, washed with water and brine. The organic phase was separated, dried (Na_2SO_4) and evaporated, and the crude material was purified by flash column chromatography unless otherwise stated. Reactions that provided 3-aminoquinolines gave these as the fastest running compounds (non-polar) from the column. The following were synthesised by this method.

2,4-Diphenyl-3-(*p*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Aa)

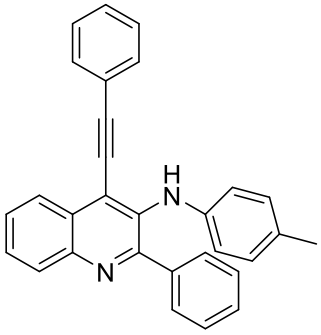


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and *p*-toluidine (0.063 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as off white crystals (0.04 g, 21%) m.p. 229 °C; HRMS found $[M+H]^+$ = 411.1859; $C_{30}H_{23}N_2$ $[M+H]^+$ requires = 411.1863.

δ_H ($CDCl_3$) 8.32 – 8.29 (1H, m, 9-*H*), 8.23 (1H, app. d, 6-*H*), 7.66 – 7.58 (2H, m, 7-*H*, 8-*H*), 7.33 (1H, s, 1-*H*), 7.25 – 7.22 (5H, m, Ph-*H*), 7.12 – 7.07 (3H, m, Ph-*H*), 7.00 – 6.95 (2H, m, Ph-*H*), 6.70 – 6.65 (4H, m, Ar-*H*), 2.23 (3H, s, Ar-*Me*). δ_c 148.62 ($_q$C), 143.53 ($_q$C), 142.32 ($_q$C), 139.14 ($_q$C), 137.23 ($_q$C), 135.44 ($_q$C), 132.25 ($_q$C), 130.22 ($_q$C), 129.73 [2 X C (CH)], 129.67($_q$C), 128.98 (CH), 128.68 (CH), 128.66 (CH), 128.10 (CH), 127.88 (CH), 127.28 (CH), 126.80 (CH), 126.50 (CH), 125.89 (CH), 122.68 (CH), 122.65 ($_q$C), 102.21 (CH), 21.02 (CH_3).

ν_{max}/cm^{-1}: 3032 w (Ar-H), 1511 s (C=C), 1380 s (CH_3), 759 s (Ph-H), 695 s (Ph-H).

2-Phenyl-4-(phenylethynyl)-*N*-(*p*-tolyl)quinolin-3-amine (4.36Aa)



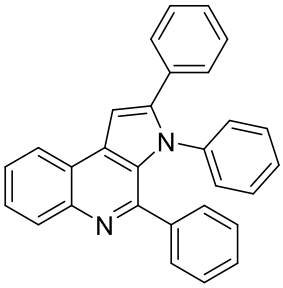
From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and *p*-toluidine (0.063 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as a bright yellow powder (0.07 g, 38%) m.p. 187 – 188 °C; HRMS found $[M+H]^+$ = 411.1860; $C_{30}H_{23}N_2$ $[M+H]^+$ requires = 411.1863.

δ_H ($CDCl_3$) 8.33 – 8.29 (1H, m, 5-*H*), 8.14 – 8.10 (1H, m, 8-*H*), 7.74 – 7.71 (2H, m, Ph-*H*), 7.66 – 7.58 (2H, m, 6-*H,* 7-*H*), 7.48 – 7.37 (3H, m, Ph-*H*), 7.34 – 7.26* (3H, m, Ph-*H*), 7.13 – 7.10 (2H, m, Ph-*H*), 7.01 (2H, d, *J* = 8.1 Hz, *m*-Ar-*H*), 6.80 (2H, d, *J* = 8.1 Hz, *o*-Ar-*H*), 6.03 (1H, s, N*H*), 2.28 (3H, s, Ar-*Me*). δ_c 154.96 ($_qC$), 144.00 ($_qC$), 140.49 ($_qC$), 138.44 ($_qC$), 135.77 ($_qC$), 131.69 (CH), 130.95 ($_qC$), 129.75 (CH), 129.25 (CH), 129.00 (CH), 128.87 [2 X C (CH)], 128.77 (CH), 128.23 (CH), 128.08 ($_qC$), 127.78 (CH), 127.42 (CH), 125.00 (CH), 122.54 ($_qC$), 118.38 (CH), 117.85 ($_qC$), 106.29 ($_qC$), 83.99 ($_qC$), 20.65 (CH_3).

ν_{max}/cm^{-1}: 3391 s (NH), 3051 w (Ar-H), 2917 w (CH_3), 1609 w (C=C), 1386 s (CH_3), 772 s (Ph-H), 700 s (Ph-H).

*Overlapping of $CDCl_3$ signal

2,3,4-Triphenyl-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Ab)

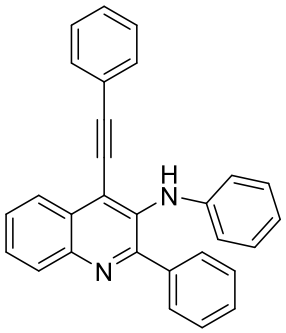


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and aniline (50 µL). From column chromatography (toluene) and resulting residue washed with pentane to give the title compound as an orange powder (0.12 g, 74%) m.p. 163 °C; HRMS found $[M+H]^+$ = 397.1695; $C_{29}H_{21}N_2$ $[M+H]^+$ requires = 397.1706.

δ_H (CD_2Cl_2) 8.40 – 8.38 (1H, m, 9-*H*), 8.20 – 8.16 (1H, m, 6-*H*), 7.71 – 7.64 (2H, m, 7-*H*, 8-*H*), 7.41 (1H, s, 1-*H*), 7.31 – 7.26 (5H, m, Ph-*H*), 7.16 – 7.03 (6H, m, Ph-*H*), 7.00 – 6.96 (2H, m, Ph-*H*), 6.90 – 6.87 (2H, m, Ph-*H*). δ_c 148.43 ($_q$C), 143.64 ($_q$C), 142.36 ($_q$C), 139.16 ($_q$C), 138.15 ($_q$C), 132.25 ($_q$C), 130.15 ($_q$C), 129.69 (CH), 129.51 (CH), 129.49 ($_q$C), 129.09 (CH), 128.86 (CH), 128.08 (CH), 128.02 (CH), 127.89 (CH), 127.39 (CH), 127.16 (CH), 127.08 (CH), 126.41 (CH), 125.81 (CH), 122.66 (CH), 122.57 ($_q$C), 102.32 (CH).

ν_{max}/cm^{-1}: 1498 s (C=C), 759 s (Ph-H), 694 s (Ph-H).

_N_,2-Diphenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ab)

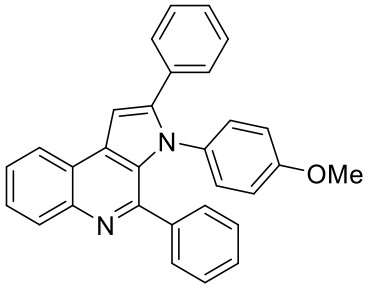


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and aniline (50 µL). From column chromatography (toluene) to give the title compound as yellow crystals (0.006 g, 3%) m.p. 136 – 137 °C; HRMS found $[M+H]^+$ = 397.1696; $C_{29}H_{21}N_2$ $[M+H]^+$ requires = 397.1706.

δ_H [$(CD_3)_2CO$] 8.26 – 8.23 (1H, m, 5-*H*), 7.96 – 7.93 (1H, m, 8-*H*), 7.71 – 7.68 (2H, m, Ph-*H*), 7.68 – 7.53 (2H, m, 6-*H*, 7-*H*), 7.18 (1H, s, N*H*), 7.15 – 7.12 (2H, m, Ph-*H*), 7.06 – 7.01 (2H, m, Ph-*H*), 6.77 – 6.74 (2H, m, Ph-*H*), 6.70 – 6.66 (2H, m, Ph-*H*). δ_c 156.35 ($_q$C), 144.79 ($_q$C), 144.53 ($_q$C), 139.23 ($_q$C), 135.37 ($_q$C), 131.69 (CH), 129.75 (CH), 129.17 (CH), 128.94 (CH), 128.68 (CH), 128.59 (CH), 128.43 (CH), 128.23 (CH), 128.07 (CH), 127.67 ($_q$C), 127.47 (CH), 125.06 (CH), 122.48 ($_q$C), 121.21 ($_q$C), 119.68 (CH), 116.29 (CH), 105.32 ($_q$C), 83.79 ($_q$C).

ν_{max}/cm^{-1}: 3392 s (NH), 3052 w (Ar-H), 2206 m (C≡C), 1597 s (C=C), 745 s (Ph-H), 694 s (Ph-H).

3-(4-Methoxyphenyl)-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Ad)

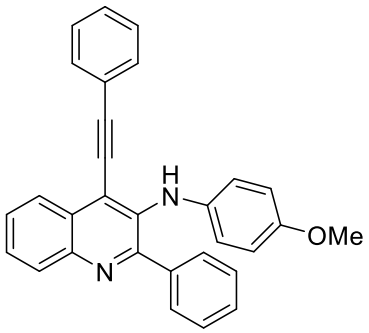


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and *p*-anisidine (0.069 g). From column chromatography (10% EtOAc – hexane) to give the title compound as red crystals (0.07 g, 35%) m.p. 195 °C; HRMS found $[M+H]^+$ = 427.1805; $C_{30}H_{23}N_2O$ $[M+H]^+$ requires = 427.1812.

δ_H [$(CD_3)_2CO$] 8.49 – 8.45 (1H, m, 9-*H*), 8.12 – 8.07 (1H, m, 6-*H*), 7.66 – 7.63 (2H, m, 7-*H*, 8-*H*), 7.52 (1H, s, 1-*H*), 7.35 – 7.29 (5H, m, Ph-*H*), 7.18 – 7.14 (3H, m, Ph-*H*), 7.08 – 7.04 (2H, m, Ph-*H*), 6.89 – 6.85 (2H, m, Ar-*H*), 6.56 – 6.52 (2H, m, Ar-*H*), 3.73 (3H, s, O-*Me*). δ_c 158.98 ($_q$C), 148.46 ($_q$C), 143.62 ($_q$C), 142.42 ($_q$C), 139.55 ($_q$C), 132.43 ($_q$C), 130.97 ($_q$C), 130.18 ($_q$C), 129.90 ($_q$C), 129.78 (CH), 129.66 (CH), 129.55 (CH), 129.10 (CH), 128.07 (CH), 127.88 (CH), 126.89 (CH), 126.71 (CH), 126.17 (CH), 125.72 (CH), 122.82 (CH), 122.76 ($_q$C), 113.38 (CH), 102.03 (CH), 54.88 (CH_3).

ν_{max}/cm^{-1}: 3031 w (Ar-H), 2925w (CH_3), 1508 s (C=C), 1383 s (CH_3), 766 s (Ph-H), 696 s (Ph-H).

***N*-(4-Methoxyphenyl)-2-phenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ad)**

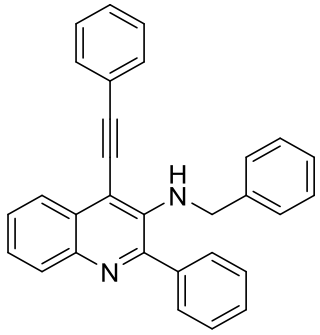


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and *p*-anisidine (0.069 g). From column chromatography (10% EtOAc – hexane) to give the title compound as bright orange crystals (0.08 g, 40%) m.p. 131 – 132 °C; HRMS found $[M+H]^+$ = 427.1800; $C_{30}H_{23}N_2O$ $[M+H]^+$ requires = 427.1812.

δ_H [$(CD_3)_2CO$] 8.21 – 8.17 (1H, m, 5-*H*), 7.90 – 7.86 (1H, m, 8-*H*), 7.67 – 7.64 (2H, m, Ph-*H*), 7.53 – 7.47 (2H, m, 7-*H*, 8-*H*), 7.27 – 7.19 (6H, m, Ph-*H*), 7.18 – 7.14 (2H, m, Ph-*H*), 6.92 (1H, s, N*H*), 6.76 – 6.72 (2H, m, *o*-Ar-*H*), 6.64 – 6.60 (2H, m, *m*-Ar-*H*), 3.55 (3H, s, O-*Me*). δ_c 155.34 ($_q$C), 154.65 ($_q$C), 144.01 ($_q$C), 139.23 ($_q$C), 137.52 ($_q$C), 136.72 ($_q$C), 131.65 (CH), 129.70 (CH), 129.03 (CH), 128.85 (CH), 128.56 (CH), 128.42 (CH), 128.16 (CH), 127.93 ($_q$C), 127.52 (CH), 127.44 (CH), 124.75 (CH), 122.64 ($_q$C), 119.27 (CH), 117.70 ($_q$C), 114.05 (CH), 105.29 ($_q$C), 83.87 ($_q$C), 54.94 (CH_3).

ν_{max}/cm^{-1}: 3393 m (NH), 3056 w (Ar-H), 2926 w (CH_3), 2200 m (C≡C), 1506 s (C=C), 1388 m (CH_3), 753 s (Ph-H), 687 s (Ph-H).

_N_-Benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine (4.36Ae)



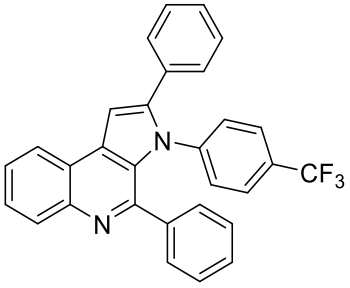
From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and benzylamine (60 µL). From column chromatography (toluene) to give the title compound as a dark orange oil (0.11 g, 60%); HRMS found $[M+H]^+$ = 411.1850; $C_{30}H_{23}N_2$ $[M+H]^+$ requires = 411.1863.

δ_H ($CDCl_3$) 8.24 – 8.22 (1H, m, 5-*H*), 8.04 – 8.02 (1H, m, 8-*H*), 7.75 – 7.72 (2H, m, Ph-*H*), 7.57 – 7.43 (8H, m, 6-*H*, 7-*H*, Ph-*H*), 7.38 – 7.35 (3H, m, Ph-*H*), 7.28 – 7.20* (4H, m, Ph-*H*), 4.72 (1H, app. s, N*H*), 4.48 (2H, d, *J* = 4.0 Hz, C*H*$_2$). δ_c 153.04 ($_q$C), 142.51 ($_q$C), 141.82 ($_q$C), 139.73 ($_q$C), 139.18 ($_q$C), 131.47 (CH), 129.64 (CH), 128.98 (CH), 128.95 (CH), 128.92 (CH), 128.69 (CH), 128.62 (CH), 128.55 (CH), 128.21 ($_q$C), 127.65 (CH), 127.40 (CH), 127.36 (CH), 126.59 (CH), 124.49 (CH), 122.76 ($_q$C), 111.89 ($_q$C), 102.73 ($_q$C), 84.08 ($_q$C), 51.54 (CH_2).

ν_{max}/cm^{-1}: 3057 w (Ar-H), 1509 w (C=C), 1491 w (CH_2), 753 s (Ph-H), 687 s (Ph-H).

*Overlapping with $CDCl_3$ signal

2,4-Diphenyl-3-[4-(trifluoromethyl)phenyl]-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Af)

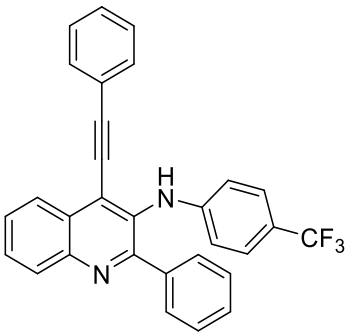


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and trifluoromethylaniline (70 µL). From column chromatography (20% toluene – hexane) to give the title compound as white needles (0.04 g, 20%) m.p. 250 °C; HRMS found $[M+H]^+$ = 465.1570; $C_{30}H_{20}F_3N_2$ $[M+H]^+$ requires = 465.1580

δ_H $[(CD_3)_2CO]$(600 MHz) 8.51 – 8.47 (1H, m, 9-*H*), 8.15 – 8.11 (1H, m, 6-*H*), 7.71 – 7.66 (2H, m, 7-*H*, 8-*H*), 7.58 (1H, s, 1-*H*), 7.34 – 7.30 (7H, m, Ph-*H*), 7.17 – 7.11 (5H, m, Ph-*H,* Ar-*H*), 7.05 – 7.01 (2H, m, Ar-*H*). δ_c (150 MHz) 148.00 ($_q$C), 143.40 ($_q$C), 142.62 ($_q$C), 141.75 – 141.74 (d, *J* = 1.4 Hz, $_q$C), 139.26 ($_q$C), 131.89 ($_q$C), 130.41 ($_q$C), 129.95 (CH), 129.80 (CH), 129.61 (CH), 129.46 ($_q$C) 129.04 (CH), 128.24 [2 X C (CH)], 127.12 [2 X C (CH)], 127.09 (CH), 126.71 – 121.32 (q, *J* = 271.78 Hz, $_q$C), 126.52 (CH), 126.00 (CH), 125.13 – 125.05 (q, *J* = 3.8 Hz, CH), 122.92 (CH), 122.66 ($_q$C), 102.99 (CH). ^{19}F $[(CD_3)_2CO]$(376 MHz) δ_F -63.14.

ν_{max}/cm^{-1}: 3057 w (Ar-H), 1597 w (C=C), 753 s (Ph-H), 687 s (Ph-H).

2-Phenyl-4-(phenylethynyl)-*N*-[4-(trifluoromethyl)phenyl]quinolin-3-amine (4.36Af)

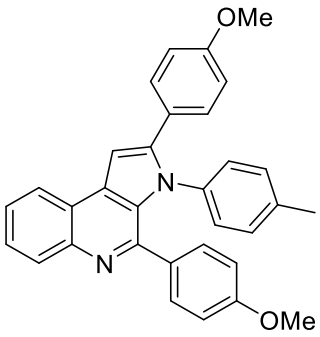


From 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.20 g) and trifluoromethylaniline (70 µL). From column chromatography (20% toluene – hexane) to give the title compound as a bright yellow solid (0.08 g, 35%) m.p. 184 – 185 °C; HRMS found $[M+H]^+$ = 465.1567; $C_{30}H_{20}F_3N_2$ $[M+H]^+$ requires = 465.1580

δ_H [$(CD_3)_2CO$](600 MHz) 8.41 (1H, dd, *J* = 8.2, 0.7 Hz, 5-*H*), 8.11 (1H, app. d, 8-*H*), 7.92 (1H, s, N*H*), 7.83 – 7.81 (2H, m, Ph-*H*), 7.80 – 7.77 (1H, m, 7-*H*), 7.73 – 7.71 (1H, m, 6-*H*), 7.50 (2H, d, *J* = 8.6 Hz, *m*-Ar-*H*), 7.43 – 7.40 (4H, m, Ph-*H*), 7.37 – 7.35 (2H, m, Ph-*H*), 7.24 – 7.23 (2H, m, Ph-*H*), 7.01 (2H, d, *J* = 8.6 Hz, *o*-Ar-*H*). δ_c (150 MHz) 157.00 ($_q$C), 148.31 – 148.29 (q, *J* = 1.0 Hz, $_q$C), 145.54 ($_q$C), 133.78 ($_q$C), 131.63 (CH), 129.83 (CH), 129.48 (CH), 129.06 [2 X C (CH)], 129.05 ($_q$C), 128.73 (CH), 128.51 (CH), 128.11 (CH), 127.88 – 122.52 (q, *J* = 269.72 Hz, $_q$C), 127.66 (CH), 127.45 ($_q$C), 126.16 – 126.08 (q, *J* = 3.8 Hz, CH), 125.36 (CH), 123.87 ($_q$C), 122.17 ($_q$C), 120.22 – 119.58 (q, *J* = 32.3 Hz, $_q$C), 114.99 (CH), 105.70 ($_q$C), 83.64 ($_q$C). ^{19}F [$(CD_3)_2CO$](376 MHz) δ_F -61.47.

ν_{max}/cm^{-1}: 3393 m (NH), 3052 w (Ar-H), 2207 m (C≡C), 1611 s (C=C), 1099 s (C-F), 755 s (Ph-H), 688 s (Ph-H).

2,4-Bis(4-methoxyphenyl)-3-(*p*-tolyl)-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Ca)



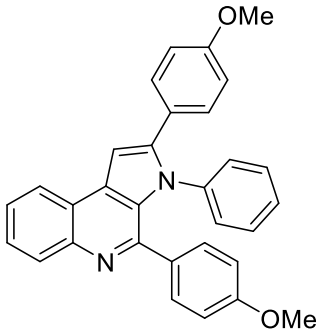
From 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (0.25 g) and *p*-toluidine (0.09 g). From column chromatography (10% EtOAc – pet ether) to give the title compound as off white powder (0.09 g, 40%) m.p. 238 – 239 °C; HRMS found $[M+H]^+$ = 471.2061; $C_{32}H_{27}N_2O_2$ $[M+H]^+$ requires = 471.2074.

δ_H ($CDCl_3$) 8.29 – 8.27 (1H, m, 9-*H*), 8.23 – 8.21 (1H, m, 6-*H*), 7.63 – 7.55 (2H, m, 7-*H*, 8-*H*), 7.25* (1H, s, 1-*H*), 7.13 – 7.10 (2H, m, Ar-*H*), 7.03 – 6.99 (2H, m, Ar-*H*), 6.75 – 6.72 (4H, m, Ar-*H*), 6.64 (2H, d, *J* = 8.3 Hz, Ar-*H*), 6.52 – 6.48 (2H, m, Ar-H), 3.75 (3H, s, O-*Me*), 3.72 (3H, s, O-*Me*), 2.23 (3H, s, Ar-*Me*). δ_c 159.27 ($_q$C), 158.95 ($_q$C), 148.22 ($_q$C), 143.48 ($_q$C), 142.32 ($_q$C), 136.97 ($_q$C), 135.68 ($_q$C), 131.65 ($_q$C), 130.91 (CH), 130.27 ($_q$C), 130.16 (CH), 129.54 [2 X C ($_q$C) (CH)], 128.77 (CH), 128.65 (CH), 126.40 (CH), 125.64 (CH), 124.62 ($_q$C), 122.65 (CH), 122.57 ($_q$C), 113.59 (CH), 112.80 (CH), 101.62 (CH), 55.33 (CH_3), 55.21 (CH_3), 21.02 (CH_3).

ν_{max}/cm^{-1}: 1607 s (C=C), 1485 s (CH_3).

*Overlapping with $CDCl_3$ signal

2,4-Bis(4-methoxyphenyl)-3-phenyl-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Cb)

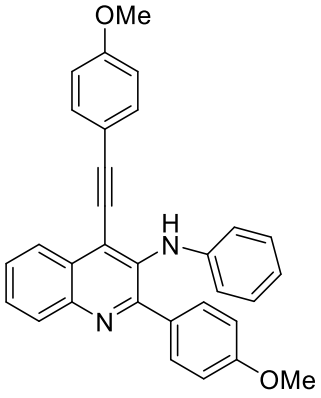


From 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (0.16 g) and aniline (33 µL). From column chromatography (10% EtOAc – pet ether) to give the title compound as a yellow solid (0.06 g, 37%) m.p. 186 – 187 °C; HRMS found $[M+H]^+$ = 457.1906; $C_{31}H_{25}N_2O_2$ $[M+H]^+$ requires = 457.1918.

δ_H ($CDCl_3$) 8.30 – 8.28 (1H, m, 9-*H*), 8.25 – 8.23 (1H, app. d, 6-*H*), 7.65 – 7.56 (2H, m, 7-*H*, 8-*H*), 7.27 (1H, s, 1-*H*), 7.11 – 7.03 (5H, m, Ar-*H*), 6.98 – 6.94 (2H, m, Ph-*H*), 6.78 (2H, app. d, Ph-*H*), 6.76 – 6.73 (2H, m, Ar-*H*), 6.53 – 6.49 (2H, m, Ar-*H*), 3.76 (3H, s, O-*Me*), 3.72 (3H, s, O-*Me*). δ_c 159.32 ($_q$C), 158.91 ($_q$C), 148.09 ($_q$C), 143.62 ($_q$C), 142.30 ($_q$C), 138.27 ($_q$C), 131.43 ($_q$C), 130.93 (CH), 130.45 ($_q$C), 130.16 (CH), 129.47 (CH), 129.29 ($_q$C), 129.08 (CH), 128.10 (CH), 127.19 (CH), 126.52 (CH), 125.72 (CH), 124.52 ($_q$C), 122.65 (CH), 122.51 ($_q$C), 113.59 (CH), 112.94 (CH), 101.87 (CH), 55.36 (CH_3), 55.22 (CH_3).

ν_{max}/cm^{-1}: 2933 w (Ar-H), 2834 w (CH_3), 1607 s (C=C), 1500 s (C=C), 1371 s (CH_3), 756 s (Ph-H), 699 s (Ph-H).

2-(4-Methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]-*N*-phenylquinolin-3-amine (4.36Cb)

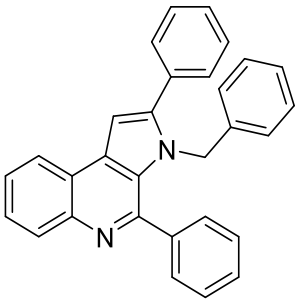


From 3-iodo-2-(4-methoxyphenyl)-4-[(4-methoxyphenyl)ethynyl]quinoline (0.16 g) and aniline (33 µL). From column chromatography (10% EtOAc – pet ether) to give the title compound as a brown solid (0.03 g, 20%) m.p. 135 – 136 °C; HRMS found $[M+H]^+$ = 457.1904; $C_{31}H_{25}N_2O_2$ $[M+H]^+$ requires = 457.1918.

δ_H ($CDCl_3$) 8.29 (1H, dd, *J* = 8.0, 1.0 Hz, 5-*H*), 8.11 (1H, dd, *J* = 8.0, 1.0 Hz, 8-*H*), 7.71 – 7.68 (2H, m, Ar-*H*), 7.66 – 7.56 (2H, m, 6-*H*, 7-*H*), 7.23 – 7.19 (2H, m, Ph-*H*), 7.06 – 7.03 (2H, m, Ar-*H*), 6.97 – 6.90 (3H, m, Ar-*H,* Ph-*H*), 6.86 (2H, app. d, Ph-*H*), 6.82 – 6.78 (2H, m, Ar-*H*), 6.04 (1H, s, N*H*), 3.83 (3H, s, O-*Me*), 3.81 (3H, s, O-*Me*). δ_c 160.26 ($_q$C), 160.21 ($_q$C), 155.03 ($_q$C), 144.45 ($_q$C), 143.26 ($_q$C), 134.69 ($_q$C), 133.32 (CH), 130.85 ($_q$C), 130.28 (CH), 129.58 (CH), 128.81 (CH), 128.05 (CH), 127.70 ($_q$C), 127.08 (CH), 125.20 (CH), 120.85 (CH), 120.12 ($_q$C), 117.37 (CH), 114.53 ($_q$C), 114.22 (CH), 113.95 (CH), 106.66 ($_q$C), 84.00 ($_q$C), 55.37 (CH_3), 55.33 (CH_3).

ν_{max}/cm^{-1}: 3390 s (NH), 2927 w (Ar-H), 2837 w (CH_3), 2200 s (C≡C), 1601 s (C=C), 1510 s (C=C), 751 m (Ph-H), 693 m (Ph-H).

<u>Synthesis of 3-Benzyl-2,4-diphenyl-3*H*-pyrrolo[2,3-*c*]quinoline (4.35Ae)</u>



Under an inert (N_2) atmosphere *N*-benzyl-2-phenyl-4-(phenylethynyl)quinolin-3-amine (0.10 g, 0.002 mmol, 1.0 equiv.) and $PdCl_2$ (10 mol %) in 5 mL of anhydrous DMF was stirred at 160 °C for 2 h. After this time the mixture was allowed to cool to r.t. and the solvent removed, the residue was purified by flash column chromatography (10% – pet ether) to give the title compound as a yellow oil (0.06 g, 60%); HRMS found $[M+H]^+$ = 411.1854; $C_{30}H_{23}N_2$ $[M+H]^+$ requires = 411.1863.

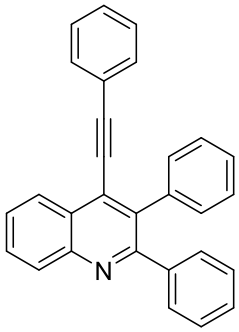
δ_H ($CDCl_3$) 8.29 – 8.27 (1H, m, 9-*H*), 8.23 – 8.21 (1H, m, 6-*H*), 7.64 – 7.57 (2H, m, 7-*H*, 8-*H*), 7.51 – 7.48 (2H, m, Ph-*H*), 7.43 – 7.37 (4H, m, Ph-*H*), 7.34 – 7.28 (4H, m, Ph-*H*), 7.26 (1H, s, 1-*H*), 7.04 – 7.00 (1H, m, Ar-*H*), 6.96 – 6.92 (2H, m, Ar-*H*), 6.11 (2H, app. d, Ar-*H*), 5.15 (2H, s, C*H*$_2$). δ_c 148.65 ($_q$C), 145.75 ($_q$C), 142.23 ($_q$C), 139.62 ($_q$C), 138.35 ($_q$C), 132.14 ($_q$C), 131.05 ($_q$C), 129.75 (CH), 129.51 (CH), 129.11 (CH), 128.91 ($_q$C), 128.78 (CH), 128.68 (CH), 128.38 (CH), 128.12 (CH), 127.96 (CH), 126.85 (CH), 126.60 (CH), 125.91 (CH), 125.13 (CH), 122.71 ($_q$C), 122.65 (CH), 102.45 (CH), 49.46 (CH_2).

ν_{max}/cm^{-1}: 3055 w (Ar-H), 2924 w (CH_2), 1566 w (C=C), 1478 s (CH_2), 769 s (Ph-H), 696 s (Ph-H).

General Method for the Suzuki-Miyaura Couplings of 3-Iodo-2-phenyl-4-(phenylethynyl)quinoline

To a mixture of degassed EtOH : PhMe (50 : 50) was added 3-iodo-2-phenyl-4-(phenylethynyl)quinoline (0.50 g, 1.16 mmol, 1.0 equiv.), the appropriate boronic acid (2.3 equiv.), potassium carbonate (0.38 g, 2.78 mmol, 2.4 equiv.) and $Pd(PPh_3)_4$ (2.5 mol %). The solution was stirred under N_2 at reflux for 22 h. After this time the mixture was cooled, diluted with EtOAc, washed with water and brine. The organic phase was separated, dried (Na_2SO_4) and evaporated. The crude material was purified by flash column chromatography (8% EtOAc – hexane) the following were synthesised by this method.

2,3-Diphenyl-4-(phenylethynyl)quinoline (4.41a)



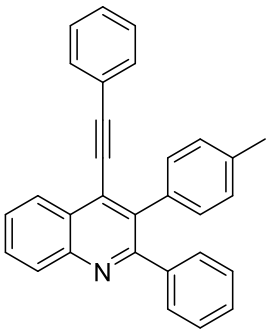
From phenylboronic acid (0.32 g, 2.67 mmol) to give the title compound as a yellow powder (0.30 g, 68%) m.p. 148 – 149 °C; HRMS found $[M+H]^+$ = 382.1590; $C_{29}H_{17}N$ $[M+H]^+$ requires = 382.1597.

δ_H ($CDCl_3$) 8.44 (1H, dd, *J* = 8.3, 0.8 Hz, 5-*H*), 8.22 (1H, app. d, 8-*H*), 7.76 – 7.72 (1H, m, 7-*H*), 7.65 – 7.61 (1H, m, 6-*H*), 7.43 – 7.39 (2H, m, Ph-*H*), 7.34 – 7.29* (10H, m, Ph-*H*), 7.24 – 7.20 (3H, m, Ph-*H*). δ_c 158.59 ($_q$C), 147.09 ($_q$C), 140.62 ($_q$C), 138.63 ($_q$C), 136.21 ($_q$C), 131.86 (CH), 131.08 (CH), 130.03 [2 X C (CH)], 129.96 (CH), 129.67 ($_q$C), 129.17 (CH), 128.46 (CH), 127.95 (CH), 127.84 (CH), 127.77 (CH), 127.45 (CH), 127.36 (CH), 126.62 ($_q$C), 126.31 (CH), 122.57 ($_q$C), 101.99 ($_q$C), 85.61 ($_q$C).

ν_{max}/cm^{-1}: 3055 w (Ar-H), 2208 w (C≡C), 1596 s (C=C), 755 s (Ph-H), 689 s (Ph-H).

*Overlapping with $CDCl_3$ signal

2-Phenyl-4-(phenylethynyl)-3-(*p*-tolyl)quinoline (4.41b)

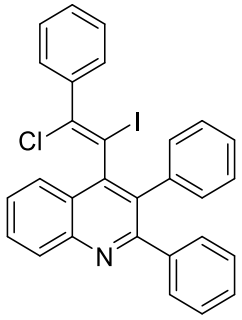


From *p*-tolylboronic acid (0.36 g, 2.67 mmol) to give the title compound as a white powder (0.32 g, 70%) m.p. 174 – 175 °C; HRMS found $[M+H]^+$ = 382.1590; $C_{29}H_{17}N$ $[M+H]^+$ requires = 382.1597.

δ_H [$(CD_3)_2CO$] 8.51 (1H, dd, *J* = 8.3, 0.9 Hz, 5-*H*), 8.14 (1H, app. d, 8-*H*), 7.87 – 7.83 (1H, m, 7-*H*), 7.77 – 7.73 (1H, m, 6-*H*), 7.47 – 7.39 (7H, m, Ar-*H*), 7.31 – 7.20 (7H, m, Ar-*H*), 2.36 (3H, s, Ar-*Me*). δ_c 158.43 ($_q$C), 147.00 ($_q$C), 140.96 ($_q$C), 137.09 ($_q$C), 136.17 ($_q$C), 135.75 ($_q$C), 131.67 (CH), 130.87 (CH), 130.04 (CH), 129.92 (CH), 129.85 (CH), 129.40 (CH), 129.06 ($_q$C), 128.66 (CH), 128.39 (CH), 127.72 (CH), 127.56 (CH), 127.44 (CH), 126.28 ($_q$C), 126.07 (CH), 122.36 ($_q$C), 101.57 ($_q$C), 85.24 ($_q$C), 20.42 (CH_3).

ν_{max}/cm^{-1}: 3055 w (Ar-H), 2980 w (CH_3), 2208 m (C≡C), 761 s (Ph-H), 695 s (Ph-H).

(*E*)-4-(1-Chloro-2-iodo-2-phenylvinyl)-2,3-diphenylquinoline (4.42a)



To a solution of 2,3-diphenyl-4-(phenylethynyl)quinoline (0.20 g, 0.55 mmol, 1 equiv.) in MeCN (15 mL) was added iodine monochloride (78 µL, 1.65 mmol, 3 equiv.) and the mixture stirred at reflux for 16 h. After this time the reaction mixture was quenched with aqueous sodium thiosulfate and diluted with EtOAc. The organic phase was separated, dried (Na_2SO_4) and evaporated to give a powder which was washed with pentane to give the title compound as an orange powder (0.26 g, 92%) m.p. 180 °C decomp; HRMS found $[M+H]^+$ = 544.0314; $C_{29}H_{17}{}^{35}ClIN$ $[M+H]^+$ requires =544.0331.

δ_H (CD_2Cl_2) (600 MHz) 8.29 (1H, app. d, 8-*H*), 8.13 (1H, app. d, 5-*H*), 7.87 (1H, app. t, 7-*H*), 7.78 (1H, app. t, 6-*H*), 7.63 (2H, d, *J* = 7.2 Hz, Ph-*H*), 7.49 – 7.39 (7H, m, Ph-*H*), 7.35 – 7.26 (7H, m, Ph-*H*). δ_c (150 MHz) 159.33 ($_q$C), 147.75 ($_q$C), 146.08 ($_q$C), 140.55 ($_q$C), 140.27 ($_q$C), 137.76 ($_q$C), 133.95 ($_q$C), 131.43 ($_q$C), 130.30 (CH), 130.08 (CH), 130.02 (CH), 129.74 (CH), 129.51 (CH), 128.74 (CH), 128.50 (CH), 127.86 (CH), 127.83 (CH), 127.75 (CH), 127.72 (CH), 127.54 (CH), 127.36 (CH), 125.01 (CH), 122.55 ($_q$C), 88.91 ($_q$C).

ν_{max}/cm^{-1}: 1483 w (C=C), 756 s (Ph-H), 693 s (Ph-H).

Chapter 7

References

Chapter 7 References

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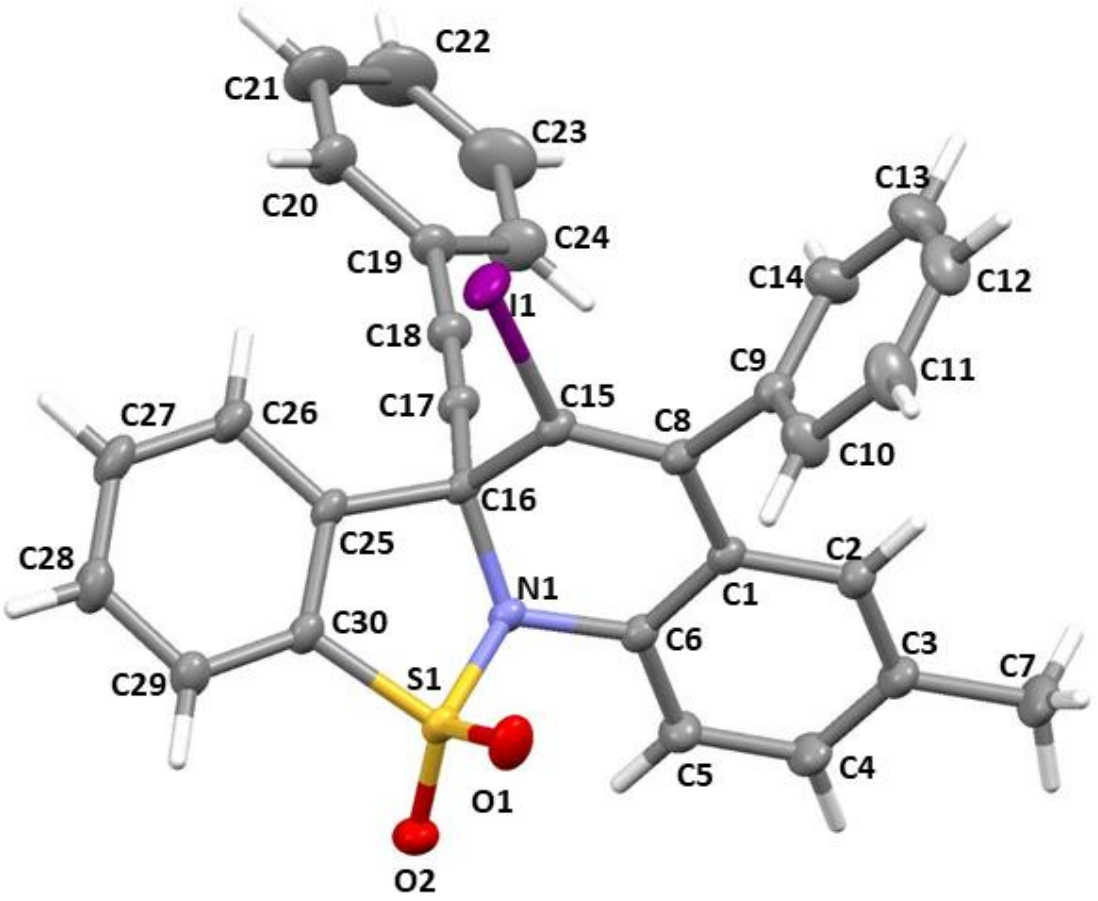
Chapter 8

Appendices

Chapter 8 Appendices

8.1 Appendices 1.0

Crystal structure information for: 6-Iodo-2-methyl-5-phenyl-6*a*-(phenylethynyl)-6*aH*-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide



Compound Reference	**2.66a-3**
Chemical Formula	C31.50 H23 I N O2.50 S (C30 H20 I N O2 S)
Formula Mass	614.47
Crystal System	Triclinic
***a*/Å**	10.4397(15)
***b*/Å**	11.991(2)
***c*/Å**	24.653(4)
***α*/°**	79.896(9)
***β*/°**	78.764(7)
***γ*/°**	64.301(7)
Unit cell volume/Å^3	2713.0(8)
Temperature/K	150 (2)
Space group	P -1
No. of formula units per unit cell, *Z*	4
No. of reflections measured	70093
No. of independent reflections	26168
R_{int}	0.0391
Final R_1 values ($I>2\sigma(I)$)	0.0422
Final $wR(F^2)$ values ($I>2\sigma(I)$)	0.1001
Final R_1 values (all data)	0.0614
Final $wR(F^2)$ values (all data)	0.1135
Goodness of fit on F^2	1.037

Table 8.1 Crystal data for 6-Iodo-2-methyl-5-phenyl-6*a*-(phenylethynyl)-6*aH*-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide **2.66-3**

Bond	Length (Å)
I1-C15	2.0890(16)
S1-O2	1.4279(18)
S1-O1	1.4361(17)
S1-N1	1.6794(13)
S1-C30	1.743(2)
N1-C6	1.430(2)
N1-C16	1.485(2)
C1-C2	1.403(2)
C1-C6	1.404(2)
C1-C8	1.476(2)
C2-C3	1.399(2)
C2-H2	0.9500
C3-C4	1.396(2)
C3-C7	1.511(3)
C4-C5	1.391(3)
C4-H4	0.9500
C5-C6	1.388(2)
C5-H5	0.9500
C7-H7A	0.9800
C7-H7B	0.9800

Bond	Length (Å)
C7-H7C	0.9800
C8-C15	1.351(2)
C8-C9	1.489(2)
C9-C14	1.391(2)
C9-C10	1.398(2)
C10-C11	1.394(2)
C10-H10	0.9500
C11-C12	1.384(3)
C11-H11	0.9500
C12-C13	1.390(3)
C12-H12	0.9500
C13-C14	1.392(3)
C13-H13	0.9500
C14-H14	0.9500
C15-C16	1.531(2)
C16-C17	1.470(2)
C16-C25	1.532(2)
C17-C18	1.200(2)
C18-C19	1.436(2)
C19-C24	1.397(3)

Bond	Length (Å)
C19-C20	1.397(3)
C20-C21	1.387(3)
C20-H20	0.9500
C21-C22	1.384(4)
C21-H21	0.9500
C22-C23	1.381(4)
C22-H22	0.9500
C23-C24	1.385(3)
C23-H23	0.9500
C24-H24	0.9500
C25-C30	1.379(2)
C25-C26	1.390(3)
C26-C27	1.395(3)
C26-H26	0.9500
C27-C28	1.389(4)
C27-H27	0.9500
C28-C29	1.383(4)
C28-H28	0.9500
C29-C30	1.395(3)
C29-H29	0.9500

Atom 1	Atom 2	Atom 3	Angle (°)
N1	S1	O1	112.26
N1	S1	O2	109.43
N1	S1	C30	92.040
O1	S1	O2	117.21
O1	S1	C30	110.03
O2	S1	C30	113.13
S1	N1	C6	115.73
S1	N1	C16	110.97
C6	N1	C16	117.14
C2	C1	C6	118.01
C2	C1	C8	123.10
C6	C1	C8	118.79
C1	C2	H2	119.27
C1	C2	C3	121.46
H2	C2	C3	119.27
C2	C3	C4	118.69
C2	C3	C7	121.11
C4	C3	C7	120.19

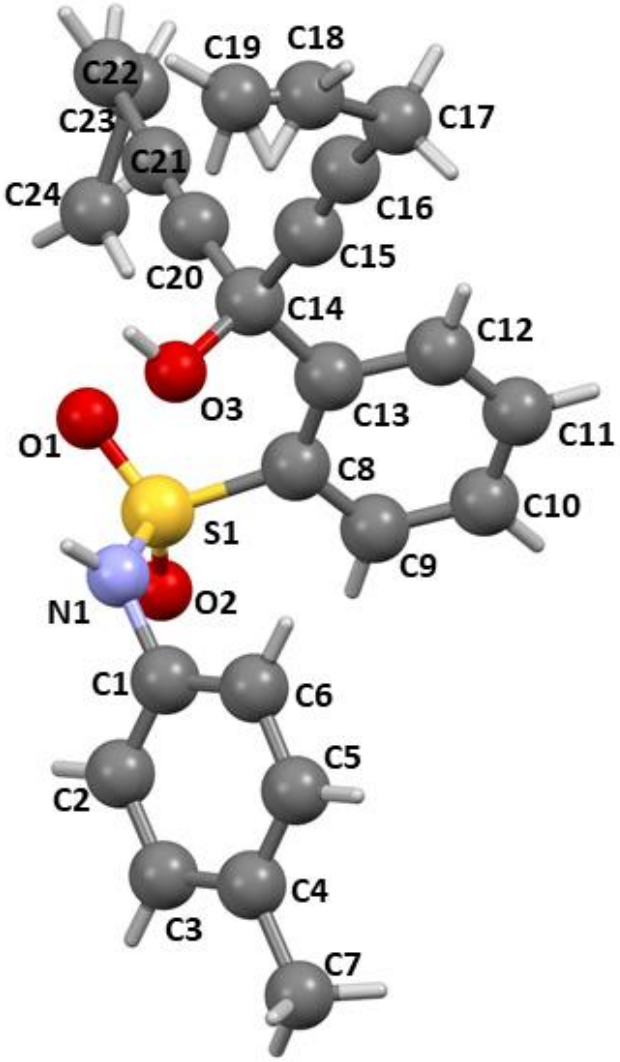
Atom 1	Atom 2	Atom 3	Angle (°)
C9	C14	C13	120.38
C9	C14	H14	119.81
C13	C14	H14	119.81
I1	C15	C8	121.92
I1	C15	C16	117.70
C8	C15	C16	120.37
N1	C16	C15	109.37
N1	C16	C17	110.68
N1	C16	C25	102.90
C15	C16	C17	109.48
C15	C16	C25	115.32
C17	C16	C25	108.93
C16	C17	C18	170.78
C17	C18	C19	177.12
C18	C19	C20	121.32
C18	C19	C24	118.88
C20	C19	C24	119.78
C19	C20	H20	120.13

C3	C4	H4	119.50
C3	C4	C5	120.99
H4	C4	C5	119.50
C4	C5	H5	120.25
C4	C5	C6	119.49
H5	C5	C6	120.25
N1	C6	C1	119.25
N1	C6	C5	119.44
C1	C6	C5	121.27
C3	C7	H7A	109.47
C3	C7	H7B	109.47
C3	C7	H7C	109.47
H7A	C7	H7B	109.47
H7A	C7	H7C	109.47
H7B	C7	H7C	109.47
C1	C8	C9	118.72
C1	C8	C15	119.77
C9	C8	C15	121.41
C8	C9	C10	120.97
C8	C9	C14	119.46
C10	C9	C14	119.55
C9	C10	H10	120.08
C9	C10	C11	119.84
H10	C10	C11	120.08
C10	C11	H11	119.90
C10	C11	C12	120.20
H11	C11	C12	119.90
C11	C12	H12	119.90
C11	C12	C13	120.21
H12	C12	C13	119.90
C12	C13	H13	120.09
C12	C13	C14	119.81
H13	C13	C14	120.09

C19	C20	C21	119.75
H20	C20	C21	120.13
C20	C21	H21	119.92
C20	C21	C22	120.16
H21	C21	C22	119.92
C21	C22	H22	119.89
C21	C22	C23	120.22
H22	C22	C23	119.89
C22	C23	H23	119.77
C22	C23	C24	120.46
H23	C23	C24	119.77
C19	C24	C23	119.61
C19	C24	H24	120.20
C23	C24	H24	120.19
C16	C25	C26	126.73
C16	C25	C30	113.83
C26	C25	C30	119.25
C25	C26	H26	120.87
C25	C26	C27	118.27
H26	C26	C27	120.87
C26	C27	H27	119.21
C26	C27	C28	121.58
H27	C27	C28	119.21
C27	C28	H28	119.69
C27	C28	C29	120.62
H28	C28	C29	119.69
C28	C29	H29	121.50
C28	C29	C30	116.99
H29	C29	C30	121.50
S1	C30	C25	110.14
S1	C30	C29	126.56
C25	C30	C29	123.27

Table 8.2 Bond lengths and angles for 6-Iodo-2-methyl-5-phenyl-6*a*-(phenylethynyl)-6*aH*-1,2-benzisothiazolo[2,3-*a*]quinoline 11,11-dioxide **2.66-3**

Crystal structure information for: 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide



Compound Reference	**2.23Bb**
Chemical Formula	C24 H25 N O3 S (C24 H27 N O3 S)
Formula Mass	407.54
Crystal System	Monoclinic
***a*/Å**	9.5567(3)
***b*/Å**	9.5472(3)
***c*/Å**	24.0477(6)
***α*/°**	90
***β*/°**	93.6090(10)
***γ*/°**	90
Unit cell volume/Å^3	2189.75(11)
Temperature/K	150.0
Space group	P 1 21/c 1
No. of formula units per unit cell, *Z*	4
No. of reflections measured	23670
***R*$_{int}$**	0.0433
Final *R*$_1$ values (*I*>2*σ*(*I*))	0.0642
Final *wR*(*F*^{2}) values (*I*>2*σ*(*I*))	0.1589
Final *R*$_1$ values (all data)	0.1047
Final *wR*(*F*^{2}) values (all data)	0.1856
Goodness of fit on *F*^{2}	1.0839

Table 8.3 Crystal data for 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide **2.23Bb**

Bond	Length (Å)
S1-N1	1.6311(17)
S1-O1	1.4345(13)
S1-O2	1.4323(13)
S1-C8	1.788(2)
N1-H1	0.8800
N1-C1	1.434(2)
O3-H3	0.8400
O3-C14	1.434(2)
C1-C2	1.385(3)
C1-C6	1.378(3)
C2-H2	0.9500
C2-C3	1.384(3)
C3-H3a	0.9500
C3-C4	1.379(4)

Bond	Length (Å)
C7-H7a	0.9800
C7-H7b	0.9800
C7-H7c	0.9800
C8-C9	1.399(2)
C8-C13	1.413(2)
C9-H9	0.9500
C9-C10	1.375(3)
C10-H10	0.9500
C10-C11	1.385(3)
C11-H11	0.9500
C11-C12	1.390(3)
C12-H12	0.9500
C12-C13	1.387(3)
C13-C14	1.544(2)

Bond	Length (Å)
C22-C23	1.532(6)
C22-C21	1.480(4)
C22-H22a	0.9900
C22-H22b	0.9900
C23-C24	1.517(5)
C23-H23a	0.9900
C23-H23b	0.9900
C24-H24a	0.9800
C24-H24b	0.9800
C24-H24c	0.9800
C18-C19	1.551(14)
C18-C17	1.332(15)
C18-H18	0.9500
C19-H19a	0.9800

C4-C5	1.377(3)
C4-C7	1.507(3)
C5-H5	0.9500
C5-C6	1.386(3)
C6-H6	0.9500

C14-C15	1.485(2)
C14-C20	1.479(2)
C15-C16	1.188(3)
C16-C17	1.472(13)
C20-C21	1.185(3)

C19-H19b	0.9800
C19-H19c	0.9800
C17-H17	0.9500

Atom 1	Atom 2	Atom 3	Angle (°)
N1	S1	O1	107.30
N1	S1	O2	106.35
N1	S1	C8	108.13
O1	S1	O2	118.73
O1	S1	C8	106.49
O2	S1	C8	109.44
S1	N1	H1	120.13
S1	N1	C1	119.75
H1	N1	C1	120.13
H3	O3	C14	109.47
N1	C1	C2	121.17
N1	C1	C6	119.41
C2	C1	C6	119.41
C1	C2	H2	120.39
C1	C2	C3	119.21
H2	C2	C3	120.40
C2	C3	H3a	118.99
C2	C3	C4	122.04
H3a	C3	C4	118.97
C3	C4	C5	117.97
C3	C4	C7	120.84
C5	C4	C7	121.19
C4	C5	H5	119.51
C4	C5	C6	120.96
H5	C5	C6	119.52
C1	C6	C5	120.41
C1	C6	H6	119.79
C5	C6	H6	119.81
C4	C7	H7a	109.48
C4	C7	H7b	109.48
C4	C7	H7c	109.47
H7a	C7	H7b	109.47
H7a	C7	H7c	109.46

Atom 1	Atom 2	Atom 3	Angle (°)
C11	C12	H12	118.87
C11	C12	C13	122.25
H12	C12	C13	118.88
C8	C13	C12	117.65
C8	C13	C14	124.53
C12	C13	C14	117.77
O3	C14	C13	106.58
O3	C14	C15	113.25
O3	C14	C20	108.98
C13	C14	C15	109.17
C13	C14	C20	112.03
C15	C14	C20	106.93
C14	C15	C16	175.32
C15	C16	C17	174.53
C14	C20	C21	172.90
H22a	C22	H22b	107.91
H22a	C22	C23	109.22
H22a	C22	H22c	58.660
H22a	C22	C21	109.21
H22b	C22	C23	109.22
H22b	C22	H22c	51.270
H22b	C22	C21	109.20
C23	C22	H22c	111.34
C23	C22	C21	111.98
H22c	C22	C21	136.50
C22	C23	H23a	108.86
C22	C23	H23b	108.86
H23a	C23	H23b	107.72
H24a	C24	H24b	109.47
H24a	C24	H24c	109.47
H24a	C24	H23c	143.19
H24b	C24	H24c	109.47
H24b	C24	H23c	47.810

H7b	C7	H7c	109.47
S1	C8	C9	114.46
S1	C8	C13	126.12
C9	C8	C13	119.42
C8	C9	H9	119.14
C8	C9	C10	121.70
H9	C9	C10	119.15
C9	C10	H10	120.41
C9	C10	C11	119.18
H10	C10	C11	120.41
C10	C11	H11	120.14
C10	C11	C12	119.73
H11	C11	C12	120.13

H24c	C24	H23c	66.050
H18	C18	C19	122.69
H18	C18	C17	122.69
C19	C18	C17	114.63
C18	C19	H19a	109.48
C18	C19	H19b	109.47
C18	C19	H19c	109.48
H19a	C19	H19b	109.46
H19a	C19	H19c	109.47
H19b	C19	H19c	109.46
C16	C17	C18	120.55
C16	C17	H17	119.72
C18	C17	H17	119.72
C20	C21	C22	170.32

Table 8.4 Bond lengths angles for 2-(6-Hydroxyundeca-4,7-diyn-6-yl)-*N*-(*p*-tolyl)benzenesulfonamide **2.23Bb**