Applications of azides in heterocyclic synthesis, macrocyclic synthesis and multicomponent reactions.

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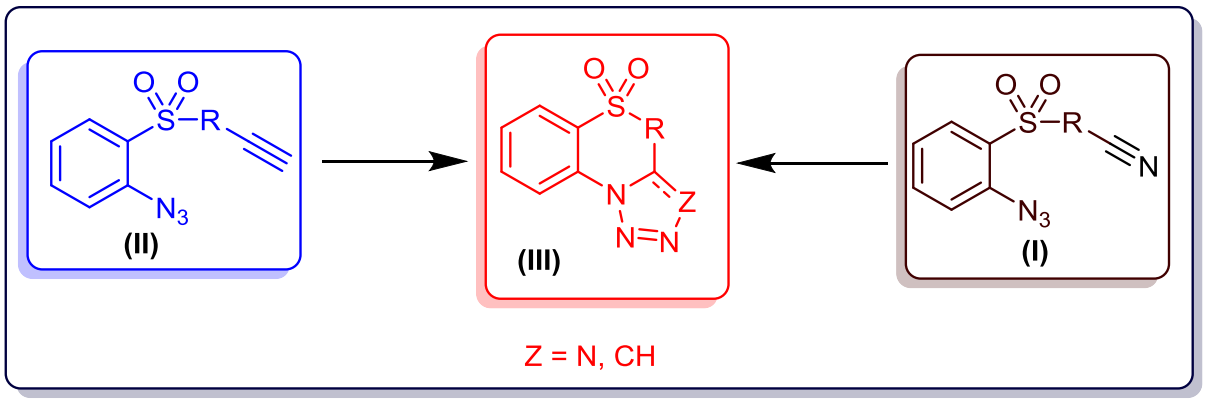
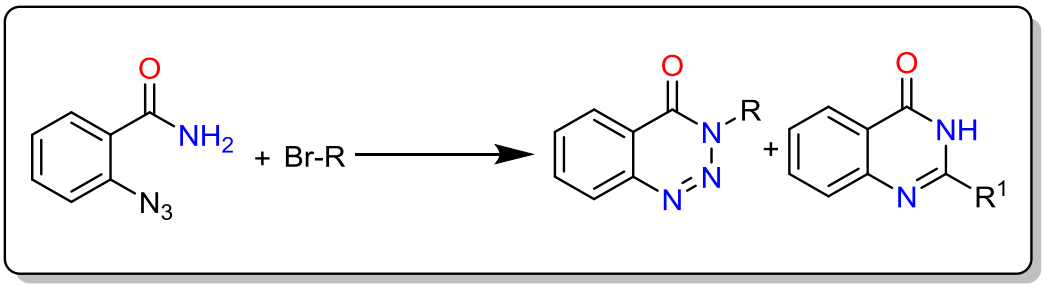
II. Abstract:

In this thesis (chapter 2), some multi-component reactions (MCRs) of aryl aldehydes incorporating the azide functional group were investigated to produce heterocyclic and other MCR products in order to investigate post-MCR azide cycloadditions. Although the MCRs were often successful, post-MCR reactions did not occur and, occasionally, cycloaddition occurred before the MCR.

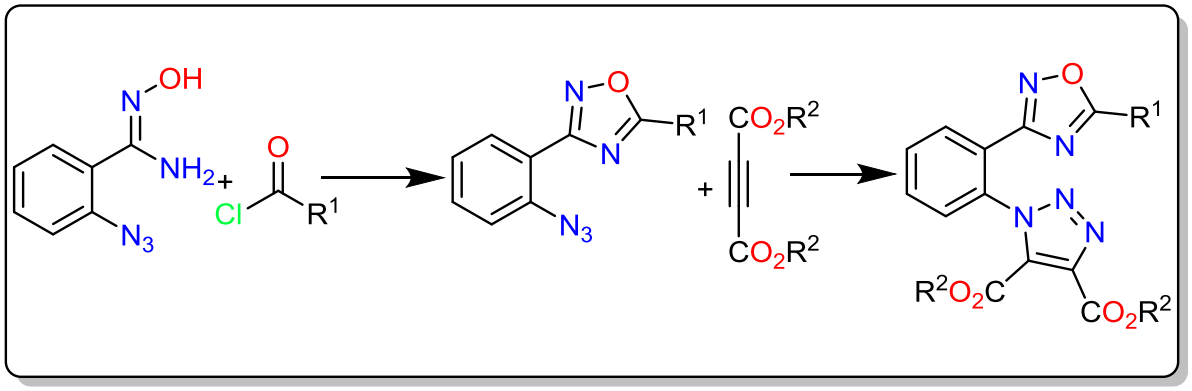
In chapter 3, the synthesis of novel tetra- and triazolo-analogues of the pyrrolobenzothiadiazepines and benzothiadiazepines are described. These compounds are of great interest as synthetic targets due to their potential medicinal properties. The key processes are the intramolecular 1,3-dipolar cycloaddition between the azide and the nitrile present in precursors (I), or the azide and the alkyne present in precursors (II) to form the novel final compounds of type (III), as shown below. The synthesis of these precursors from readily available starting materials is discussed.



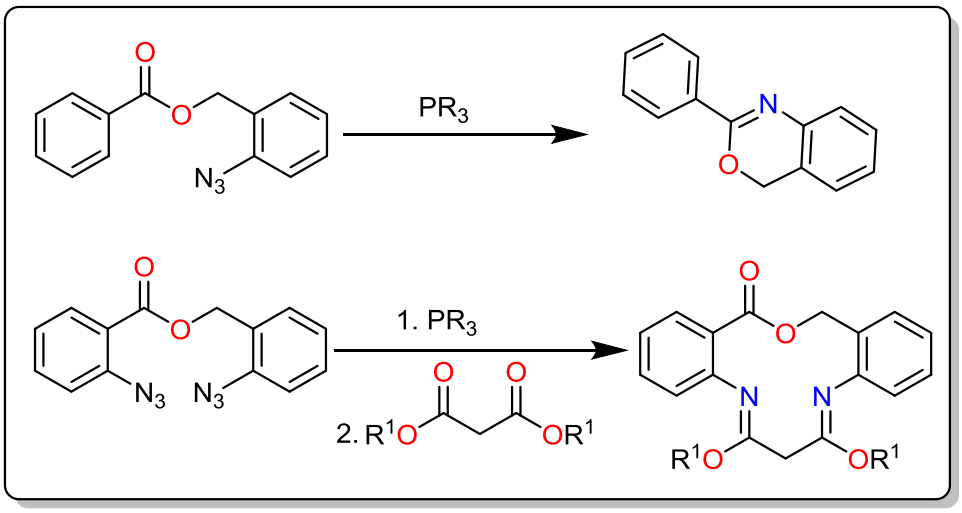
In chapter 4 of this thesis, some azide chemistry of 2-azido aryl compounds is investigated. In chapter 4.1, it was found that attempted *N*-alkylation of 2-azidobenzamide with alkyl halides gave mixtures of benzotriazinones and quinazolinones, as shown below:



In chapter 4.2 of this thesis other functionalised 2-azido aryl compounds were studied in order to produce 1,2,4-oxadiazoles as a potential new ligand system in supramolecular chemistry. For example, 1,2,4-oxadiazoles were synthesised when an amidoxime reacted with an acid chloride and then reaction of the azide moiety with an alkyne furnished 1,2,3-triazoles:



In chapter 4.3 of this thesis, some simple heterocycles and some macrocycles were synthesised by aza-Wittig reaction and Staudinger reaction of a further series of 2-azido aryl compounds, for example:



In the final chapter of this thesis, the attempted synthesis of sulfur analogues of the circumdatins and fuligocandins was attempted. These two pyrrolobenzodiazepine natural products and their analogues have interesting biological activities.

III. Abbreviations:

RT	Room temperature	**m/z**	Mass-to-charge ratio
$(COC)_2$	Oxalyl chloride	**MCRs**	Multicomponent reaction
^{13}C NMR	Carbon nuclear magnetic resonance	**Me**	Methyl
^{1}H NMR	Proton nuclear magnetic resonance	**MeCN**	Acetonitrile
Ar	Aromatic	**MeOH**	Methanol
Bu	Butyl	**mg**	Milligram
Bu_3P	Tributylphosphine	**$MgSO_4$**	Magnesium
$CDCl_3$	Deuterated chloroform	**mol**	Mole(s)
CH_2Cl_2 or DCM	Dichloromethane	**Na_2CO_3**	Sodium carbonate
$CHCl_3$	Chloroform	**NaH**	Sodium hydride
d	Doublet	**$NaHCO_3$**	Sodium bicarbonate
D	Deuterium	**NaN_3**	Sodium azide
DABCO	Diazabicyclo[2.2.2]octane	**NCS**	*N*-Chlorosuccinimide
DCC	Dicyclohexylcarbodiimide	**^{o}C**	Degree Celsius
dd	Doublet of doublets	**$P(OMe)_3$**	Trimethyl phosphite
DIBAC	Dibenzoazocyclooctyne	**PBD**	Pyrrolobenzodiazepine
DIBAL-H	Diisobutylaluminium hydride	**PBTDs**	Pyrrolobenzothiadiazepine
DMAC	Dimethylacetamide	**PCC**	Pyridinium chlorochromate
DMAP	Dimethylaminopyridine	**Ph**	Phenyl

DMF	*N*,*N*'-Dimethylformamide	**PIDA**	Phenyliodine diacetate
DMSO	Dimethylsulfoxide	**$POCl_3$**	Trichlorophosphate
DNA	Deoxyribonucleic acid	**PPh_3**	Triphenylphosphine
dt	Doublet of triplets	**PPm**	Parts per million
EDC	*N*-Ethyl-*N*′-(3-dimethylaminopro-pyl) carbodiimide	**q**	Quatet
eq.	Equivalents	**Ref.**	Reflux
Et	Ethyl	**Rf.**	Retention
Et_3N	Triethylamine	**S**	Singlet
EtOAc	Ethyl acetate	**$SOCl_2$**	Thionyl chloride
g	Grams	**t**	Triplet
HCl	Hydrochloric acid	**TBAHS**	Tetrabutylammonium hydrogen sulfate.
Hz	Hertz	**THF**	Tetrahydrofuran
IMCRs	Isocyanide-based multicomponent reactions	**TLC**	Thin layes chromatography
IR	Infrared	**TPP**	Thiamine pyrophosphate
M	Molarity	**TsOH**	p-Toluenesulfonic acid
J	Coupling constant	**υ**	Wavenumber = frequency
L	Litre	**δ**	Chemical shift (in ppm)
M	Molarity	**σ**	Sigma
m	Multiplet		

1. Introduction

1.1. Multicomponent reactions (MCRs).

1.1.1. General aspects of multicomponent reactions (MCRs).

The ideal synthesis should lead to the desired product in as few steps as possible[1,2] (Figure 1.1), in good overall yield and by using environmentally acceptable reagents. The variables that have to be optimized are overall yield, cost, time, environmental acceptability, simplicity of performance and safety. Purification and isolation steps such as extraction, distillation, crystallization or chromatography must also be considered.

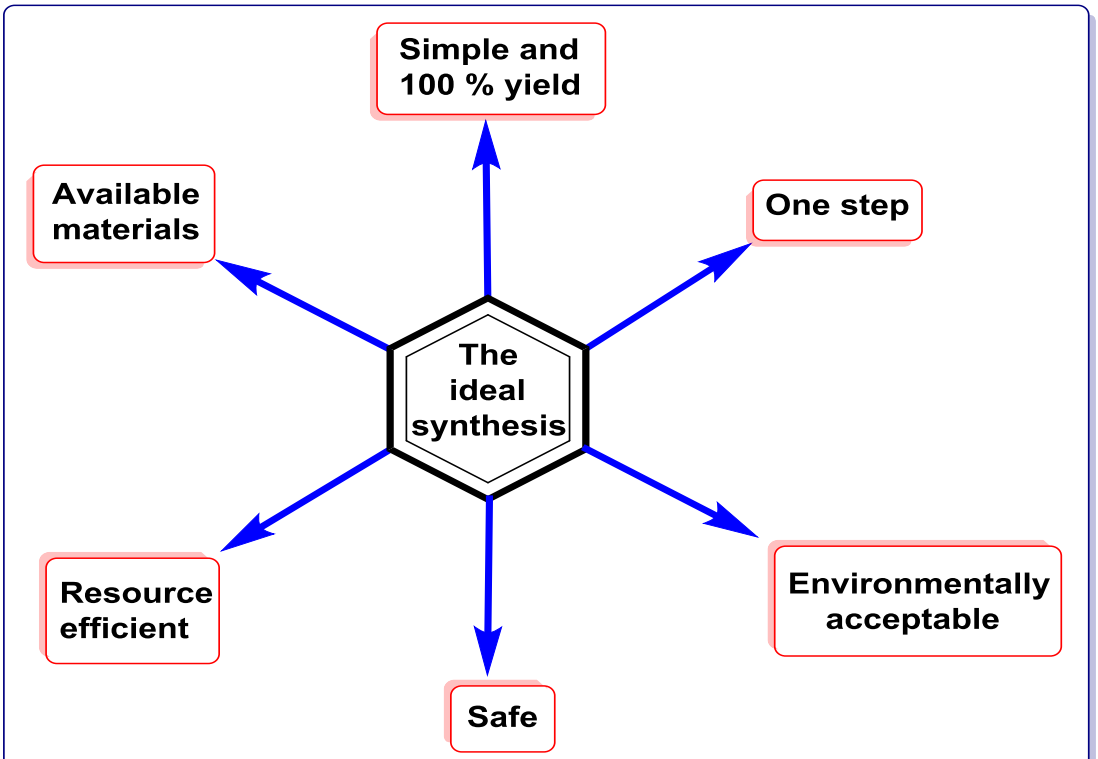


Figure 1.1: The ideal chemical synthesis

A good and efficient way of gaining the product is a one pot reaction of three or more starting compounds, i.e. by using multicomponent reactions (MCRs). Multicomponent reactions (MCRs) are one of the most valuable tools in making chemical structures. MCRs are methods in which three or more starting materials are converted in one chemical step to form a specific product[3] .

Mechanistic study for a number of MCRs has shown three different types as shown in Figure 1.2. Type (1) MCRs are combinations of equilibria between all participating starting materials, including the last step that forms the desired product. Type (2) MCRs are collections of equilibria where just the final step which is irreversible and drives the process towards the desired product. MCRs of type (3) create of a sequence of irreversible starting materials that all proceed towards the main product.

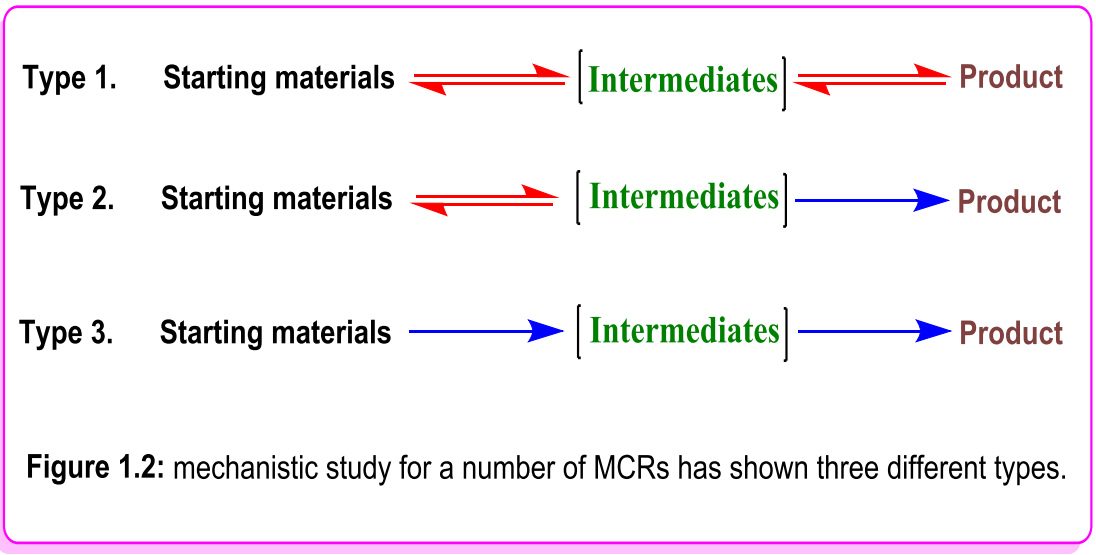


Figure 1.2: mechanistic study for a number of MCRs has shown three different types.

The result of an MCR is dependent on the nature of the starting materials in addition to the reaction conditions[4]. For an MCR to be efficient and feasible, the compatibility of all the possible pairs of reagents must be looked at during the planning stages.[5] Having in mind this general principle, it is obvious that this task increases when the number of reagents increases, as there will be more combinations. MCRs have emerged as a useful tool for the formation of chemical libraries of drug-like compounds with high levels of molecular complexity and diversity in drug discovery programs.

1.1.2. The history of multicomponent reactions (MCRs).

The historical development of multicomponent reactions is outlined in Figure 1.3, and will be discussed below.

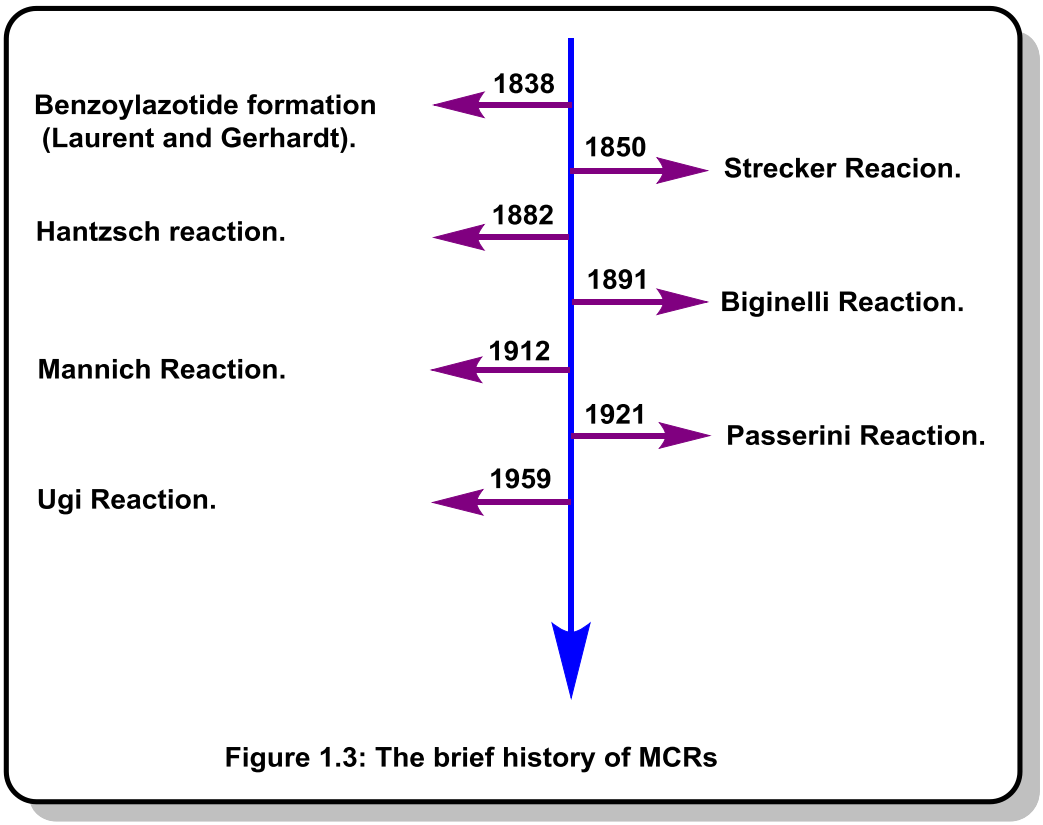
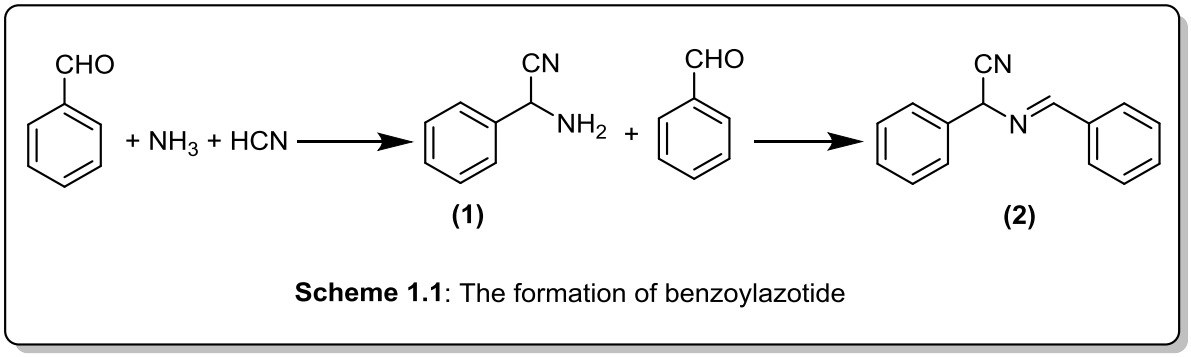


Figure 1.3: The brief history of MCRs

1.1.2.1. Reaction of Laurent and Gerhardt.

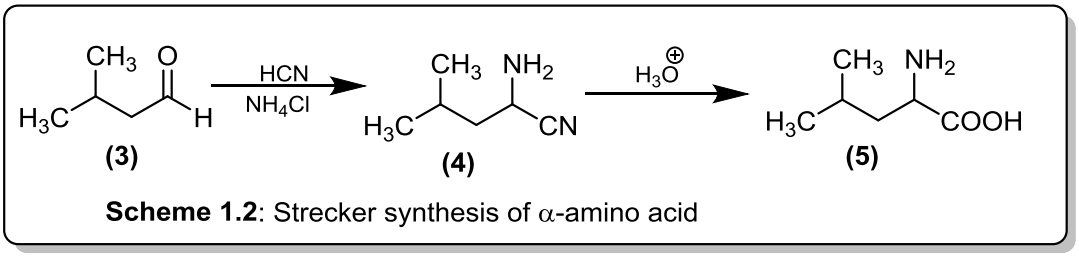
The first examples of MCRs appeared in the mid-19th century. The first was discovered by Laurent and Gerhardt in 1838. In this, benzoylazotide was prepared from ammonia and bitter almond oil.[6,7] In chemistry terms, this was a four component condensation of benzaldehyde with hydrogen cyanide and ammonia to form an intermediate α–amino cyanide (**1**) which underwent condensation with another benzaldehyde molecule to prepare a Schiff base (benzoylazotide (**2**))[7] , as shown below:



Scheme 1.1: The formation of benzoylazotide

1.1.2.2. Multicomponent Strecker reaction.

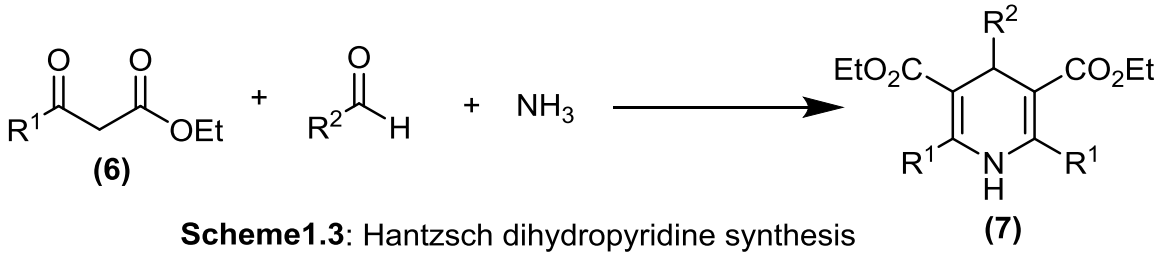
1850 is the year that the chemistry of MCRs is considered to have officially started, with the introduction by Strecker[8] of a methodology for producing α–amino acids **(5)** via the synthesis of α–amino cyanides from aldehydes followed by a post MCR hydrolysis of the cyanide functionality[9-11]. An example is given in Scheme 1.2.



Scheme 1.2: Strecker synthesis of α-amino acid

α-Amino acids are a particularly important class because they have difunctional groups, and are the building blocks from which proteins are constructed.[12] They are widely utilized as components of medicinally active molecules and as chiral catalysts.[13-17]

1.1.2.3. Multicomponent Hantzsch reaction.



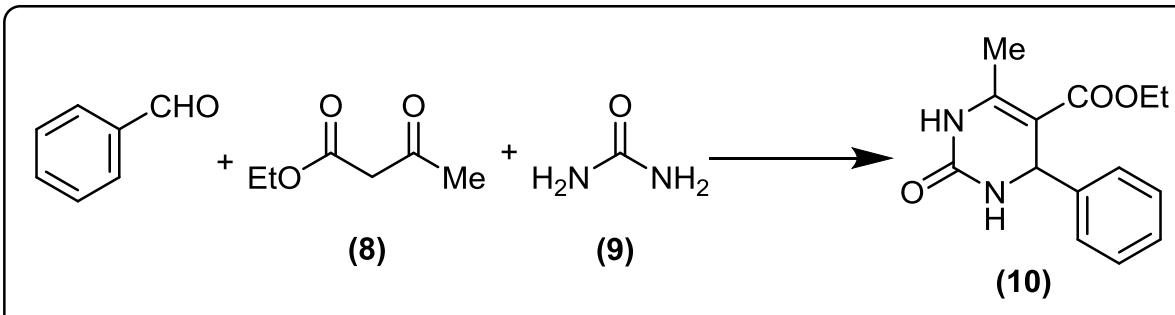
Scheme1.3: Hantzsch dihydropyridine synthesis

The Hantzsch dihydropyridine synthesis was introduced[4] in 1882. This is a four component process involving ammonia, two molecules of an acetoacid ester **(6)** and an aldehyde to form dihydropyridines (**7**) (see Scheme 1.3).[18-20]

1,4-Dihydropyridines, the products of the Hantzch reaction, are an important class of calcium channel blockers and have been commercialized in, for example, nifedipine[21], amlodipine[22] and nimodipine[23].

1.1.2.4. Multicomponent Biginelli reaction.

In 1893 the Biginelli three component reaction was shown to yield 3,4-dihydropyrimidin-2(1H)-ones (**10**), another medicinally interesting heterocycle[24]. In this process benzaldehyde condenses with an acetoacid ester (**8**) and urea (**9**) in the presence of HCl as catalyst. The product usually precipitates out upon cooling making this method very useful and very practical.

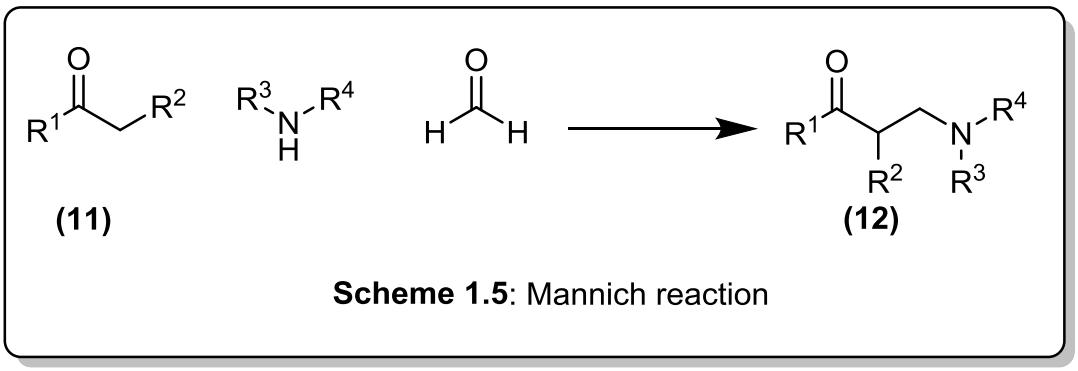


Scheme 1.4 : Biginelli 3,4-dihydropyrimidin-2(1H)-one synthesis.

The scope of this reaction has been extended by changes of the components used, allowing access to a large number of functionalized dihydropyrimidinone analogues,[25,26] a field of very active research due to the important biological properties they show,[27-31] including the first enzymatic example.[32]

1.1.2.5. Multicomponent Mannich reaction.

The next big advance after the Biginelli reaction, the Mannich reaction[33] was discovered by Mannich in 1912. This process is one of the most cited and used reactions in organic synthesis[34]. The Mannich reaction is a three compound condensation between an enolizable CH-acidic carbonyl compound (**11**), a non-enolizable aldehyde (often formaldehyde) and an amine to produce a β-aminocarbonyl compound (**12**), as shown below:



Scheme 1.5: Mannich reaction

The mechanism[19] for the Mannich reaction is shown below in Figure 1.4.

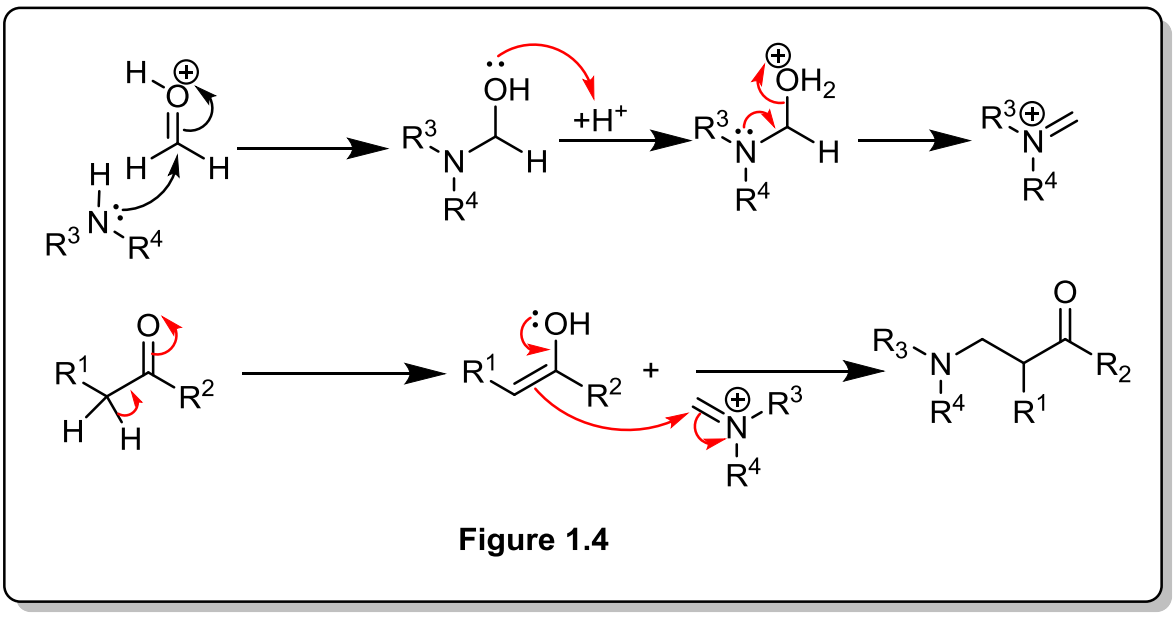
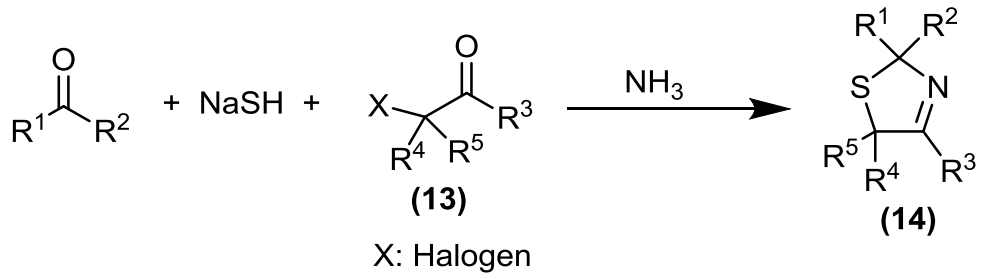


Figure 1.4

Mannich reactions are widely used in medicinal chemistry, for example, in the synthesis of fluoxetine (antidepressant), tolmetin (anti-inflammatory drug), rolitetracycline (Mannich base of tetracycline), azacyclophanes and tramadol.[35,36] The Mannich reaction is also employed in the synthesis of natural compounds such as antibiotics, peptides, alkaloids (e.g. tropinone) and nucleotides.[37]

1.1.2.6. Asinger synthesis of thiazolines.

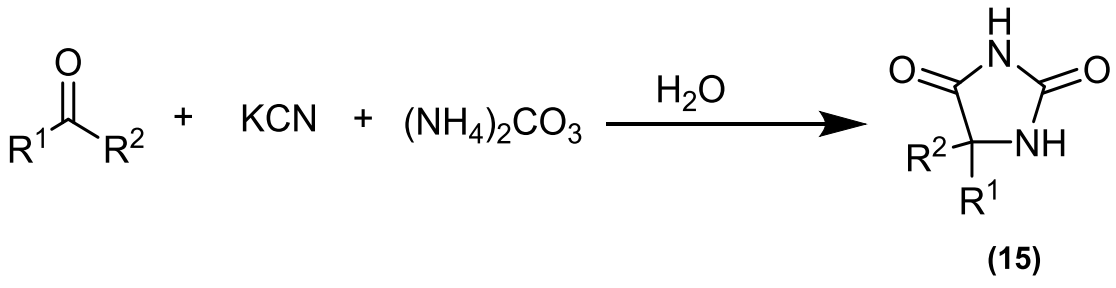
In 1959, Asinger introduced an MCR process for thiazolines[38]. Two types of the reaction have been discovered. The first one is a three component condensation between ammonia, sulfur and an oxo compound while the second involves four components, namely sodium hydrogen sulfide, an oxo compound, ammonia and an α-halo oxo compound[39], as shown in Scheme 1.6 below:



Scheme 1.6: Asinger synthesis of thiazolines

1.1.2.7. Multicomponent Bucherer-Bergs reaction.

The Bucherer-Bergs reaction, a method to make hydantoins was discovered[40,41] in 1934.



(15)

Scheme 1.7: Bucherer-Bergs hydantoin synthesis.

This method used four components being concerned with the condensation between hydrogen cyanide, a carbonyl compound, ammonia and carbon dioxide[42]. The reaction is performed by the use of KCN and $(NH_4)_2CO_3$ (besides the carbonyl component) which in the course of the reaction generates the NH_3 and CO_2 units in-situ that eventually get incorporated in the hydantoin (**15**) skeleton.

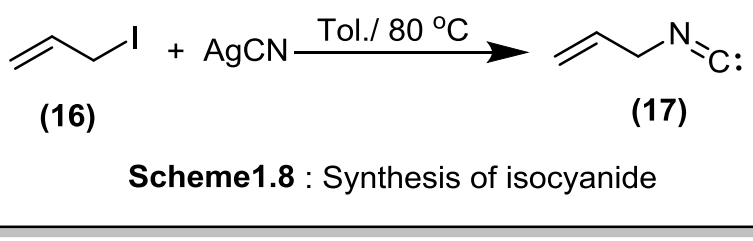
The hydantoins have many applications. They are an important heterocyclic scaffolds in biology and have pharmacological activity, for example, 5,5-diphenylhydantoin (also called Dilantin). The also have useful applications in carbohydrate chemistry.[43-45]

1.1.2.8. Isocyanide-based multicomponent reactions (IMCRs).

1.1.2.8.1. Synthesis of isocyanides

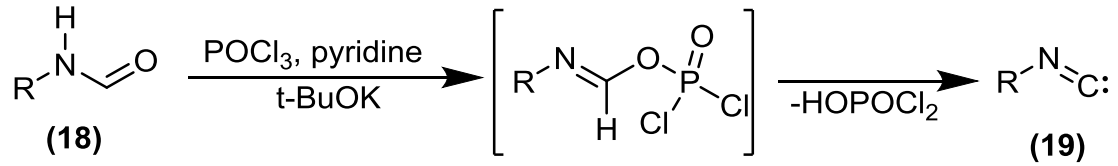
Another class of MCRs began with the development of the chemistry of the isocyanides[46-48]. Isocyanides, also known as isonitriles, are compounds with an interesting functional group. They are one of the few classes of organic compounds with a divalent carbon (C^{2+}) and their chemical reactions change the divalent (C^{2+}) into the tetravalent carbon atom (C^{4+}). Isocyanides have the ability to react with both nucleophiles and electrophiles at the same position, the carbon atom leading to the so called α-adduct[49]. Isocyanide chemistry started in

1859 when allyl isocyanide (**17**) was prepared from allyl iodide (**16**) and silver cyanide[50-53], as shown in Scheme 1.8.

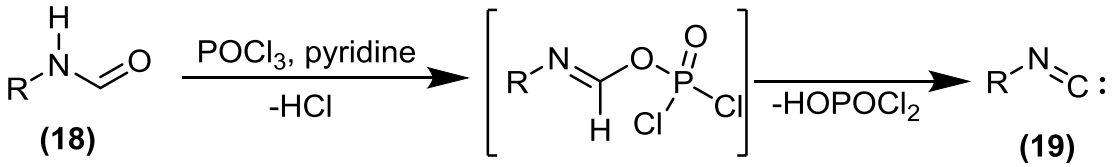


Scheme1.8 : Synthesis of isocyanide

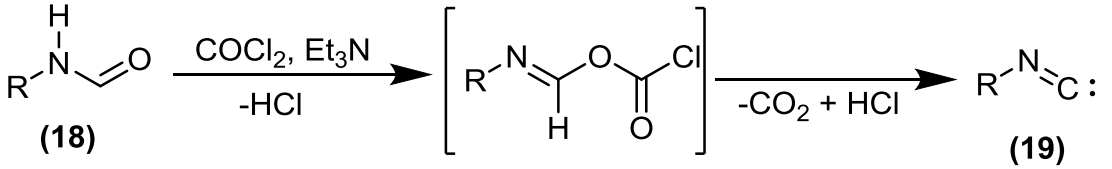
Their wider use in synthesis was started after a more general method for the production of isocyanides (**19**) by dehydration of formylamines (**18**) appeared in 1958[53], as shown in Scheme 1.9 and 1.10 below. This eventually led to the development of the isocyanide-based MCRs (IMCRs) which compose the most well-known and versatile class of MCRs[54].



Scheme 1.9



a) Using $POCl_3$ as a dehydrating agent

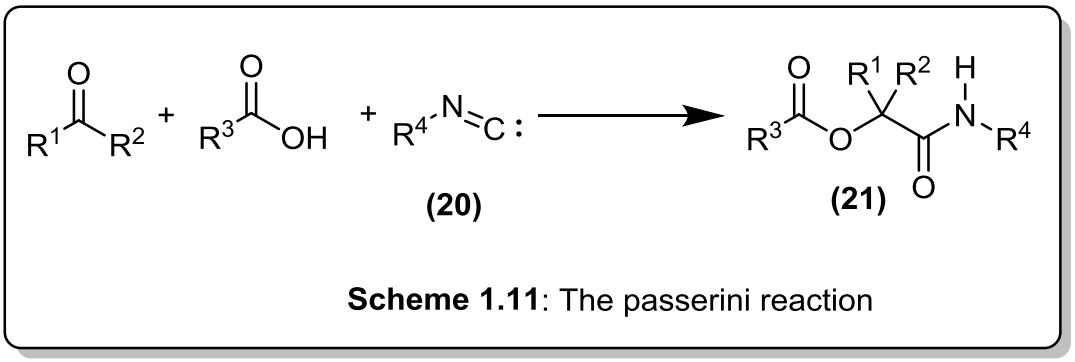


b) Using phosgene as a dehydrating agent

Scheme 1.10: Synthesis of isocyanide by dehydration of formamides

1.1.2.8.2. Multicomponent Passerini reaction.

The first IMCRs were developed by Passerini[55] in 1921 shortly after the reactivity of isocyanides was recognized. The Passerini condensation is a three component reaction between a carbonyl compound, an isocyanide (**20**) and a carboxylic acid to form α–acyloxycarboxamides (**21**), as shown in Scheme 1.11 below:



Scheme 1.11: The passerini reaction

A mechanism has been proposed[55-57], based on the large amount experimental data gained and on the mechanistic studies performed. It concerns the formation of a hydrogen-bonded adduct from the acid and the carbonyl component, thus activating both components, which subsequently react with the isocyanide to form an α–adduct. This α-adduct is unstable, cannot be isolated, and rearranges to the stable α-acyloxycarboxamide, as shown below (Figure 1.5):

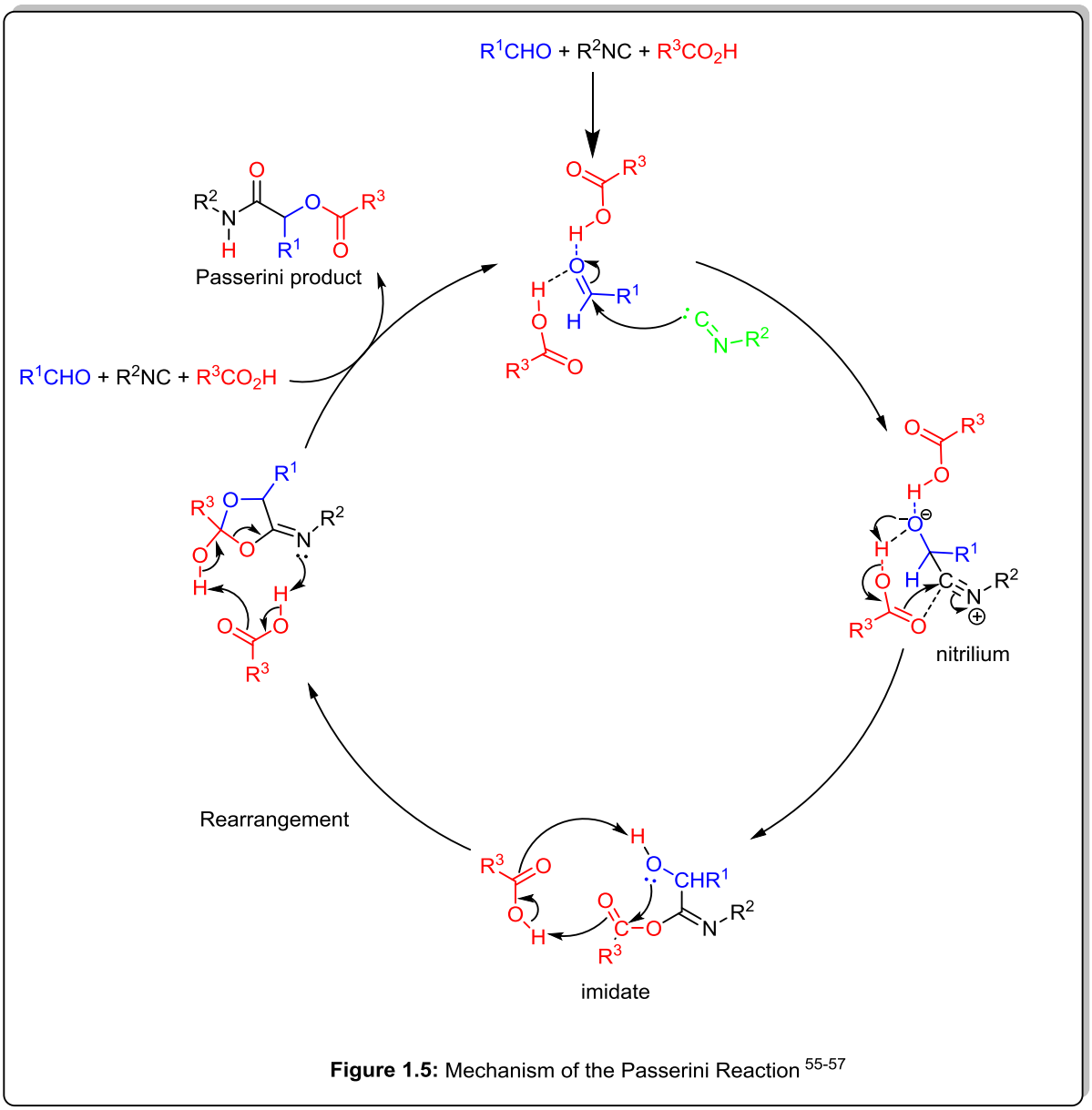
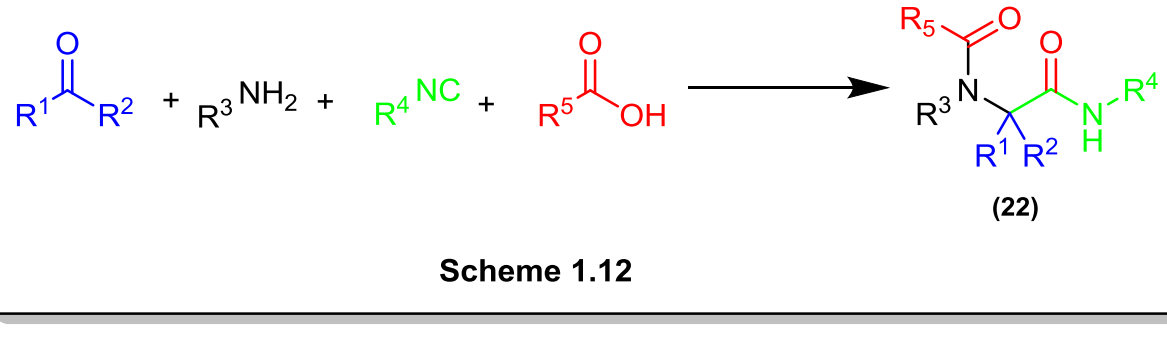


Figure 1.5: Mechanism of the Passerini Reaction [55-57]

The Passerini reaction has been used by the pharmaceutical industry for the synthesis of drug-like compounds, and for the synthesis of heterocycles, polycyclics and the total synthesis of natural products.[58,59]

1.1.2.8.3. Multicomponent Ugi reaction.

In 1959, a major advance in MCRs was set by Ugi by using four compounds.[60,61] In the Ugi reaction a carbonyl component, isocyanide, a carboxylic acid and an amine are reacted to form α–acylamido amides (**22**), as shown in the Scheme 1.12.



Scheme 1.12

The Ugi reaction is similar to the Passerini reaction but the fourth component (the amine) adds one more point of diversity giving a higher number of molecules that can potentially be synthesized[62]. The proposed mechanism[63] for the Ugi condensation concerns the production of an imine from the carbonyl and the amine which in the presence of the isocyanide and the carboxylic acid reacts in a similar fashion to the Passerini reaction, yielding the α-adduct which then undergoes a rearrangement, yielding the final product.

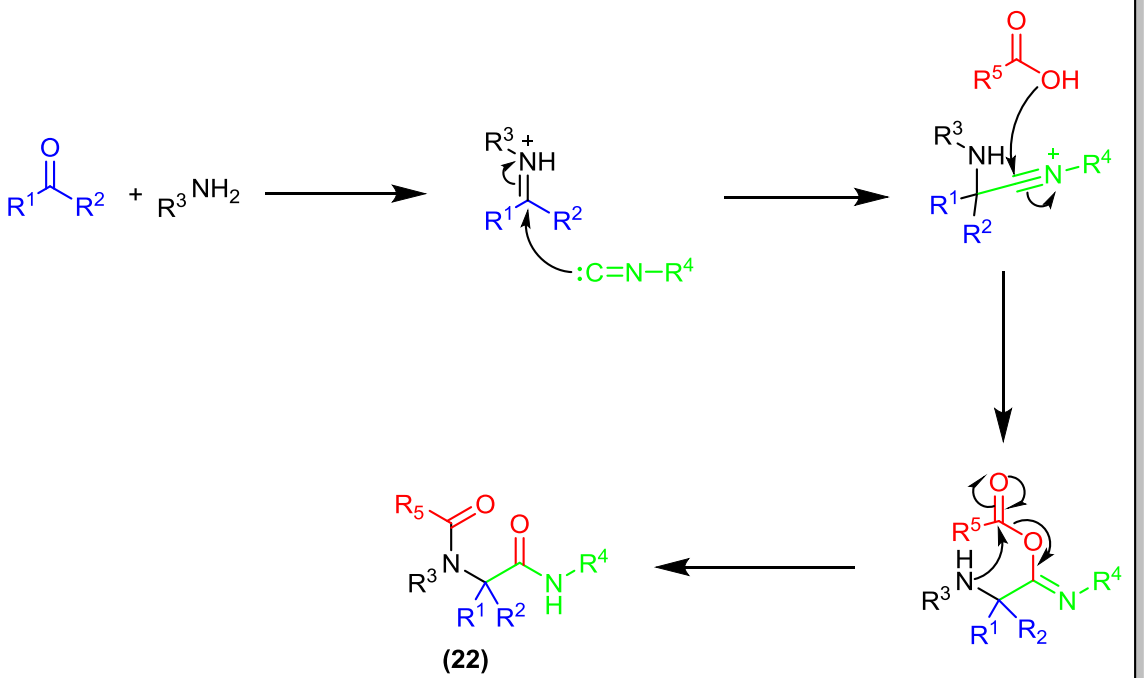


Figure 1.6: Mechanism of the Ugi 4-component reaction

The use of bifunctional components can lead to cyclic structures through intramolecular condensation. The number of Ugi-derived products can be developed even more by the

incorporation of post-MCR modifications[5,9]. Figure 1.7 gives a list of types of structures made using Ugi-type MCRs.[64]

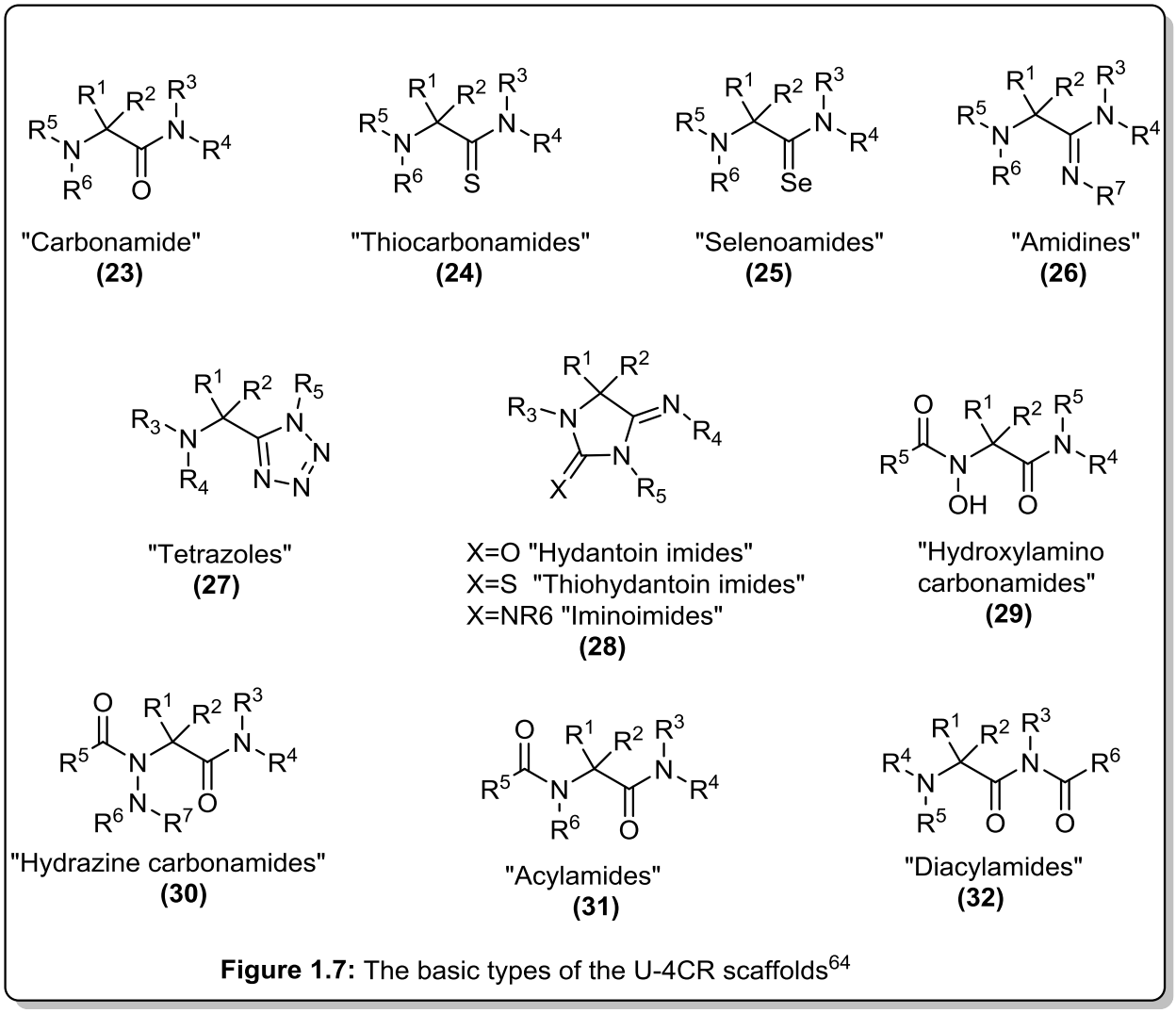
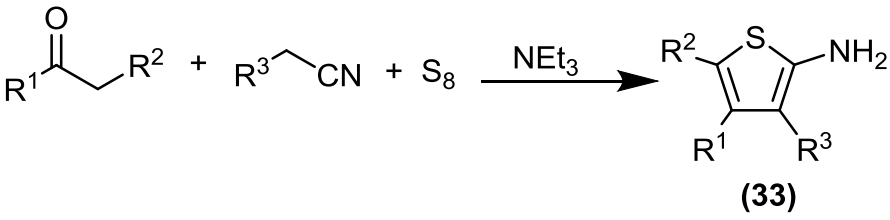


Figure 1.7: The basic types of the U-4CR scaffolds[64]

The Ugi reaction is used in pharmaceutical products such as Crixivan[65], and for many of the caine-type anesthetics including bupivacaine[66] and lidocaine.[67]

1.1.2.9. Multicomponent Gewald reaction.

In 1961 Gewald reported[68] the production of poly-substituted thiophenes (**33**) from the reaction between a carbonyl compound (ketone, aldehyde or 1,3-dicarbonyl) with elemental sulfur and activated nitriles in the presence of an amine base[69].

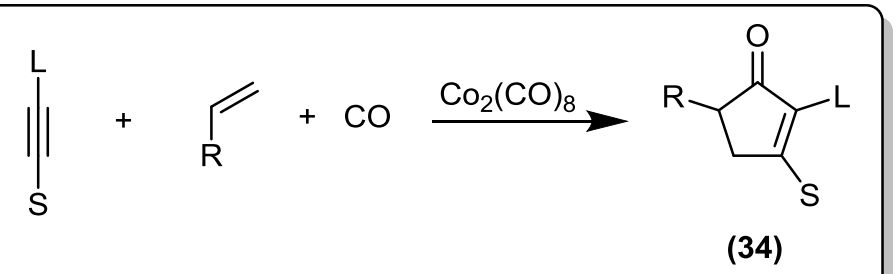


(33)

Scheme 1.13: The Gewald reaction

1.1.2.10. Multicomponent Pauson and Khand.

In 1971 another well-known MCR was developed by Pauson and Khand[70,71]. The transformation yields cyclopentenones (**34**) and involves the [2+2+1] cycloaddition reaction between an alkyne, an alkene and CO, in the presence of $Co_2(CO)_8$ as catalyst. It has found application in producing prostaglandin analogues.



(34)

Scheme 1.14: The Pauson-Khand reaction

1.2. Quinazolinones:

1.2.1. An introduction to quinazolinones:

Later in this thesis an unexpected synthesis of quinazolinones will be discussed. A brief introduction to these heterocycles is hence included here.

Quinazolinones are an important class of heterocycle with a wide range of pharmacological and biological activities such as antiviral, anticancer, antidiabetes, antiobesity, anti-inflammatory, anti-tubercular[72], antiulcer, insecticidal, anticonvulsant, hypolipidemic activity and antimicrobial properties. They are also potent and selective ALK5 inhibitors[73]. Quinazolines also have tranquilizer, sedative, analgesic, diuretic, antihypertensive, anesthetic, and muscle relaxant properties[74-76]. Some examples, compounds **(40-44)**, are shown in Figure 1.8.

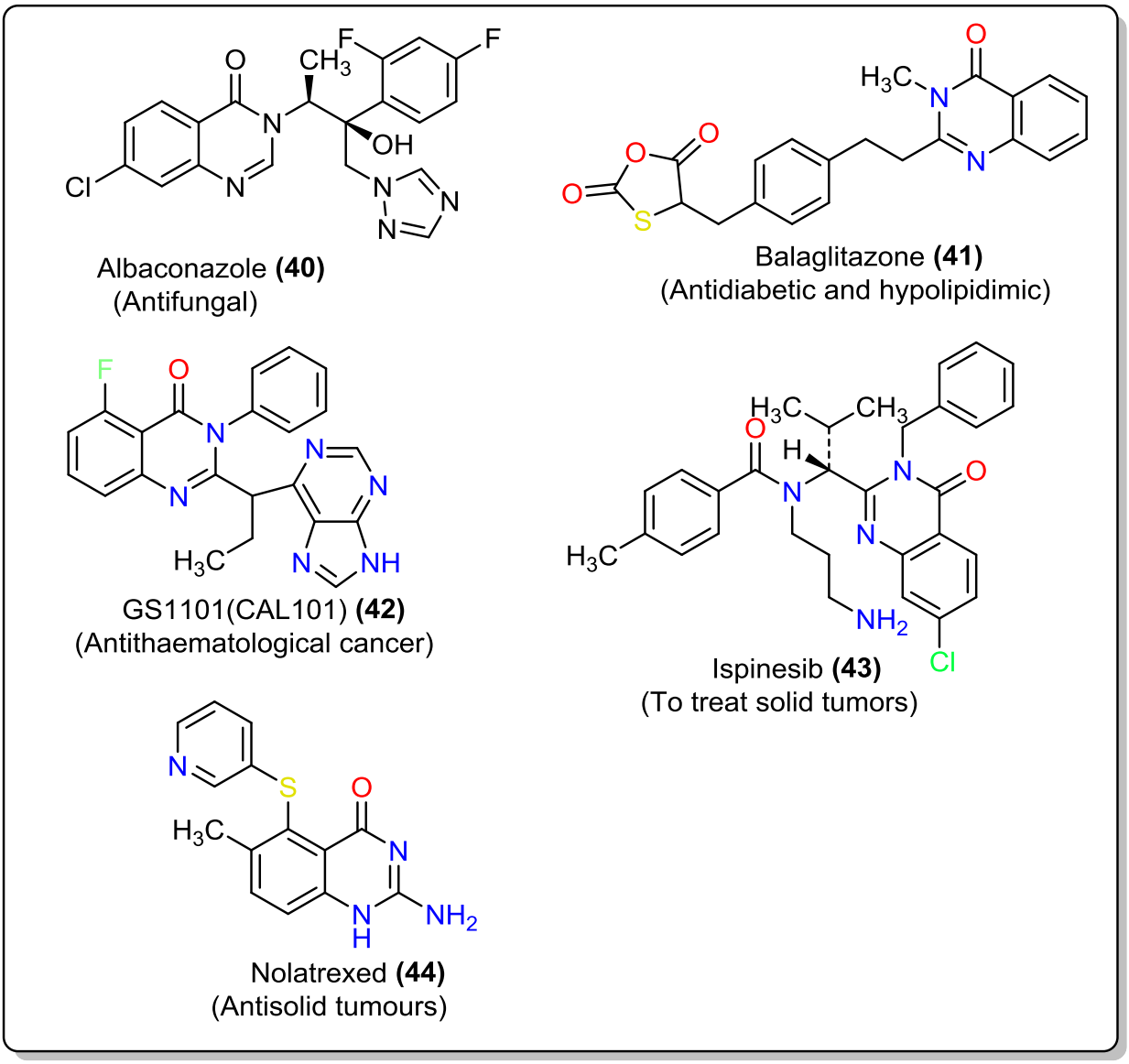


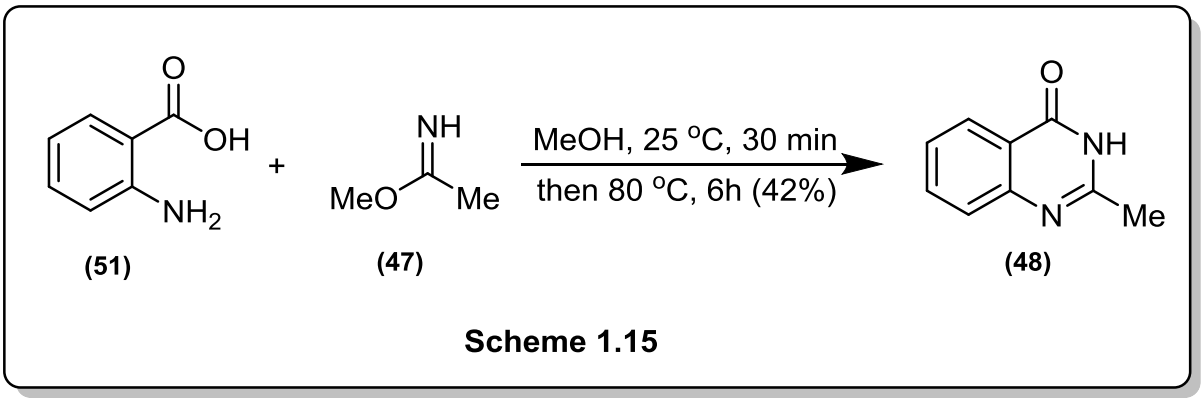
Figure 1.8: Pharmaceutical compounds containing the quinazolinone moiety[74].

The quinazoline moiety is present in approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, animals and microorganisms.[77-81] An example is febrifugine, from the Asian plant *dichroa ferifuga*[82] and the garden plant Hydrangea[83], used as a chinese herbal remedy effective against malaria (Fig. 1.9).

Figure 1.9

1.2.2. Synthesis of quinazolinones.

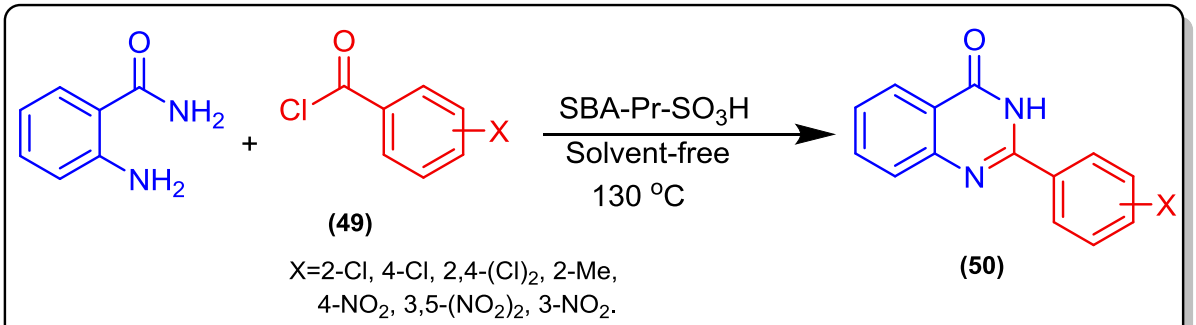
2-Methyl-4(3H)-quinazolinone (**48**) was synthesized via the reaction of anthranilic acid with various imidates in methanol (Scheme 1.15)[84].



(51) (47) (48)

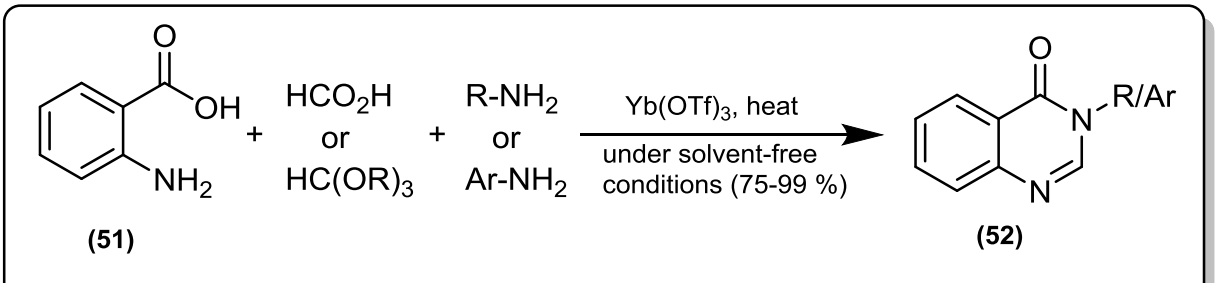
Scheme 1.15

Quinazolinones (**50**) were efficiently synthesized in good to excellent yields via reaction of aromatic benzoyl chlorides (**49**) with 2-aminobenzamide using SBA-Pr-SO_3H as a nano solid acid catalyst under solvent-free conditions[85] as shown in Scheme 1.16.



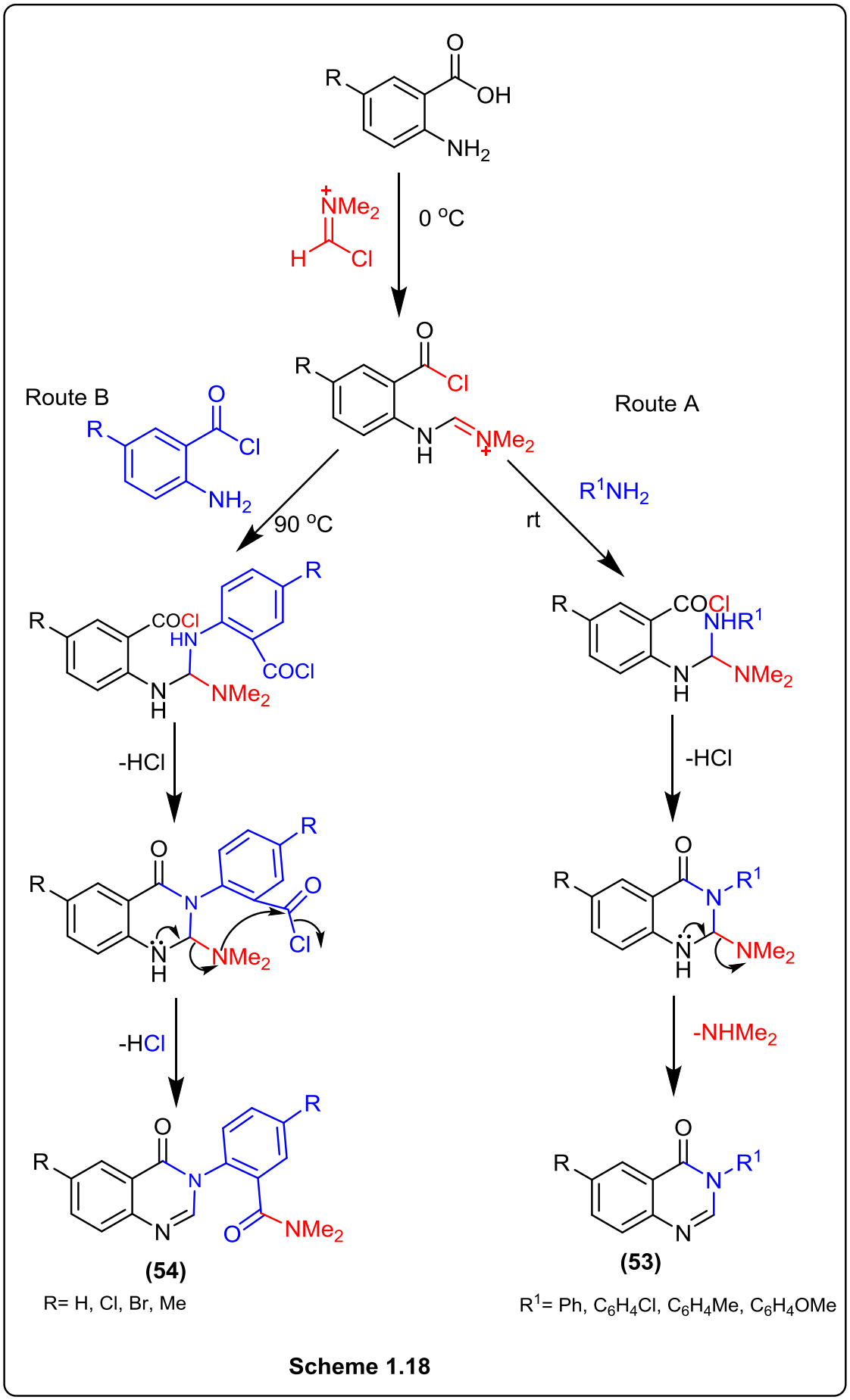
Scheme 1.16: Synthesis of Quinazolinones **(50)**

The quinazolin-4-ones (**52**) were synthesized in high to excellent yield (75-99 %) via the reaction of anthranilic acid, amines, and esters (or formic acid) under solvent-free conditions using $Yb(OTf)_3$ as a catalyst[86], as shown in Scheme 1.17.



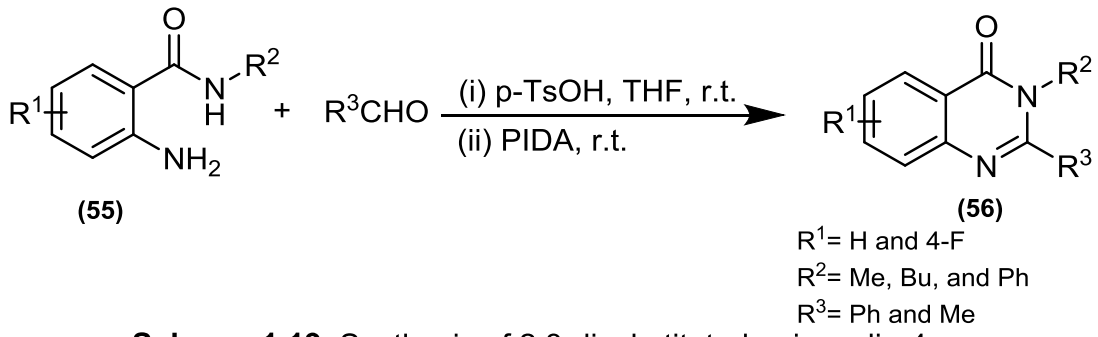
Sceme 1.17

Another approach describes a novel reaction to provide 3-substituted-4(3H)-quinazolinones (**53**) or (**54**) in high yield by the reaction of the Vilsmeier reagent with 5-substituted-2-aminobenzoic acid derivatives (Scheme 1.18)[87]. The reaction was found to be temperature dependent with compound (**53**) formed at room temperature and compound (**54**) formed at 90 ^{o}C.


Route B
Route A
0 °C
90 °C
rt
-HCl
-HCl
-HCl
-NHMe2
(54)
R= H, Cl, Br, Me
(53)
R1= Ph, C6H4Cl, C6H4Me, C6H4OMe

Scheme 1.18

Finally, quinazolinones **(56)** can be made by reaction of aldehyde with 2-aminobenzamides (**55**) via a p-toluene sulfonic acid catalysed cyclocondensation followed by oxidative dehydrogenation mediated by phenyliodine diacetate (PIDA) as shown in Scheme 1.19.[88]



(55) **(56)**

R^1= H and 4-F
R^2= Me, Bu, and Ph
R^3= Ph and Me

Scheme 1.19: Synthesis of 2,3-disubstituted quinazolin-4-one

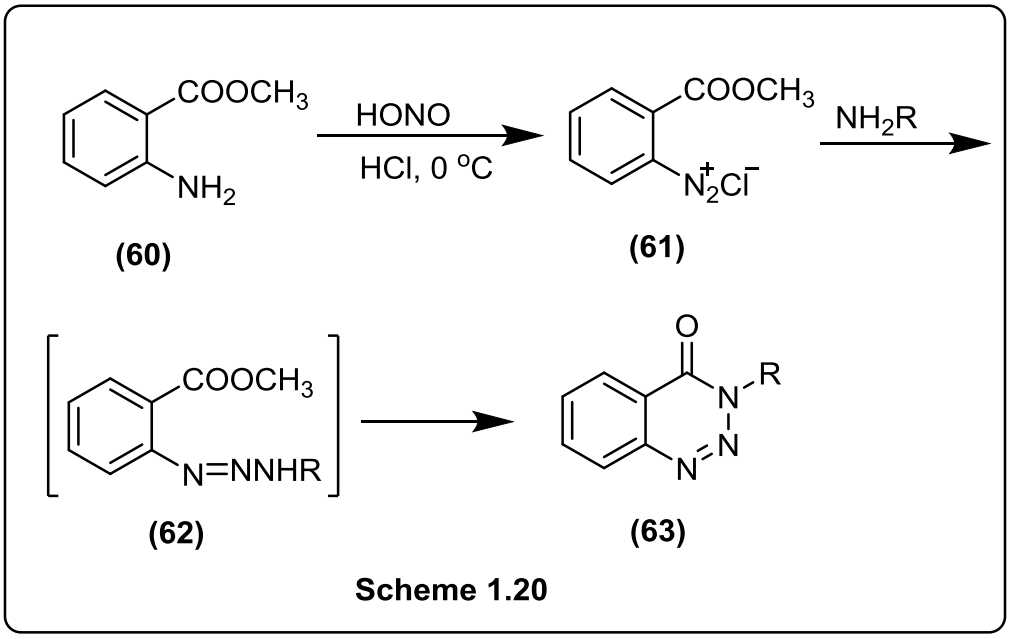
1.3. Benzotriazinones.

1.3.1. An introduction to benzotriazinones.

Benzotriazinones will also feature later in this thesis (see discussion) and so are briefly introduced here.

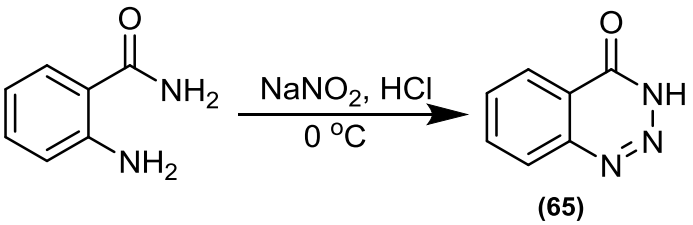
Benzotriazinones are an important class of heterocycle and have attracted attention in medicinal and bioorganic chemistry[89-91]. For example, benzotriazinones have been reported having diuretic[92], sedative[93], antiarthritic[94], antitumor[95], anesthetic[96] and antitubercular activities[97].

Traditionally[98-100], methyl anthranilate (**60**) (Scheme 1.20) was reacted with $NaNO_2$ and HCl at 0 ^oC to form a diazonium **(61)** as an intermediate and then reaction between the diazonium intermediate and aliphatic amines gave 3-substituted 1,2,3-benzotriazine-4-ones (**63**).



Scheme 1.20

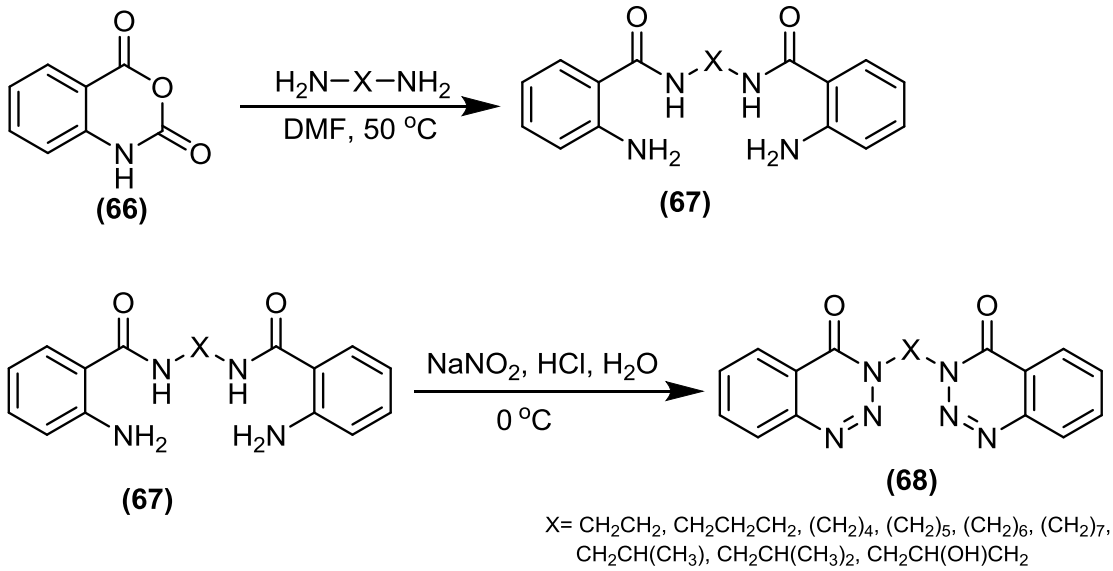
Alternatively, the parent 1,2,3-benzotriazin-4-one (**65**) can be prepared as shown in Scheme 1.21[101] and can then be substituted at the 3-position.



(65)

Scheme 1.21: Synthesis of 1,2,3-benzotriazine-4(3H)-ones

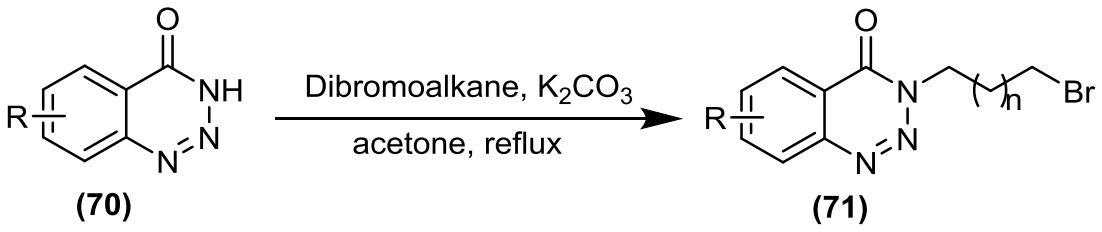
bis-1,2,3-Benzotriazin-4(3H)-ones (**68**), shown in Scheme 1.22, were prepared by reaction of isotoic anhydride (**66**) with an alkanediamine in the presence of DMF at 50 °C under mild conditions.[102] The diazotization of the intermediate *bis*-[(2-aminobenzoyl-)amino]alkanes (**67**) in aqueous solution afforded good yields of the *bis*-1,2,3-benzotrizine-4-ones (**68**).



Scheme 1.22: Synthesis of 1, x-bis-(4-oxo-3,4-dihydro-1,2,3-benzotrizin-3-yl) alkanes

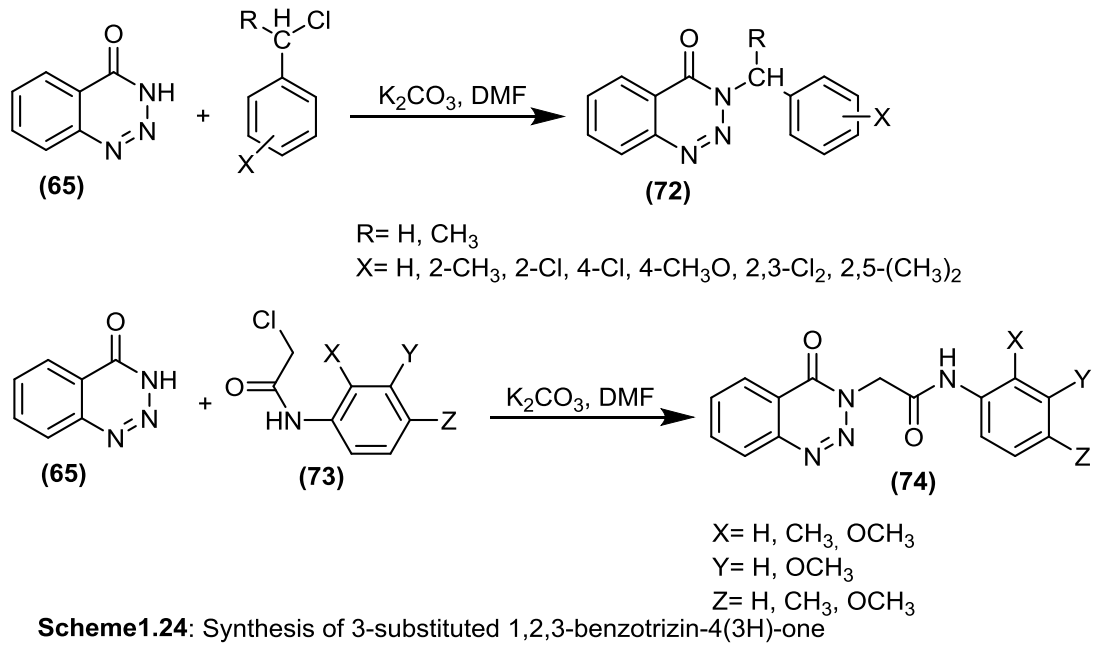
1.3.2. Reactivity of 1,2,3-benzotriazinones.

The 1,2,3-benzotrizin-4-ones (**70**) were alkylated at the N3 position with dibromoalkane in the presence of K_2CO_3 as a weak base to afford 3-(3-bromoalkyl)-1,2,3,-benzotriazin-4(3H)-ones (**71**)[103], using 1,4-dibromobutane and 1,3-dibromopropane (Scheme 1.23).



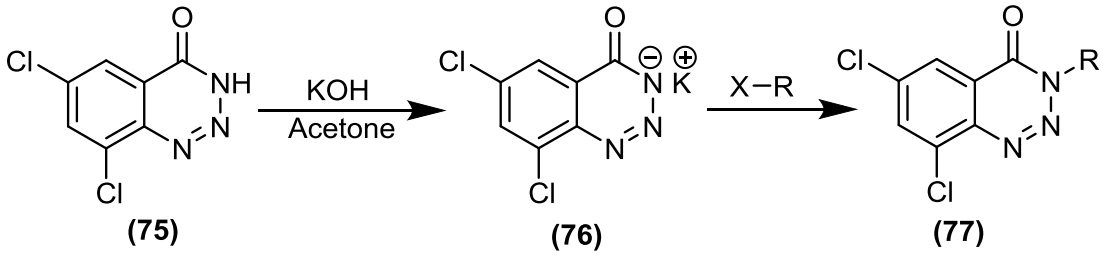
Scheme1.23: Synthesis of compound **(71)**

3-Benzyl-1,2,3-benzotriazin-4(3H)-ones[104,105] (**72**) have been prepared by alkylation of the 1,2,3-benzotriazin-4(3H)-one (**65**) with benzyl halides in anhydrous DMF in the presence of potassium carbonate. Compound (**74**) was prepared by alkylation of 1,2,3-benzotriazin-4(3H)-one (**65**) with compound (**73**) under the same conditions, as shown in Scheme 1.24.



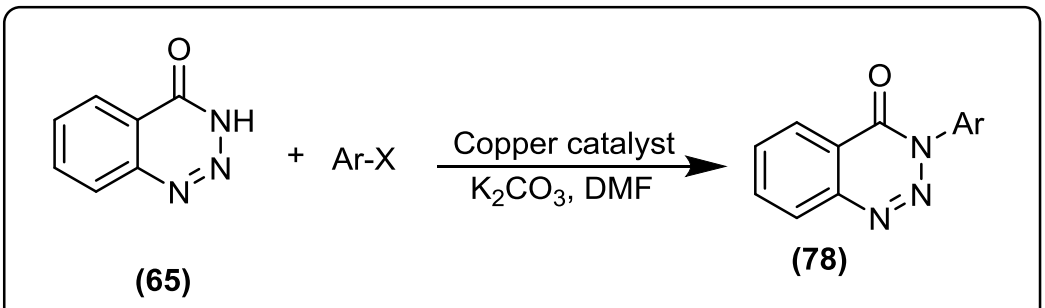
Scheme1.24: Synthesis of 3-substituted 1,2,3-benzotrizin-4(3H)-one

Another method for the preparation of 3-substituted 1,2,3-benzotriazin-4(3H)ones involves the intermediate salt (**76**) which was reacted with haloalkanes to afford 3-substituted 1,2,3-benzotriazin-4(3H)-ones (**77**)[106] (Scheme 1.25).



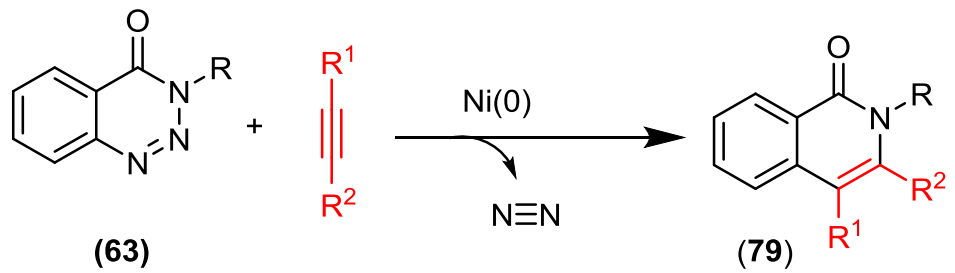
Scheme 1.25: Synthesis of 3-substituted 1,2,3-benzotriazin-4(3)-ones

3-aryl-1,2,3-benzotriazin-4(3*H*)-ones (**78**) were prepared from 1,2,3-benzotriazin-4(3)-one (**65**) and aryl halides[107] in the presence of 10 mol % of various copper catalysts (CuI, CuBr, Cu_2O, $CuBr_2$, Cu) and K_2CO_3 (used to neutralize the released acid, HX) in DMF (Scheme 1.26).



Scheme 1.26: Synthesis of 3-phenyl-1,2,3-benzotriazin-4(3)-ones

1,2,3-Benzotriazin-4(3)-ones (**63**) react with alkynes such as diphenyl ethyne in the presence of a nickel (0)/phosphine catalyst to give substituted 1(2H)-isoquinolones (**79**)[108](Scheme 1.27).



R^1= Ph, CH_2OBn, Me, n-Pr
R^2= Ph, CH_2OBn, Me, p-$MeOC_6H_4$, CO_2Et

Scheme 1.27: Reaction of 1,2,3-benzotrizin-4(3H)-one with alkynes.

1.4.1. Pyrrolobenzodiazepines.

These heterocycles will also appear in the later discussion section. The pyrrolo[2-1-c][1,4] benzodiazepine (PBD) group of natural products includes tomaymycin[109] (**90**), prothracarcin[110] (**91**), sibanomicin[111] (**92**), sibiromycin[109,112] (**89**), chicamycin[113] A (**96**), neothramycins[114] A (**93**) and B (**94**), DC-81[115] (**95**), anthramycin[116] (**86**), mazethramycin[117] (**87**) and porothramycin[118] (**88**), as shown in Figure 1.10.

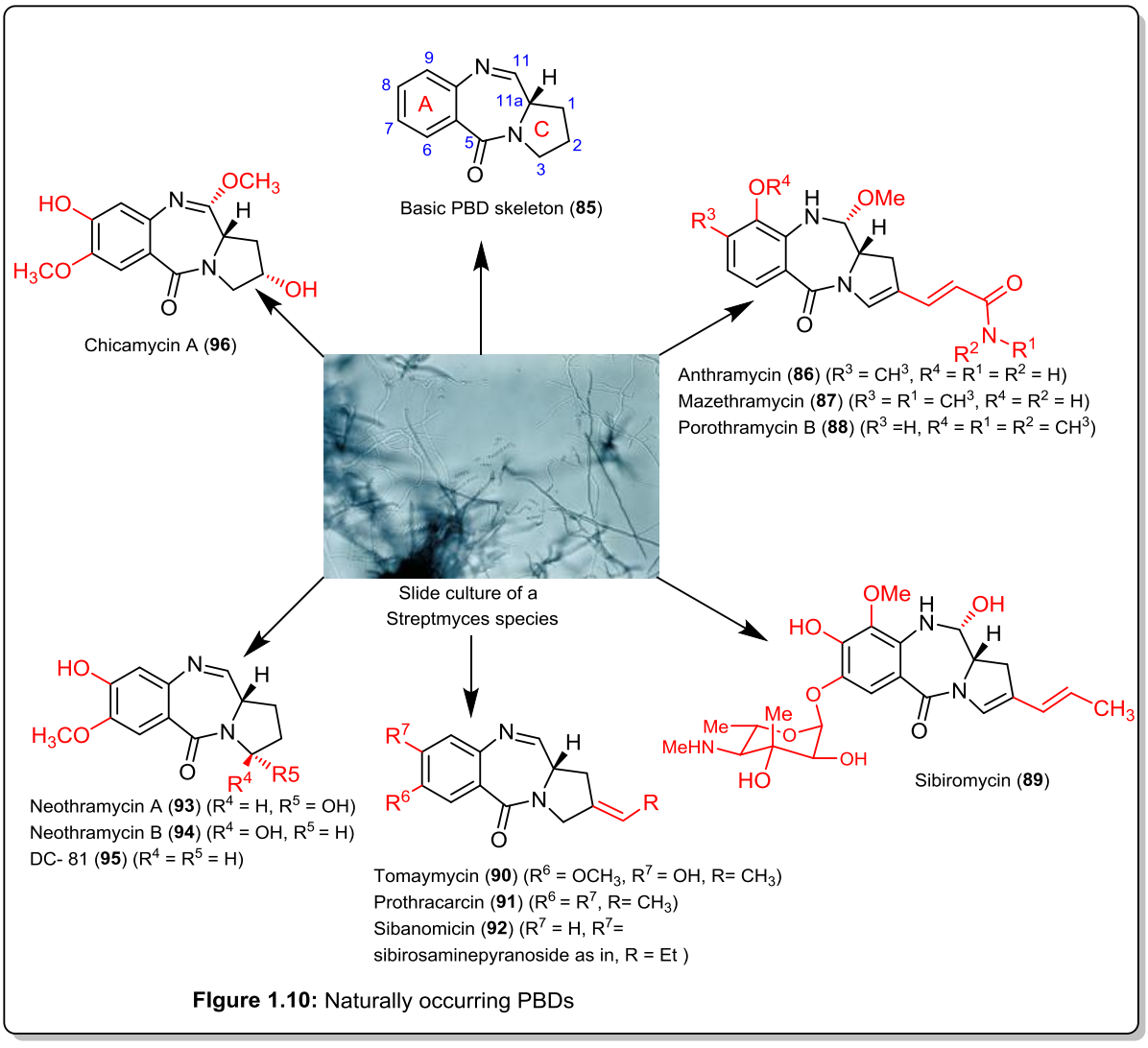


FIgure 1.10: Naturally occurring PBDs

The PBDs are of interest because of their biological activity. The minor groove of DNA is the biological target, by interaction with an electrophilic carbinolamine or imine functionality at N10-C11 of the PBD. The resulting DNA adduct inhibits DNA replication and gives the PBDs potent antitumour antibiotic activity (see Figure 1.11)[118-122].

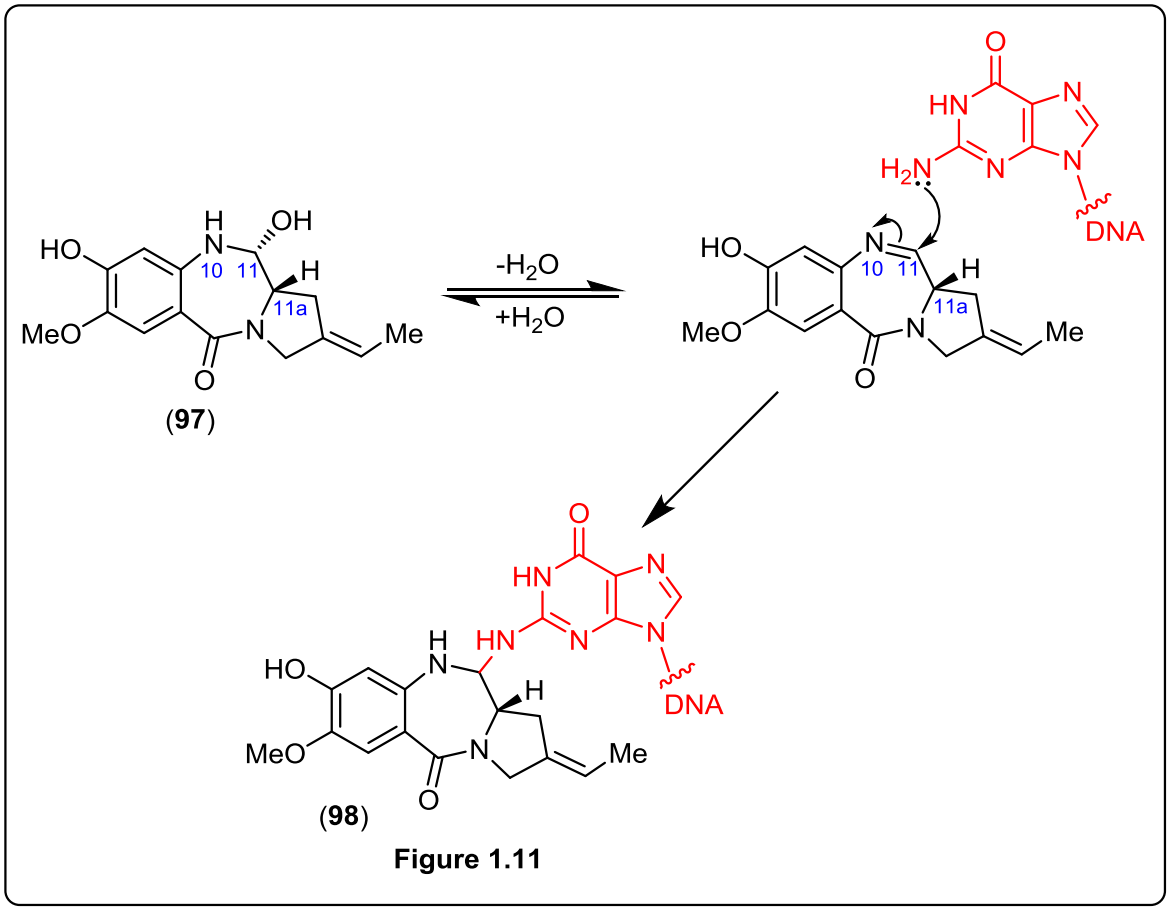


Figure 1.11

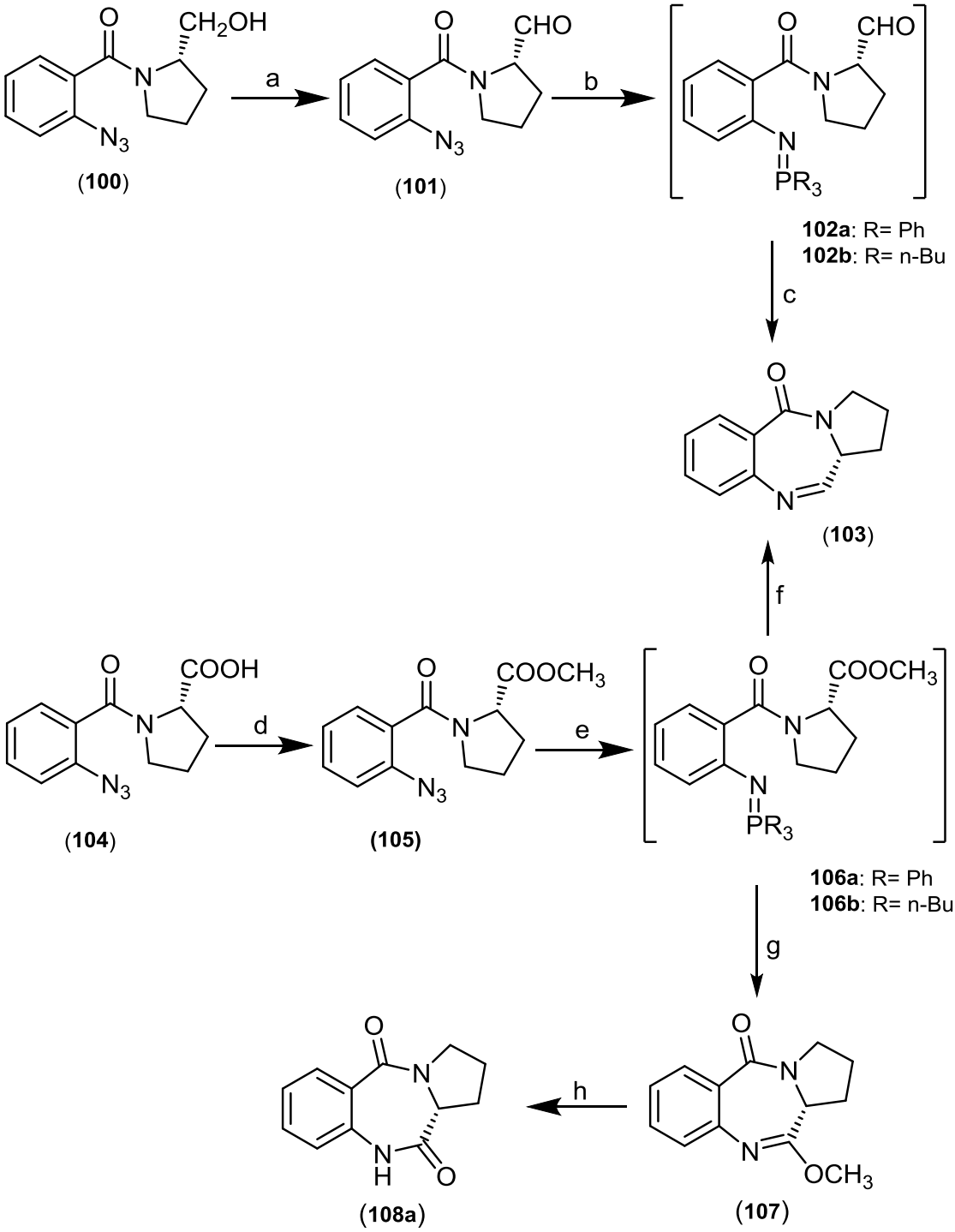
1.4.2. Preparation of pyrrolobenzodiazepines (PBDs).

Synthesise of compounds in the PBD class was involved: 1) seven membered cyclic dilactam reduction;[123-125] 2) reductive cyclization of an acyclic nitro aldehyde;[126,127] 3) cyclic iminothioether reduction;[124] 4) expansion of *N*-pentenylphthalimides by photochemical[128,129] means; 5) amino acetal cyclization;[130] 6) carbonylation of *o*-haloanilides catalyzed by palladium,[131-133] and 7) azide based routes.[120]

Azide based routes are relevant to the work in this thesis. In an azide based literature synthesis (Scheme 1.28), reaction of 2-azidobenzoyl chloride[134] with L-prolinol gave the *o*-azidobenzamide derivative **(100).** Oxidation of compound **(100)** with pyridinium chlorochromate (PCC) at room temperature gave aldehyde **(101)** in 81% yield. The iminophosphorane **(102a)** was prepared via the reaction between triphenylphosphine and compound **(101)** at 0 ^{o}C. Compound **(102a)** was converted to PBD **(103)** at room temperature in 1 hour. The formation of the alternative iminophosphorane **(102b)** was also used as the

more reactive tributylphosphine could be used at -10 ^{o}C with a short reaction time (30 min). This resulted in a more efficient cyclisation to give PBD **(103).**[120]

An alternative route for the preparation of compound **(103)** used L-proline. Reaction of *o*-azidobenzoyl chloride and L-proline gave the azidobenzamide **(104)** in 82% yield. The compound **(104)** was esterified into the methyl ester drivative **(105)** by methanol in 96% yield. Reaction of compound **(105)** with triphenylphosphine or tributylphosphine gave the iminophosphoranes **(106)** at ambient temperature. Reduction to the aldehyde with DIBAL and aza-Wittig cyclisation gave the PBD **(103)** in 57 % yield[120]. Alternatively, aza-Wittig cyclisation of **(106a or b)** gave iminoether **(107)** which was hydrolysed to the lactam **(108a)** [Scheme 1.28].[120]

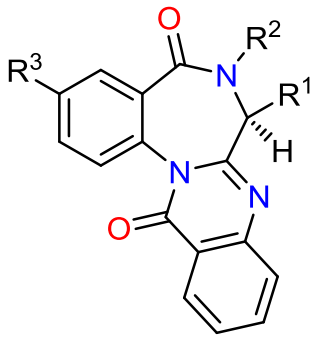


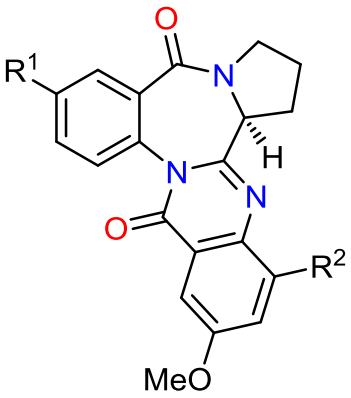
Reagents and conditions: a) PCC, CH_2Cl_2, r.t., b) TPP, Et_2O, 0 ^oC (for **102a**), or n-Bu_3P, Et_2O, -10 ^oC (for **102b**) c) Et_2O, r.t., d) $SOCl_2$, benzene, r.t., then CH_3OH r.t. e) TPP, CH_2Cl_2, r.t., f) DIBAL, Et_2O, -78 ^oC to r.t., g) toluene, 140 ^oC sealed tube, 24 h **(106a)** or toluene, reflux, 3h (for **106b**), h) H_2O, reflux, 30 min.

Scheme 1.28: Synthesis of benzodiazepines[120]

1.4.3. The Circumdatins.

There is a large class of quinazolinobenzodiazepine natural products.[135,136] Examples are circumdatins F and C (**110 and 111**), benzomavin A (**112**) and sclerotigenin (**113**). Circumdatins D-J (**114-117**) which have an additional tetrahydropyrrole ring as shown in Figure 1.12 below[137,138], and are of great relevance to the pyrrolobenzodiazepine derivatives targeted in this thesis.





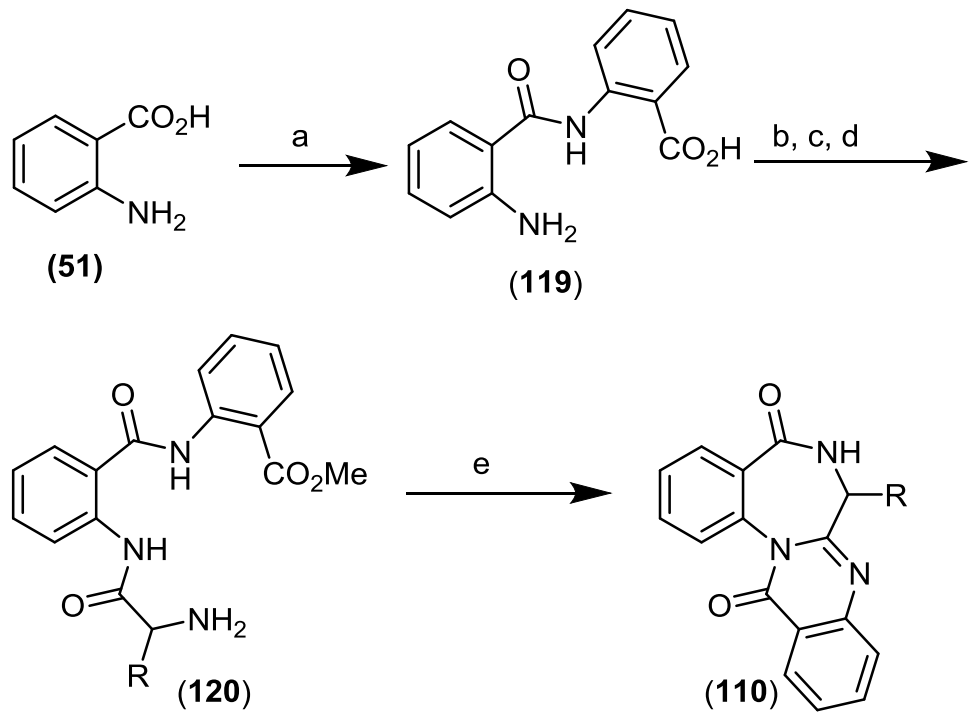
110: R^1= Me, R^2 =R^3= H (circumdatin F)
111: R^1= Me, R^2 =R^3= OH (circumdatin C)
112: R^1= Bn, R^2 =R^3= H (benzomavin A)
113: R^1= R^2 =R^3= H (sclerotigenin)

114: R^1= OMe, R^2 = OH (circumdatin D)
115: R^1= H, R^2 =OH (circumdatin E)
116: R^1= H, R^2 = H (circumdatin H)
117: R^1= OMe, R^2 = H (circumdatin J)

Figure 1.12: Structures of quinazolinobenzodiazepine alkaloids.

1.4.4. Synthesis of Circumdatins.

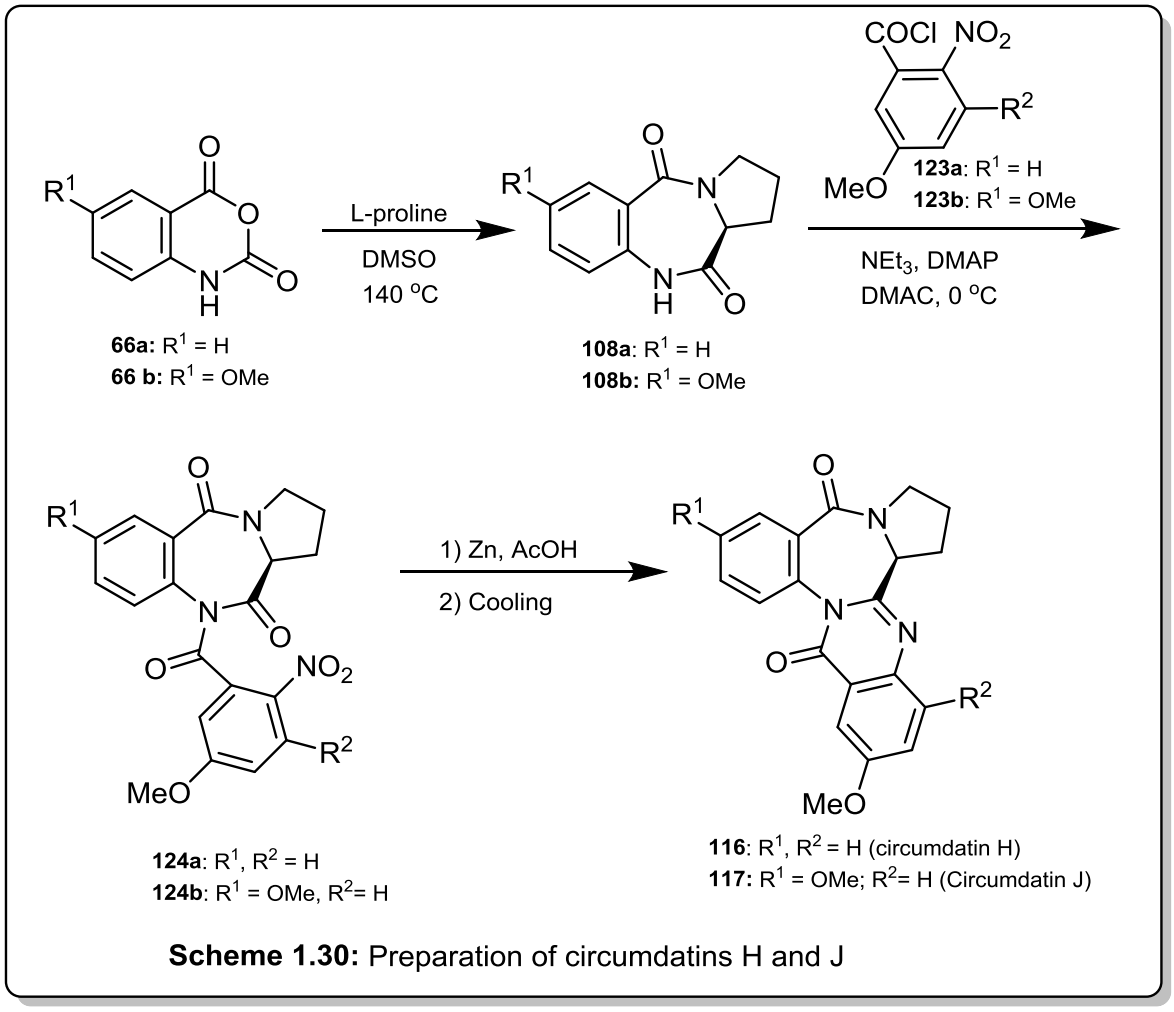
Circumdatin F (**110**)[139] was obtained by treating precursor (**120**) with $Sc(OTf)_3$ in DMF. Compound (**120**) was prepared by direct coupling of anthranilic acid with isatoic anhydride in heated water to make (**119**) in 87 % yield, which was converted to the methyl ester with a high isolated yield (80 %) in hot acidic methanol. Coupling with a Cbz-L-amino acid in the presence of EDC in DCM, and hydrogenation by catalytic $Pd(OH)_2$ gave compound (**120**), as shown in Scheme 1.29.



a) isatoic anhydride, H_2O, reflux, 2 h; b) H_2SO_4/MeOH (1:25, v/v) reflux, 5 d; c) Cbz-L- amino acid, EDC CH_2Cl_2, rt, 2-6 h; d) H_2, $Pd(OH)_2$/C, rt, MeOH, 0.5 h; e) $Sc(OTf)_3$, DMF, 10-15 min, 140 ^oC.

Scheme 1.29: Synthesis of Circumdatin F

In another route, shown in Scheme 1.30, reaction of the isatoic anhydride (**66a**) with L-proline[140] in DMSO at 140 ^oC afforded the corresponding the PBD (**108a**) with a high yield of 91 %. The PBD (**108a**) was treated with acid chloride (**123a**)[141] in DMAC in the presence of DMAP and NEt_3 to give the desired 2-nitrobenzamide (**124a**) in a yield of 82 %. The 2-nitrobenzamide (**124a**) was treated with excess acetic acid and zinc to give the desired circumdatin[142] H (**116**) in high yield 72 %. The same approach was used to synthesise circumdatin J **(117),** also shown in Scheme 1.30.



Scheme 1.30: Preparation of circumdatins H and J

1.4.5. The Fuligocandins

Several new PBD compounds were isolated from the extract of the fruiting bodies of the myxomycete Fuligocandida. These compounds were the known cycloanthranilylproline **(108a)** and three unknown derivatives **(126-128),** which were named as fuligocandin A-C (Figure 1.13).

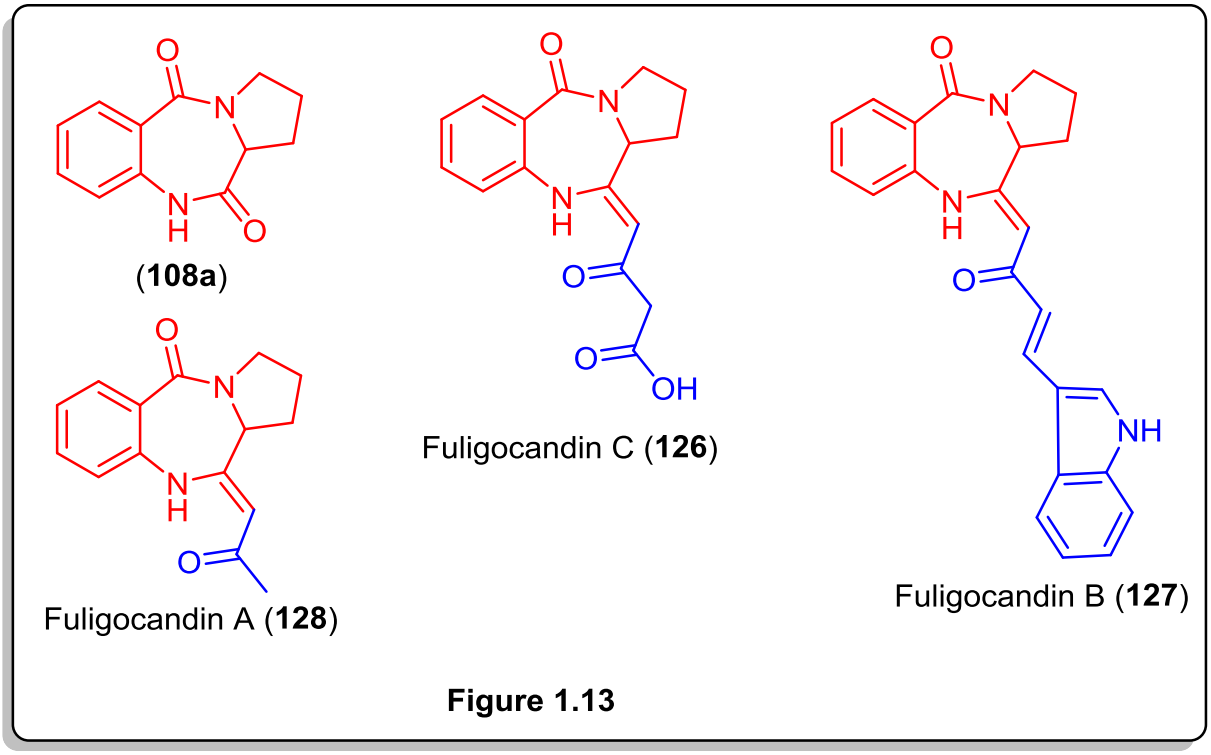


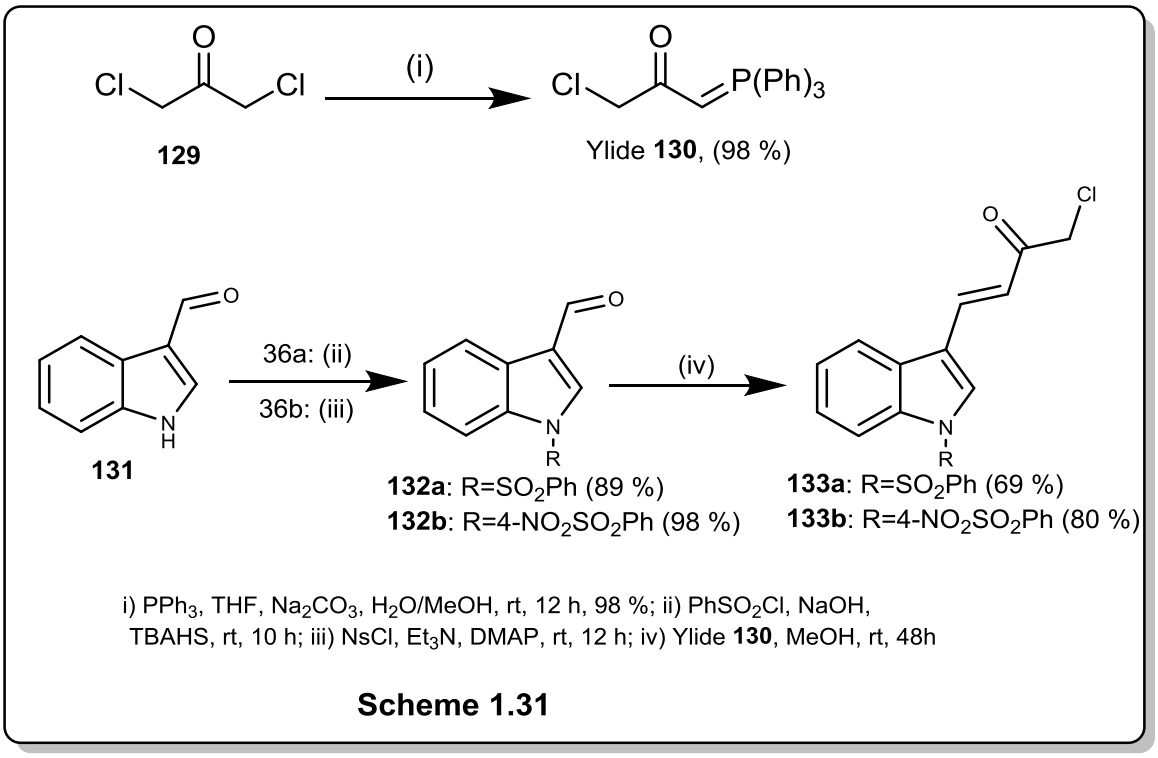
Figure 1.13

Compound **(126)** was unstable and easily converted into compound **(128).** Compound **(127)** (Fuligocandin B) was isolated as a yellow pigment, which was found to be derived from condensation of an acetone and a cycloanthranilic acid and indole-3-carbaldehyde.

1.4.6. Synthesis of Fuligocandins

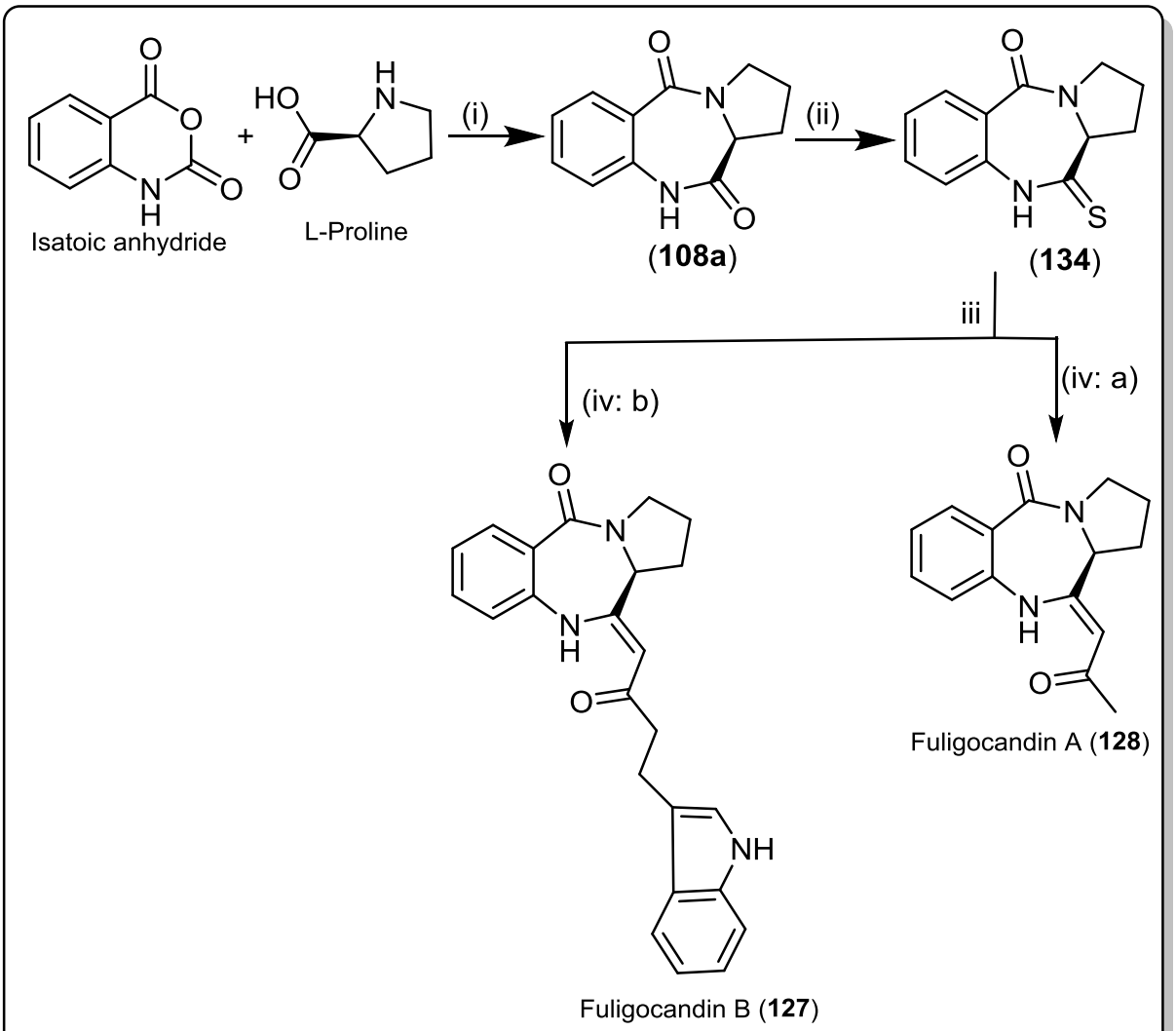
The synthesis of fuligocandins A and B has been reported, as shown in Schemes 1.31 and 1.32. Thus, 1,3-dichloroacetone was reacted[143] with triphenylphosphine and the product intermediate phosphonium salt was neutralized with a base to provide the desired ylidic product **(130)**. Indole-3-carbaldehyde was coupled with benzensulfonyl chloride to give **(132a)** and with 4-nitrobenzenesulfonyl chloride to give (**132b)**. The aldehydes (**132a and**

132b) were reacted with the phosphorus ylide via Wittig reaction to give indole derivatives **(133a and 133b),** as shown in Scheme 1.31**.**



Scheme 1.31

The synthesis continued as shown in Scheme 1.32. The reaction of isatoic anhydride with L-proline in DMSO gave the pyrrolo-1,4-benzodiazepine derivative **(108a)**. Compound **(108a)** was selectively thionated using the P_2S_5-Py_2 complex to provide the known monothione **(134)**. In the final reaction in this process, the monothione **(134)** was reacted with chloroacetone to give Fuligocandin A (**128**) via episulfide contraction. Fuligocandin B (**127**) was prepared by one–pot alkylation of the monothione with **133a** or **133b** and subsequent sulfur extrusion and deprotection.



Scheme 1.32: Synthesis of fuligocandins A and B. Reagents and condition: (i) L-proline, DMSO, 100 ^{o}C, 4h (95%); (ii) P_2S_5-Py_2. 60 ^{o}C, 4h, (75%); (iii) NaH, DMSO, rt, 30 min; (iv) a) chloroacetone, rt, 40 min and $P(OMe)_3$, DABCO, 100 ^{o}C, 24 h, (60%); (b) **133a/133b**, rt, 40 min and $P(OMe)_3$, DABCO, 100 ^{o}C, 30 h, 20%.

In this final key step using sulfur extrusion, there is an episulfide contraction reaction driven by alkylation. The process begins by alkylation of thioamide (A) (Figure 1.14) with the enolizable halocarbonyl compound (B). Enolisation followed by electrocyclic closure of the enolate thiocarbonyl ylide of (C) gave the episulfide, which was converted to vinylogous amide (E), after desulfurisation with trimethyl phosphite.[143]

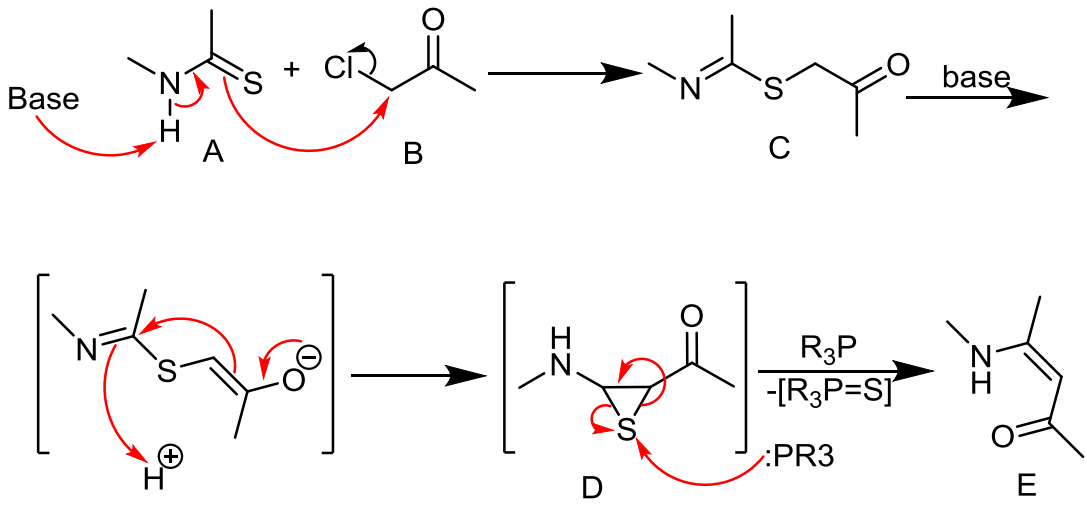


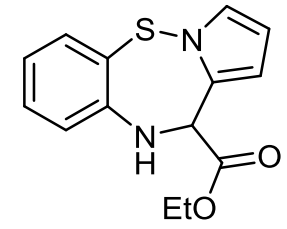
Figure 1.14: General mechanism for the Episulfide contraction via alkylative precoupling

1.5. Benzothiadiazepines.

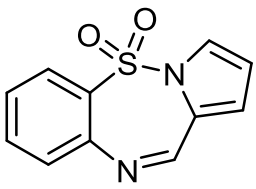
1.5.1. An introduction to benzothiadiazepines.

Sultams of the benzothiadiazepines type are a key target in this thesis. The sultam moiety is the backbone of many heterocyclic compounds of pharmaceutical and synthetic importance.[144-146] The sultam derivatives display potent activities such as antiblastic, apoptotic, antitumor and antihypertensive activities,[147-151] and sulfonamides are well known in medicinal chemistry in general. This made us look at sulfonamide analogues of the pyrrolobenzodiazepines as potential biologically active molecules, and a brief introduction follows.

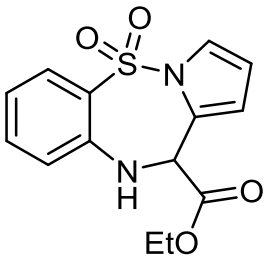
Pyrrolo[1,2,5]benzothiadiazepine **(140)** was prepared by Artico as a non-nucleoside reverse transcriptase inhibitor, but did not display appreciable activity against HIV-1. Compound **(141)**, however, was a useful inhibitor of reverse transcriptase.[152-154] The same research group have reported that compounds **(142)** and **(143)** have shown activity that is of interest in the potential treatment of chronic myelogenous leukemia.[155,156]



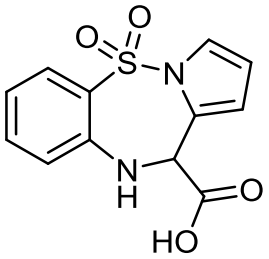
Pyrrolo-[1,2,5]benzothiadiazepine **(140)**



(**141**)



(**142**)

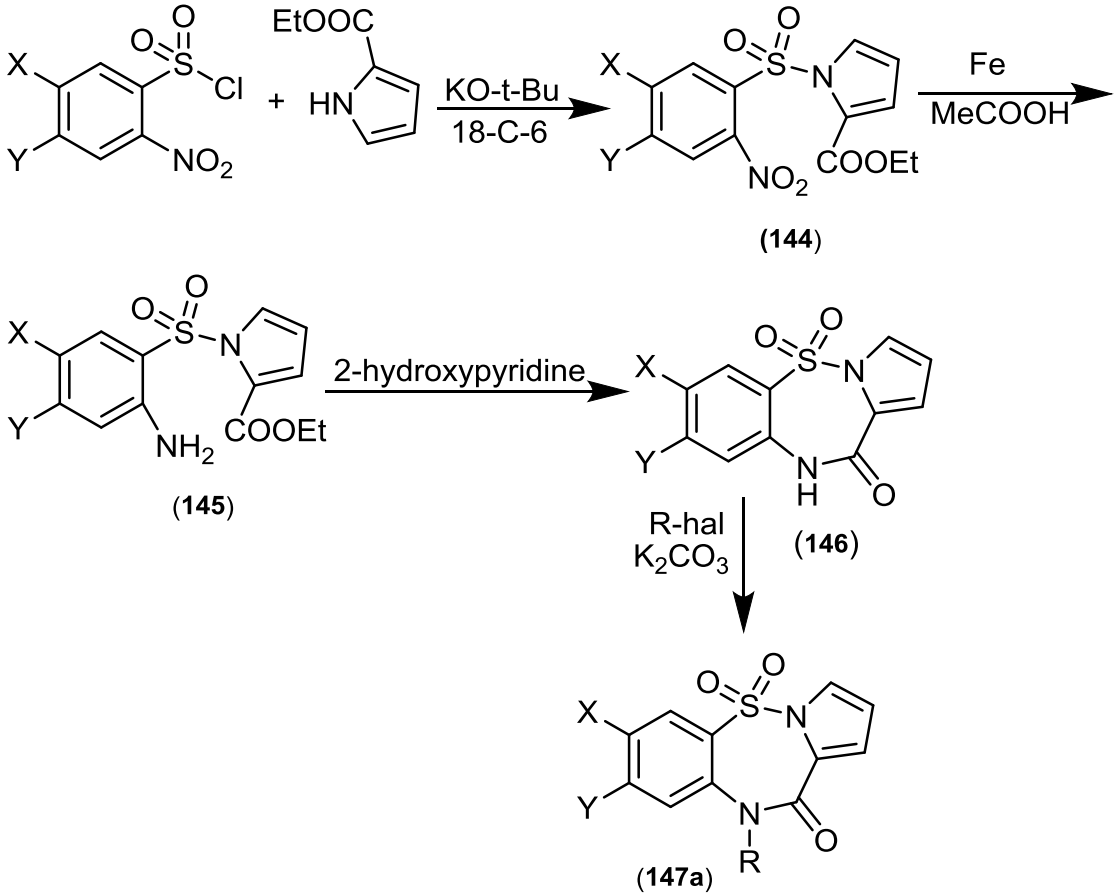


(**143**)

Figure 1.15: Structure of Pyrrolo-[1,2,5]benzothiadiazepine derivatives

Some typical published routes to these PBD thia analogues will now be reviewed as they are of interest in this thesis. For example, precursor **(144)** was obtained by reacting an aryl sulfonyl chloride with a pyrrolo ester analogue. Reduction of the nitro ester **(144)** with iron in

acetic acid gave the corresponding amino ester **(145)**. Compound **(146)** was synthesized by intramolecular cyclisation of the amino ester in the presence of 2-hydroxypyridine as a bifunctional catalyst. Alkylation of compound **(146)** in the presence of potassium carbonate[152] (shown in Scheme 1.33) gave a wide range of pyrrolobenzothiadiazepines **(147a).**

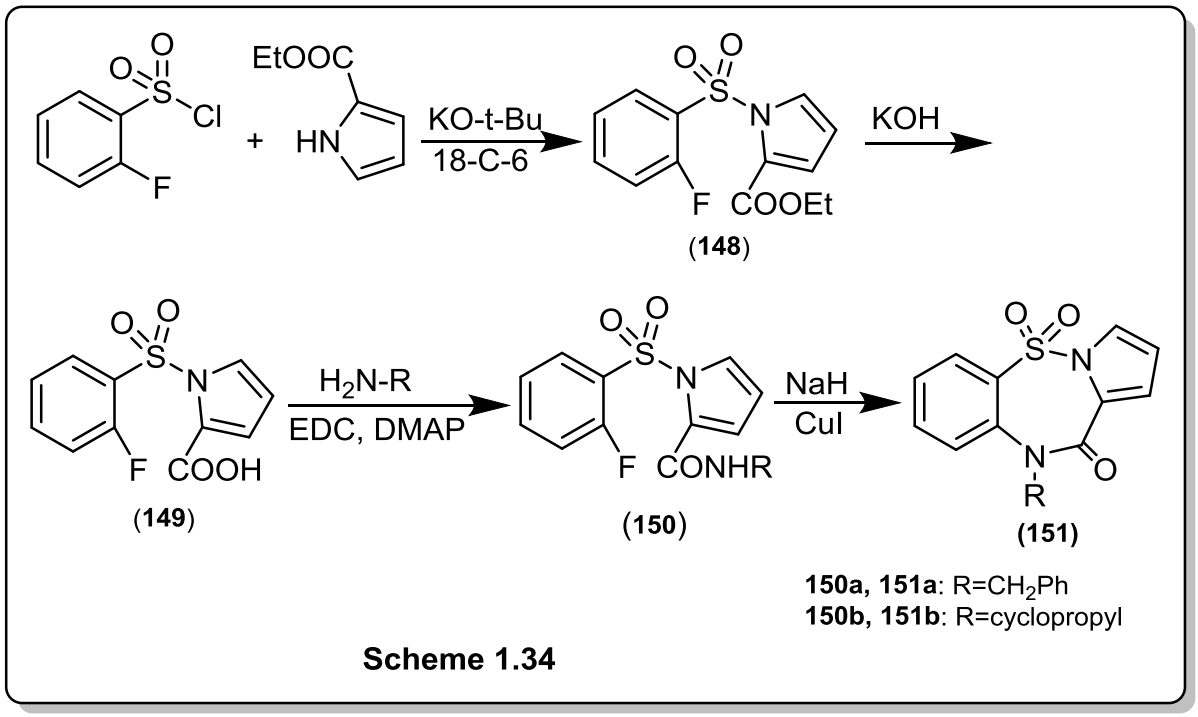


R= Me, Et, i-Pr, n-Bu, i-Bu, 2-propenyl, 2-butenyl, 3-Me-2-butenyl, CH_2COOMe, CH_2COOEt, CH_2COOBz, CH_2OMe, CH_2Ph.
X= Y= H, or X=H, Y= Cl, or X= Cl, Y=H

Scheme 1.33

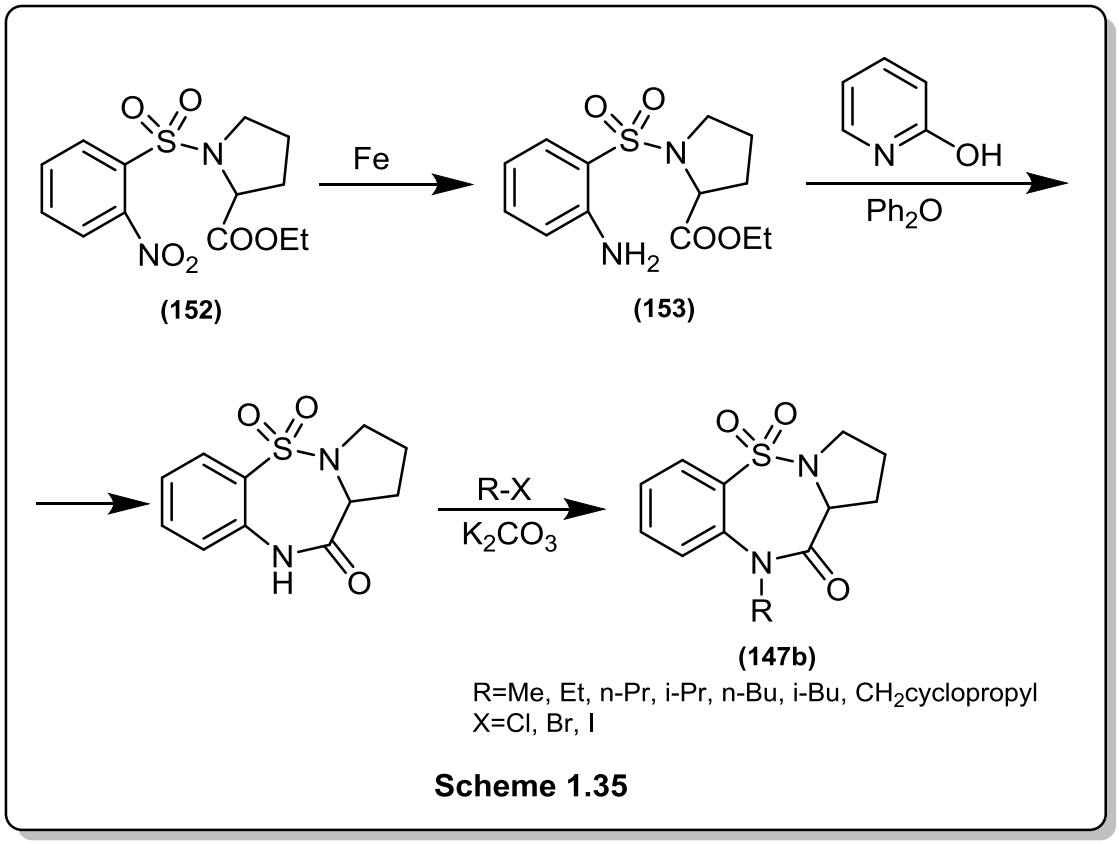
The benzyl and cyclopropyl analogues **(151)** (Scheme 1.34) were obtained by intramolecular[152] cyclization of the 1-(2-fluorobenzene-1-sulfonyl)-1H-pyrrole-2-(N-cyclopropyl)carboxyamide **(150)** in the presence of sodium hydride (NaH) and cuprous iodide. The amide compound **(150)** was prepared by treating the acid **(149)** with cyclopropylamine in the presence of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (DMAP). Compound **(149)** in turn was prepared by alkaline hydrolysis of ester **(148)**, which was prepared by reacting 2-

fluorobenzenesulfonyl chloride with 2-ethoxycarbonyl-1H-pyrrole (as shown in Scheme 1.34).



Scheme 1.34

In another route, pyrrolidino derivatives **(147b)** were synthesized[152] from 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl) pyrrolidine **(152),** which was reduced to the amino ester **(153)** with iron powder in glacial acetic acid. Intramolecular cyclization of compound **(153)** was done by heating in the presence of 2-hydroxypyridine. Alkylation with alkyl halides in the presence of potassium carbonate gave the saturated pyrrolidino derivatives **(147b),** as shown in Scheme 1.35.



Scheme 1.35

1.5.2. Tetracyclic (PBDs) and (PBTDs).

Another of the aims of this thesis is to make pyrrolobenzothiadiazepines with additional fused rings[120,157]. The analogous pyrrolobenzodiazepines have attracted interest in the literature as potential antitumour compounds (see above), neurological agents and protease inhibitors.[137,158,159]

The specific targets in this thesis are those formed by intramolecular azide 1,3-cycloaddition reaction, as shown in the Figure 1.16, and this work builds upon previous work in our research group.[160,161]

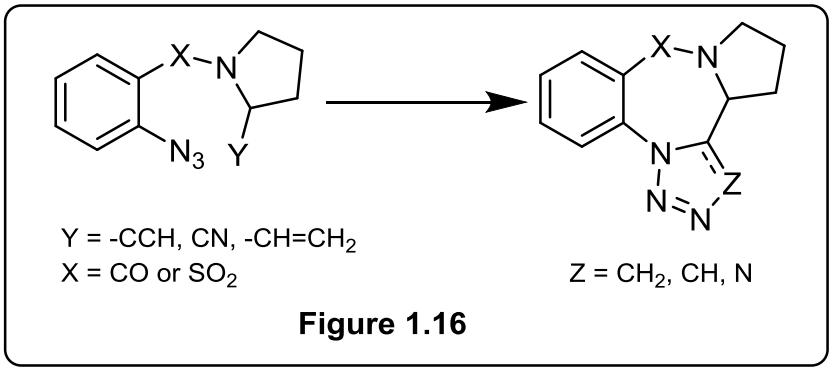
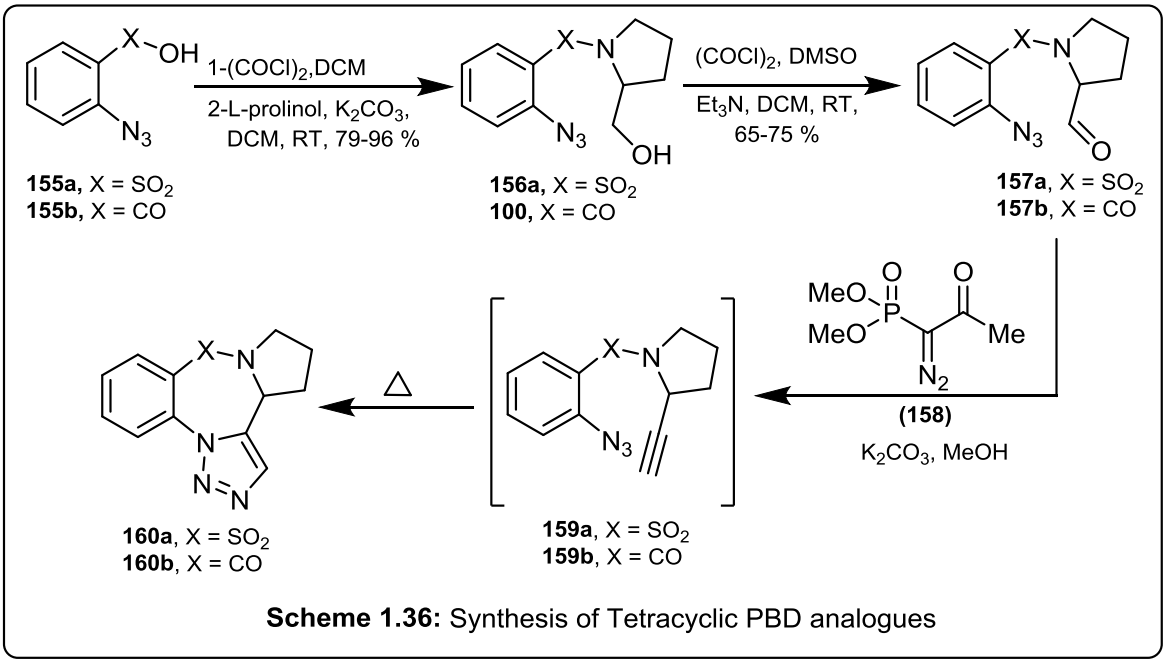


Figure 1.16

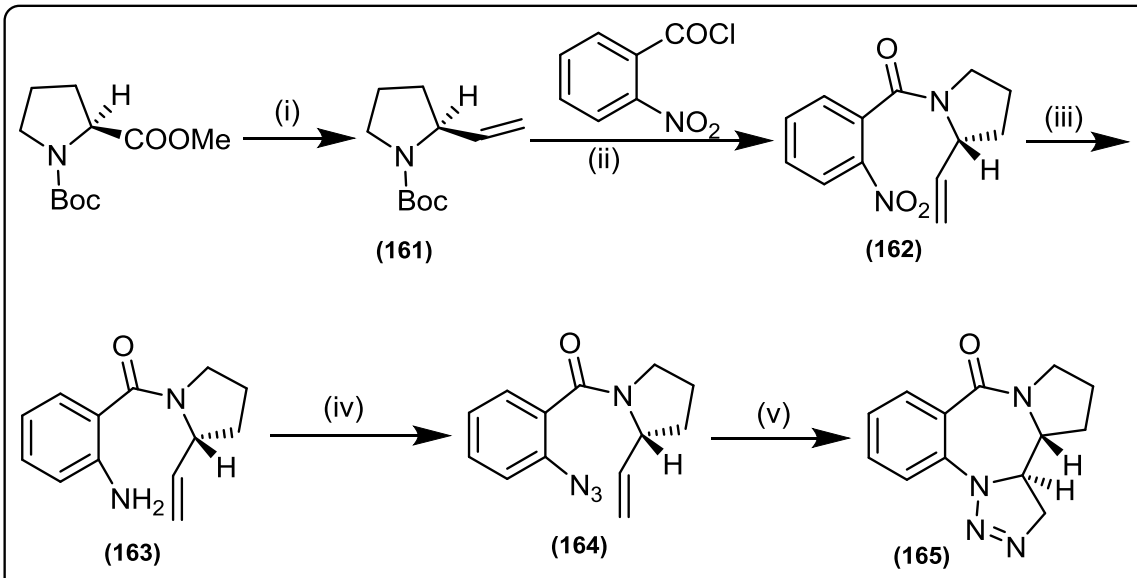
In the group previously[162], 2-azidobenzenesulfonic acid or 2-azidobenzoic acid was converted to the corresponding acid chloride (as shown in Scheme 1.36) and coupled with L-prolinol to give the alcohols **(156a)** and **(100)** in yields of 96 and 79 %, respectively. The alcohols were oxidised into the aldehydes **(157a, 157b)** by Swern oxidation or Dess-Martin periodinane. The conversion of the aldehydes **(157a and 157b)** into the alkynes **(159a)** and **(159b)** was achieved using the Bestmann-Ohira reagent **(158)**. The alkynes **(159a and 159b)** could not be isolated, as they underwent cyclisation to form the triazoles **(160a)** and **(160b)**[163], as shown in Scheme 1.36.



Scheme 1.36: Synthesis of Tetracyclic PBD analogues

It is relevant to note that Broginni[164,165] showed that the (S)-N-Boc protected proline derivative was reduced in the presence of DIBAL-H to give alkene (**161**) which was coupled to 2-nitrobenzoyl chloride to give the nitro compound (**162**). Reduction of the nitro (**162**) with iron powder in acetic acid gave the corresponding amino compound (**163**). Diazotisation with sodium nitrite and HCl followed by reaction with sodium azide afforded compound (**164**). The azide (**164**) gave stable triazoline (**165**) in carbon tetrachloride or toluene at 80 ^{o}C, as per Scheme 1.37.

One of the aims of this thesis (see figure 1.16 and also Chapter 3) was to attempt the synthesis of the nitrile systems (Y = CN) and to explore the use of azide-nitrile reactions to make tetrazolo-fuzed systems.



Scheme 1.37: Reagents and conditions: (i) a. DIBAL-H, dry toluene, N_2 atmosphere, -60 ^oC; b. $Ph_3PMe^+ I^-$, t-BuOK, dry THF, N_2 atmosphere, 0 ^oC; c. CF_3COOH, N_2 atmosphere, 1h, 52 %,; (ii) K_2CO_3, dry toluene, reflux, 4h, 60 %; (iii) Fe, AcOH, EtOH, reflux, 2h, 80 %; (iv) a. $NaNO_2$, HCl, Et_2O, 0 ^oC, 30 m; b. NaN_3, rt, 40 m, 75 %; (v) CCl_4, reflux, 5h, 68 %.

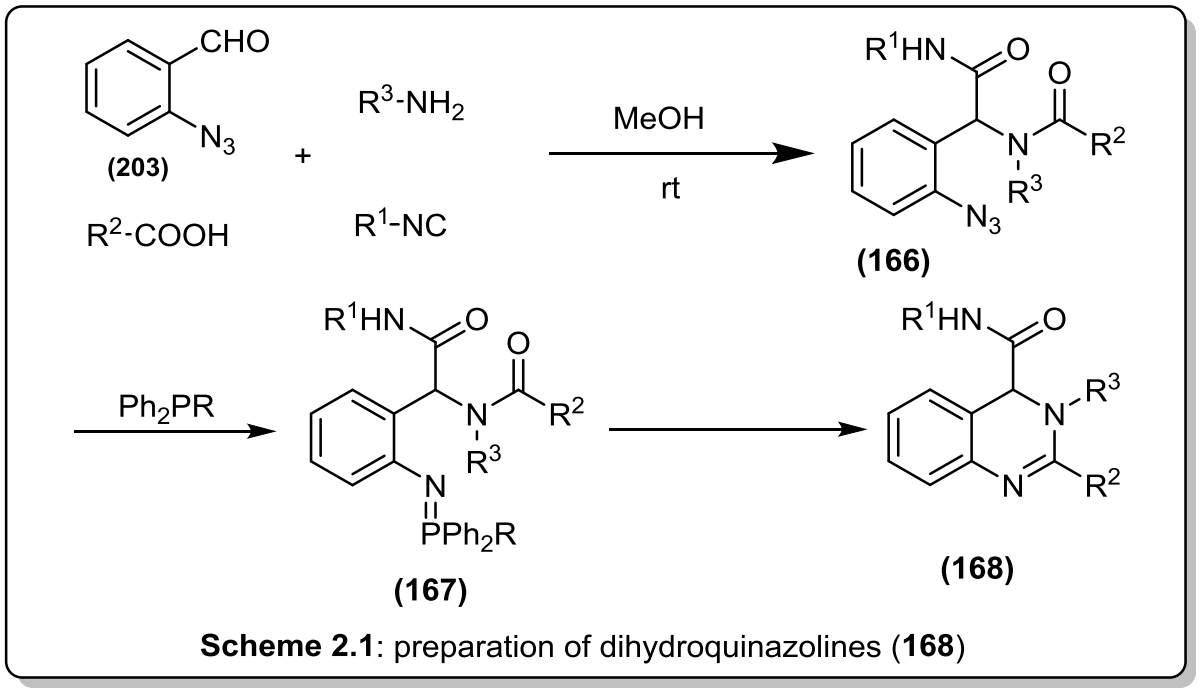
Chapter 2:

2. Results and Discussion: Multicomponent reactions (MCRs).

2.1. Introduction.

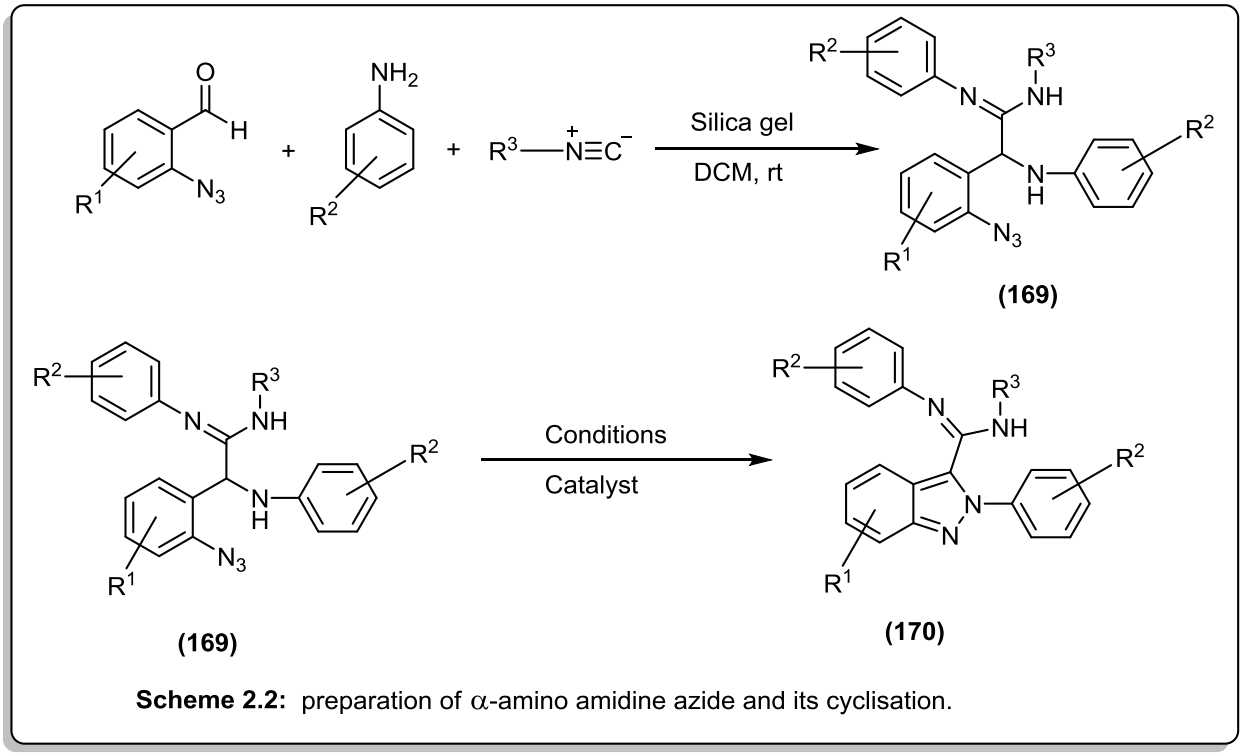
Multicomponent reactions (MCRs) are chemical methods in which three or more starting materials are converted in one chemical step to form a specific product.[166] Nowadays MCRs are considered as a powerful tool for making target molecules of biological relevance efficiently, especially in drug discovery[167]. We decided to use o-azidobenzaldehyde **(203)** as a starting material in multicomponent reactions. The azide product was available from 2-amino benzyl alcohol.

The azide groups offers extra reactivity, as azides have a lot of chemistry open to them. We looked to use 2-azidobenzaldehyde in MCR processes involving nitriles in the hope that, as the group had seen previously[168], some interesting post-MCR azide-nitrile reactions would occur. The use of o-azidobenzaldehyde in multicomponent reactions has been explored by Ying Zhong, where reaction of o-azidobenzaldehyde, amine, isocyanide and carboxylic acid give the azide product (**166**) through the Ugi-four component condensation (Ugi-4CC).[169] Staudinger reaction and intramolecular aza-Wittig reaction gave 3,4-dihydroquinazolines (**168**) via diphenylmethyliminophosphorane (**167**) (Scheme 2.1).



Scheme 2.1: preparation of dihydroquinazolines (**168**)

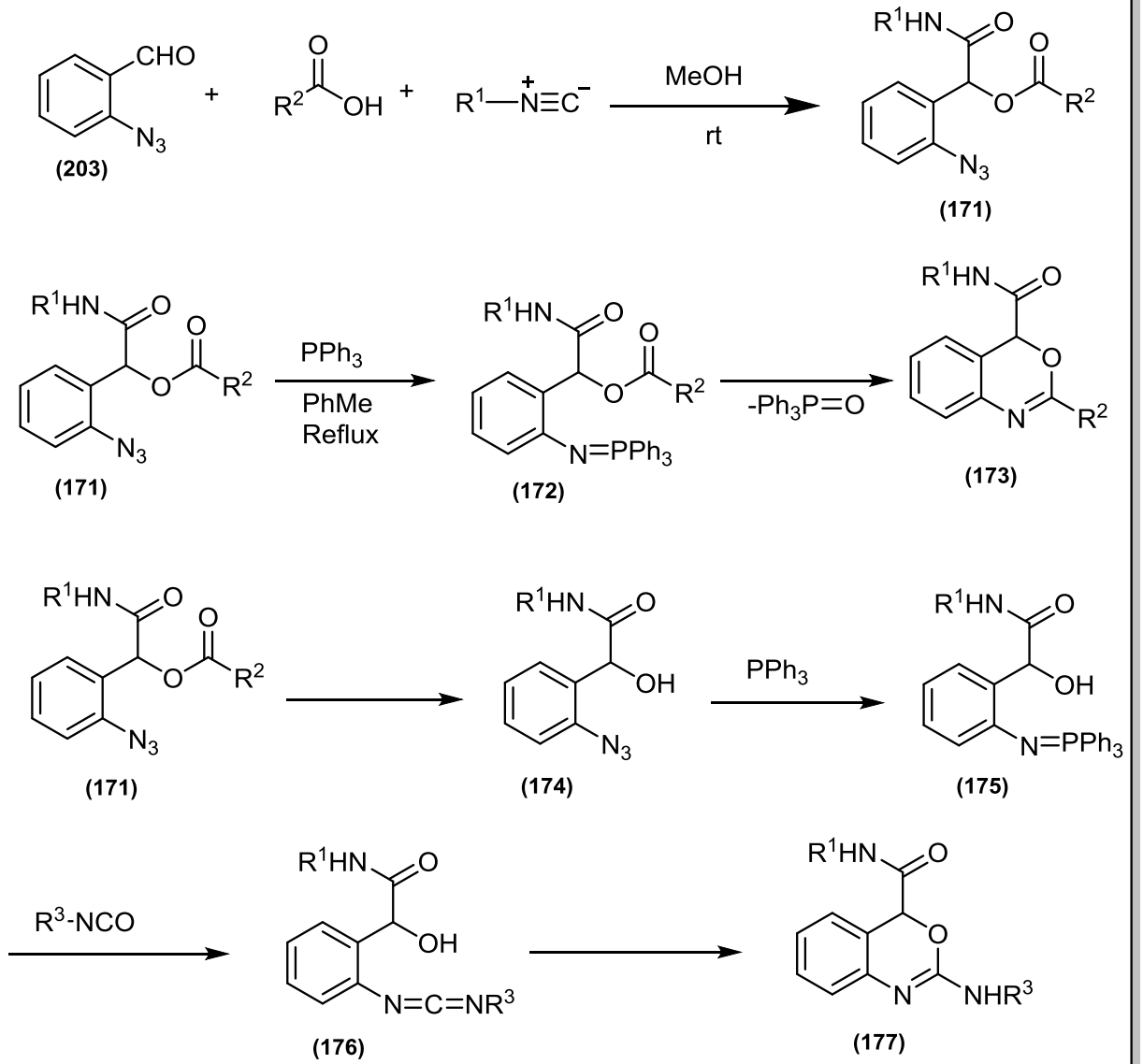
The same group used 2-azidobenzaldehyde in a Ugi-three component reaction (U-3CR) with aniline, tert-butyl isocyanide and silica gel to make α-amino amidine azides (**169**). The azides could undergo an intramolecular cyclization with the secondary amine in which the α-amino amidine azide was converted into an amidino substituted indazole (**170**) (Scheme 2.2).[170]



Scheme 2.2: preparation of α-amino amidine azide and its cyclisation.

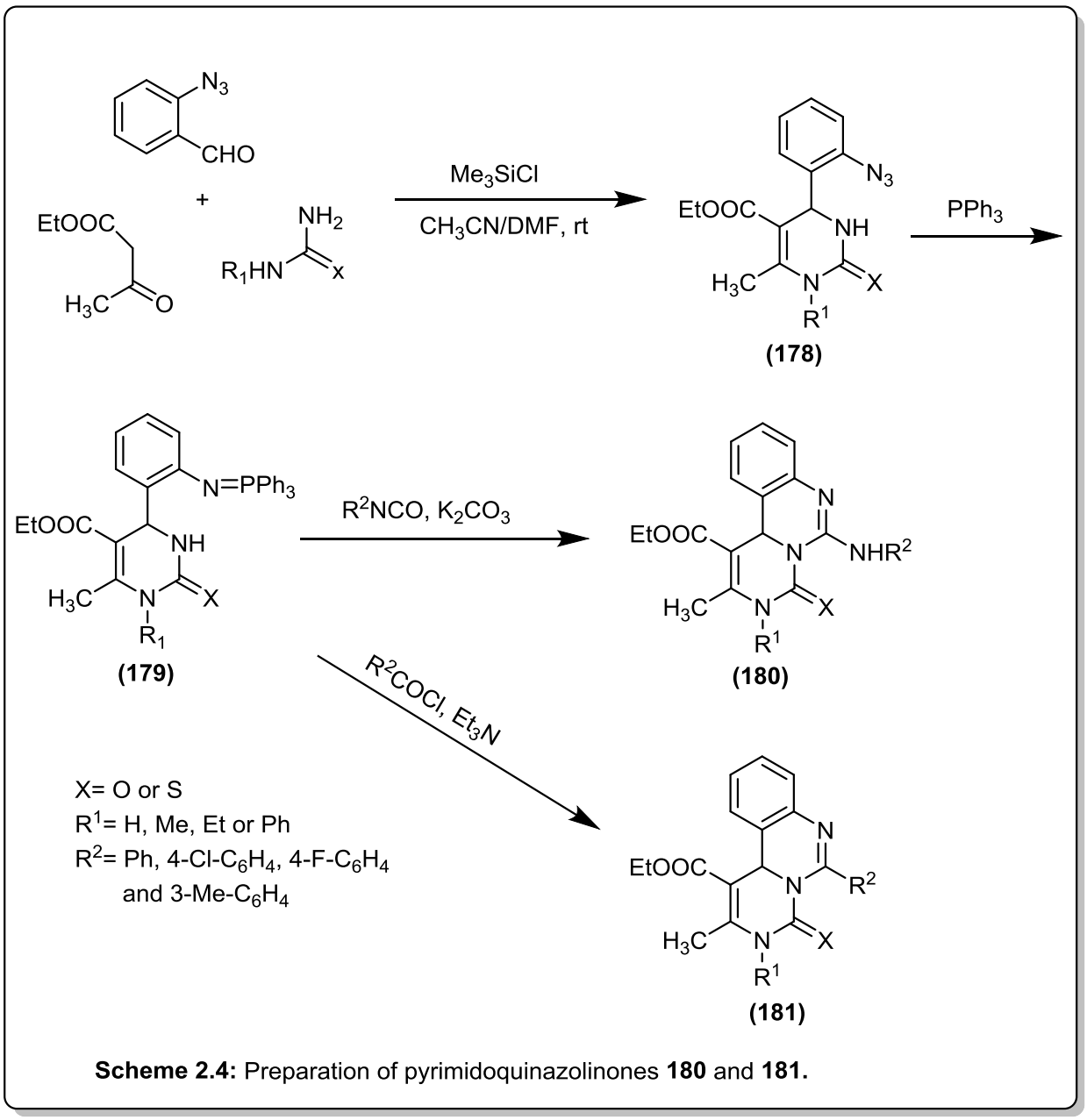
2-Azidobenzaldehyde has also been used in the Passerini reaction[171] with isocyanides and carboxylic acids by the same group to make α-acyloxy-carboxamide azides (**171**) as shown in Scheme 2.3. Using the Staudinger and intermolecular aza-Wittig reaction, the azides were reacted with triphenylphosphine to give 4H-1,3-benzoxazines (**173**) (Scheme 2.3).[171]

Again using the Staudinger reaction, the de-acetylated product (**174**) was reacted with triphenyl phosphine to give iminophosphorane (**175**). The iminophosphorane **(175**) was reacted with isocyanate to give the diimide (**176**) which cyclised to give 2-amino-4-aminocarbonyl substituted 4H-3,1-benzoxazines (**177**) (also shown in Scheme 2.3).



Scheme 2.3: Preparation of benzoxazines **167**and **171.**

2-Azidobenzaldehyde has been also used in the Biginelli-three component reaction with ethyl accetoacetate and urea (or thiourea) in the presence of trimethylsilyl chloride as catalyst to make dihydropyrimidinone azide (**178**) (Scheme 2.4) which was reacted with triphenylphosphine to give iminophosphorane (**179**) via Staudinger reaction which was then treated with aromatic isocyanates or acid chlorides in the presence of K_2CO_3 or Et_3N to synthesise pyrimido[1,6-*c*]quinazolin-4-ones (**180** and **181**), via aza-Wittig reaction and cyclisation.[172]



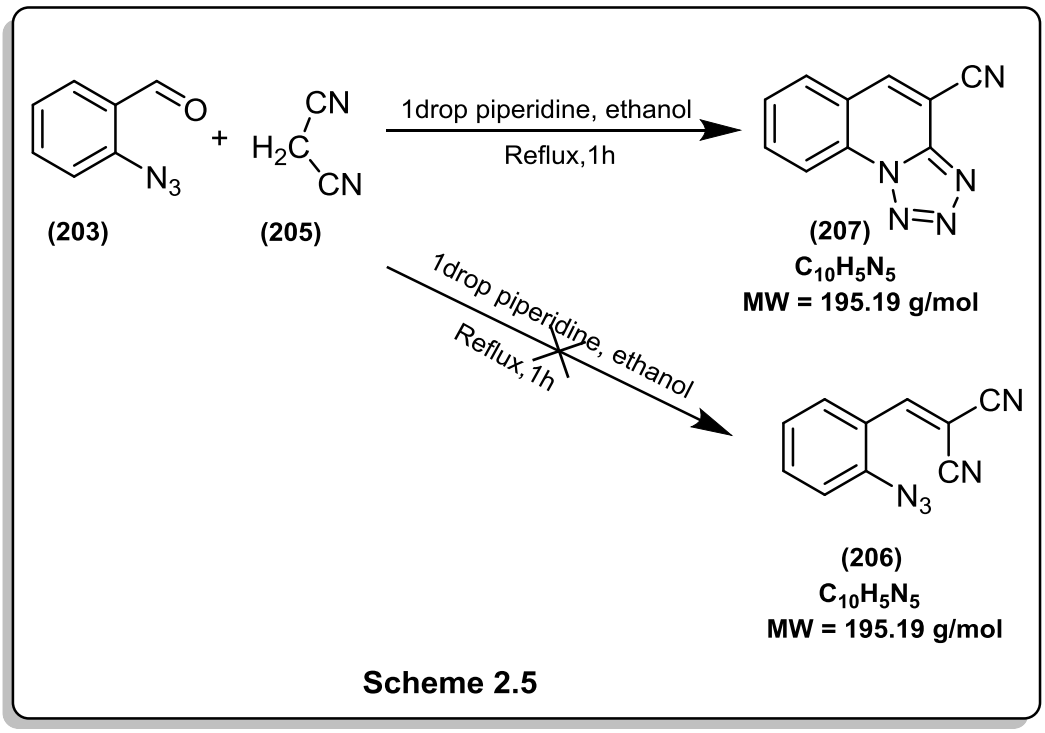
Scheme 2.4: Preparation of pyrimidoquinazolinones **180** and **181.**

In our work, we selected known MCRs incorporating a nitrile and benzaldehyde and looked to replace benzaldehyde with o-azidobenzaldehyde to look, for the first time, at post-MCR azide

to nitrile cycloaddition. Some of the reactions investigated with o-azidobenzaldehyde gave the desired MCR and a new product with an azide and a nitrile but the azide did not react with the nitrile. Some of the attempted reactions resulted in the MCR stopping after one reaction between just two of the components. These processes are discussed in detail below, as either 3 or 4 component MCRs.

2.2. The use of three component MCRs

2.2.1. Knoevenagel Condensation of Malononitrile with o-Azidobenzaldehyde.



(203) **(205)** **(207)** $C_{10}H_5N_5$ **MW = 195.19 g/mol**

(206) $C_{10}H_5N_5$ **MW = 195.19 g/mol**

Scheme 2.5

Compound (**206**) was needed as a precursor for another MCR reaction (see next section).

2-Azidobenzaldehyde (**203**) was condensed with malononitrile (**205**) in the presence of piperidine as an organic base. The mixture was heated at reflux for 1 hour. Instead of the desired product (**206**), the tetrazoloquinoline (**207**) was isolated in 68 % yield.

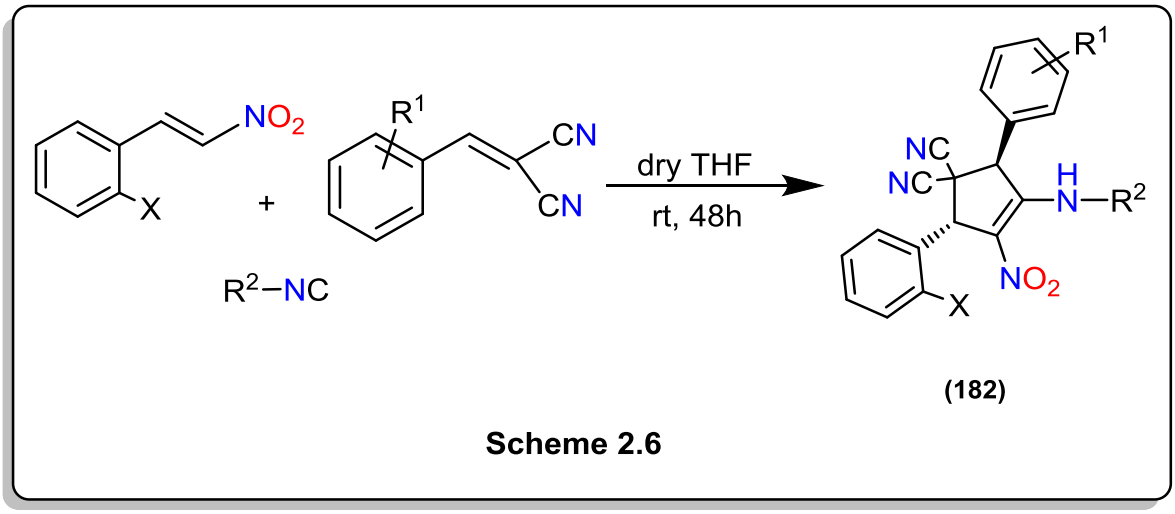
The structure of product (**207**) was confirmed by IR spectroscopy, and by its ^{1}H NMR spectrum, ^{13}C NMR spectrum, mass spectrometry and melting point.

The ^{1}H NMR spectrum indicated the absence of the aldehyde (CHO) proton at 10.37 ppm with the appearance of the alkenyl (C**H**=C-CN) proton at 8.08 ppm.

The ^{13}C NMR spectrum showed the disappearance of the aldehyde carbon signal at 188.63 ppm with the presence of the nitrile (CN) carbon signal at 114.04 ppm and the alkenyl (**C**H=C-CN) signal at 145.73 ppm. It was further determined that the compound contained a CN group from the peak at υ_{max} 2200.0 cm^{-1} while IR also showed the absence of the azide absorption peak at υ_{max} 2127.0 cm^{-1}, in addition to the disappearance of the aldehyde (CHO) group at υ_{max} 1735.0 cm^{-1}. The correct measured mass of 196.0627 for the ion [M+H^{+}] gave further evidence for the structure. This is a known molecule, although it is formed by a different route in the literature.[173]

2.2.2. 3-(2-Morpholinoethylamino)-4-nitro-2,5-diphenylcyclopent-3-ene-1,1-dicarbonitrile derivatives.

This MCR (Scheme 2.6) was based on a previous reaction by Knight[174] who had shown the reaction to work with β-nitrostyrene (X=H)[175], 2-morpholinoethyl isocyanide and a range of easily synthesised benzylidenemalononitriles[176,177].



Scheme 2.6

182	**X**	**R^1**	**R^2**	**Yield**	**Notes**
1	H	H	Cyclohexyl	0%	No reaction
2	H	H	CH_2CH_2-morpholino	45%	Successful
3	H	o-N_3	CH_2CH_2-morpholino	30%	o-N_3-pre-cyclised
4	H	p-Cl	CH_2CH_2-morpholino	42%	Successful
5	N_3	H	CH_2CH_2-morpholino	89%	Successful
6	N_3	p-Cl	CH_2CH_2-morpholino	78%	Successful
7	N_3	p-NO_2	CH_2CH_2-morpholino	67%	Successful
8	N_3	p-OCH_3	CH_2CH_2-morpholino	20%	Successful

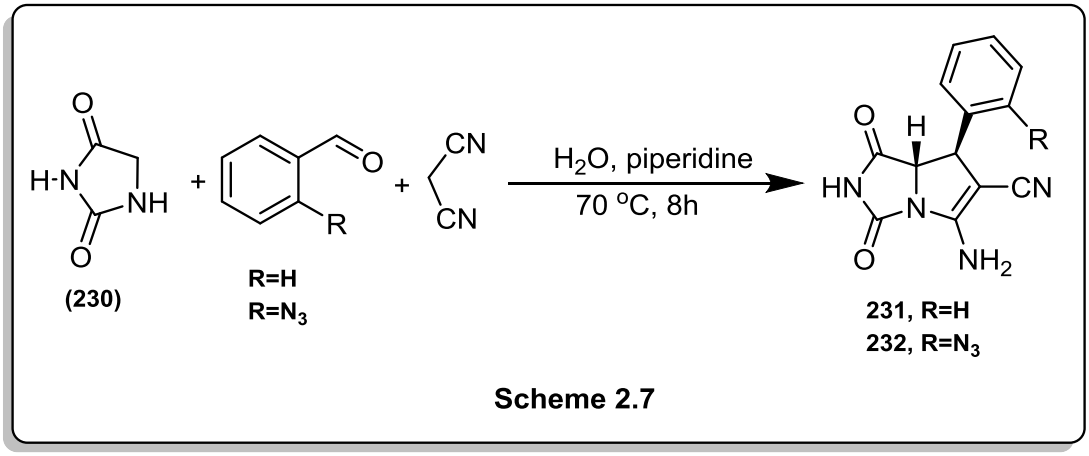
Table 2.1: Synthesis of cyclopentene Derivative (**182**)

We repeated the Knight[174] reaction successfully with the morpholino system (entries 2 and 4 in Table 2.1) and then attempted it with the o-azido derivative of β-nitrostyrene in the hope that the product (**182**, X=N_3)[162] could undergo a post-MCR azide to nitrile 1,3-dipolar cycloaddition and hence form some novel highly functionalied tetrazolo systems. The 2-azido nitrostyrene was easily made from 2-azidobenzaldehyde and nitromethane as described previously[161]. Arylidene-malononitriles came from simple Knoevenagel condensation[176,177].

The formation of the desired (X = N_3) 3-component MCR products was successfully achieved (see Table 2.1 entries 5-8) but none of the azido products (**182**) could be made to undergo tetrazole formation. When the azido group was on the malononitrile component (R^1=o-N_3) the system cyclised to give compound **(207)** before any MCR could occur as discussed above (Scheme 2.5).

IR spectra, ^{1}H NMR spectra, ^{13}C NMR spectra, mass spectrometry and physical characteristics identified the new products **(182**, X = N_3**)**. In the IR-spectra, azido absorptions showed at around 2123.0-2128.5 cm^{-1} and strong nitro absorptions arose at around 1626.1-1638.9 cm^{-1}, in addition to cyano absorptions at around 2190-2251.5 cm^{-1}, as well as the absorption band at 3300 cm^{-1} indicating the formation of the new NH group in the product. In the ^{1}H-NMR spectra, the proton on the NH group appeared in the region of 9.72-9.86 ppm as a singlet and the protons of the cyclopentene ring appeared at around 4.76-5.76 ppm. As for ^{13}C-NMR spectra, the most deshielded absorptions were observed for cyclopentene ring alkene carbons at around 156.58-158.13 ppm. The compounds synthesised previously (entries 2 and 4 in Table 2.1) had data identical to that reported by Knight[174] and other compounds gave fully consistent data (see experimental).

2.2.3. 5-Amino-2,3,7,7a-tetrahydro-1,3-dioxo-7-phenyl-1*H*-pyrrolo[1,2-e]imidazole-6-carbonitrile derivatives.



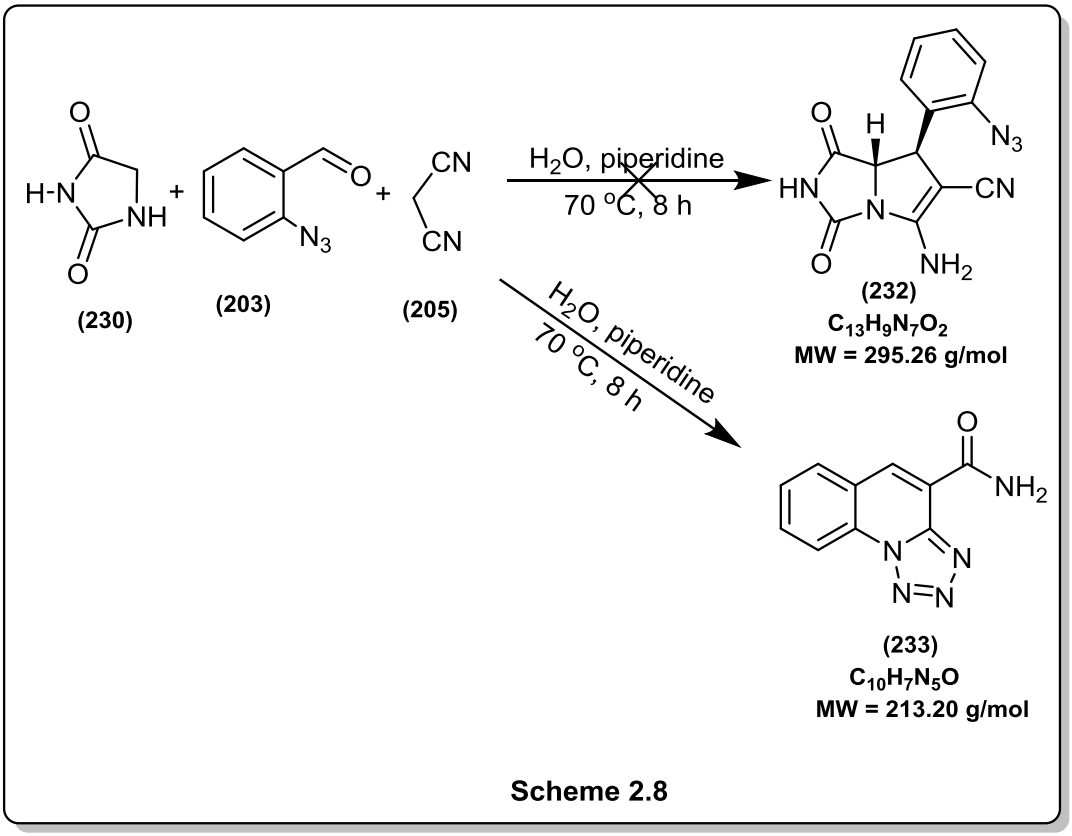
Scheme 2.7

A. R=H (literature reaction)

Reaction of hydantoin, benzaldehyde and malononitrile in water gave a product which was isolated from the reaction mixture by filtration and washed with PE/EtOAc (60 %). The structure of the product (**231, R=H**) was confirmed by IR, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, mass spectrometry and physical characteristics. With benzaldehyde (R=H) this is a known literature 3-component MCR[178], and data was fully consistent with that reported in the literature[178].

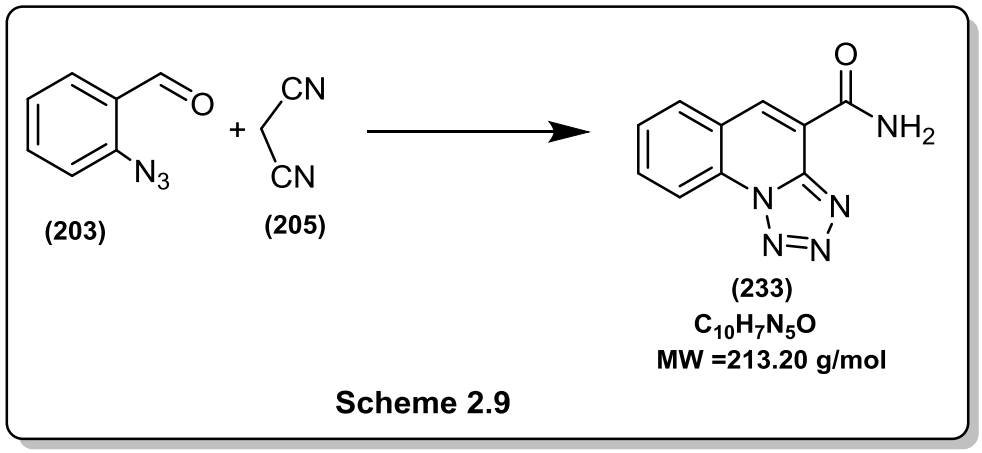
B. R=N_3 (new reaction)

Reaction of hydantoin, 2-azidobenzaldehyde and malononitrile in water under the same conditions gave a new product. After completion of the reaction which was monitored by TLC at regular intervals, a different product was identified to that predicted from the model reaction with benzaldehyde. Instead of the expected poly-substituted cyclopentene (**232**), the tricyclic tetrazole (**233**) was isolated.



Scheme 2.8

In this case, it is assumed that reaction of *o*-azidobenzaldehyde and malononitrile formed a product before any reaction involving the hydantoin could occur. Compound **(233**) was formed in 34 % yield.



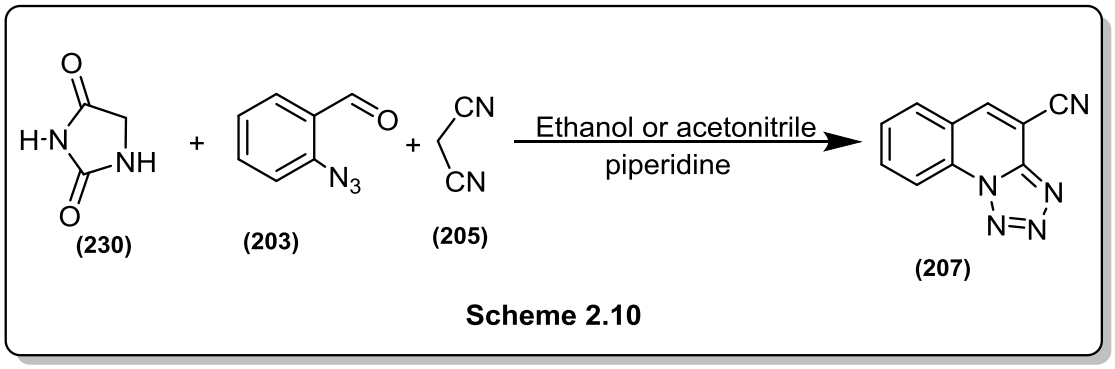
Scheme 2.9

The structure of compound (**233**) was deduced from its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry. IR spectroscopy showed the presence of a peak at 1703.0 cm^{-1} (C=O) and an amide NH_2 at 3385.4 cm^{-1}. IR confirmed that both the azide and the nitrile were not present. ^{1}HNMR spectroscopy also confirmed the structure of the product (**233**). A broad singlet at 8.33-8.49 ppm showed the 2 protons of the NH_2 group and a

multiplet at 8.67-7.89 ppm appeared for the 4 protons of the aryl group and at 8.96 ppm one proton confirmed the alkene CH group. ^{13}C NMR spectroscopy also confirmed the structure of the product (**233**) with the correct number of C, CH plus the carbonyl group at 162.44ppm. The structure of the product (**233**) was confirmed by mass spectrometry.

Compound (**233**) did not react with hydantoin (confirmed by a test reaction) and hence the reaction stopped at this point. The product forms due to condensation, 1,3-dipolar cycloaddition [to give compound **(207)** again] and then hydrolysis of the remaining nitrile under the aqueous reaction conditions.

It was thought that water as solvent had hydrolysed the nitrile to the amide. Thus, this reaction also was attempted with dry ethanol and acetonitrile as solvents. This was successful and gave the non-hydrolysed compound (**207**) this time in 76 % yield. The absence of water meant that hydrolysis did not occur, allowing the nitrile to be isolated. The data for compound (**207**) was identical to that in section 2.2.1, above.

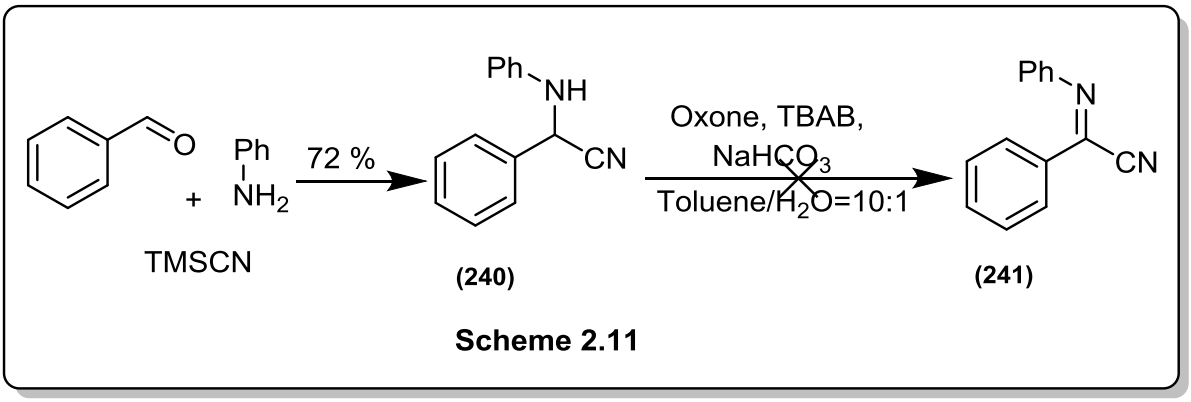


(230) (203) (205) (207)

Scheme 2.10

Reaction of 2-azidobenzaldehyde and malononitrile in water also gave the hydrolysed product (**233**), showing that the hydantoin is not required. The nitrile (**207**) underwent easy hydrolysis to give the amide (**233**).

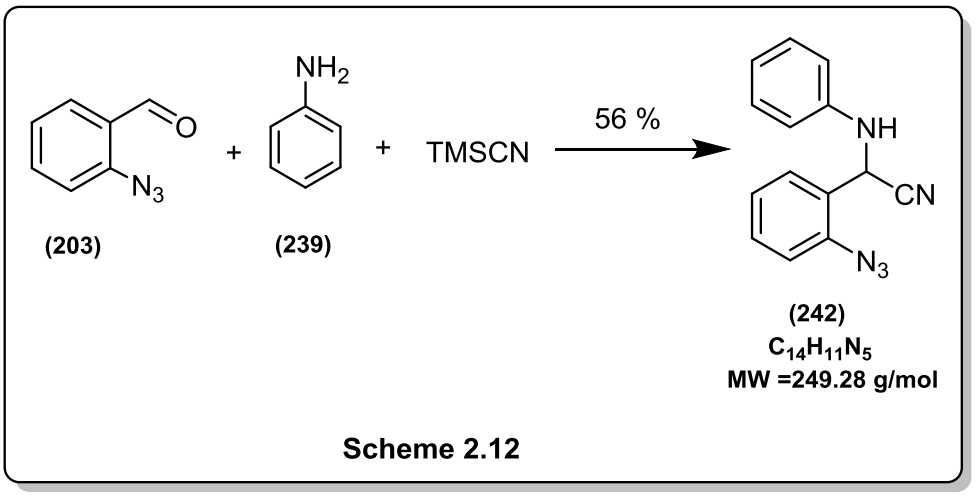
2.2.4. 2-Phenyl-2-(phenylamino)acetonitrile derivative.



Scheme 2.11

Three component reactions of benzaldehyde, amines and trimethylsilyl cyanide (TMSCN) in the biphasic system (toluene/H_2O = 10/1) tetrabutylammonium bromide (TBAB), sodium bicarbonate and Oxone was claimed in the literature to allow oxidation of the aminonitrile to the iminonitrile.[179] With aniline and benzaldehyde, however, we could only isolate the "Strecker" product-aminonitrile (**240**), a well-known product.[180]

When these conditions were applied to 2-azidobenzaldehyde and aniline (Scheme 2.12), we also isolated the "non-oxidised" aminonitrile (**242**).

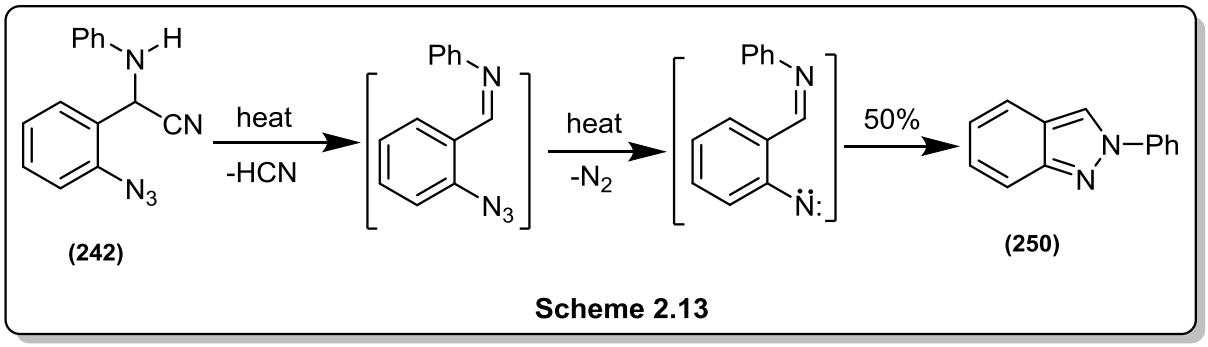


Scheme 2.12

In the IR spectrum, the nitrile group was seen at 2190.4 the azido group absorption band appeared at 2121.9 cm^{-1}. The structure of the product (**242**) was confirmed by its ^{1}H NMR spectrum, in which the NH group showed at 8.70 ppm and the CH was seen at 4.06 ppm. In the ^{13}C NMR spectrum, the same non-aromatic CH group was seen at 45.99 ppm. The

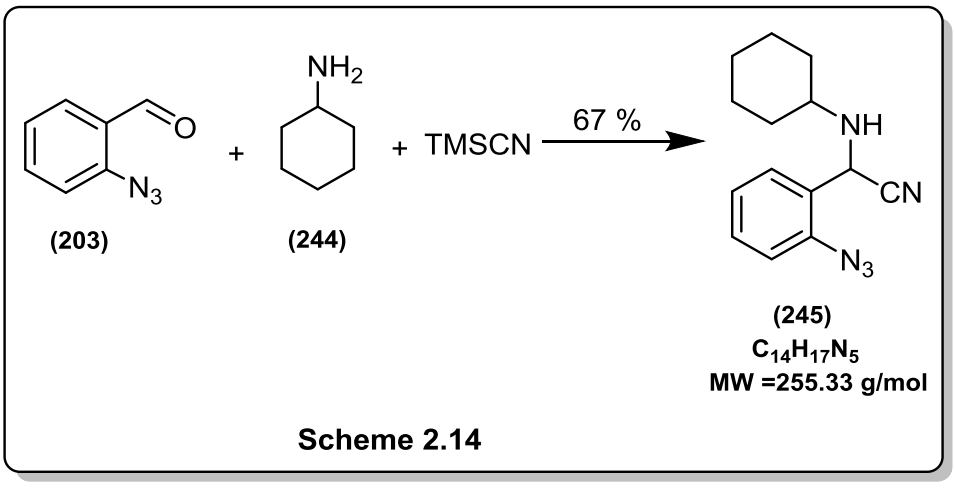
structure of the product was confirmed by mass spectrometry, in which the molecular mass of the compound was equal to 250.1092 g/mol ($M+H^+$).

When heated in toluene for 4 days at reflux, compound (**242**) was stable, but in xylene at reflux for 4 days, the compound unexpectedly gave the known[181] indazole (**250)** in 50 % yield. Similar indazoles, formed by azides reacting with imines, were also reported by Sagar[170] (see Scheme 2.2, above)

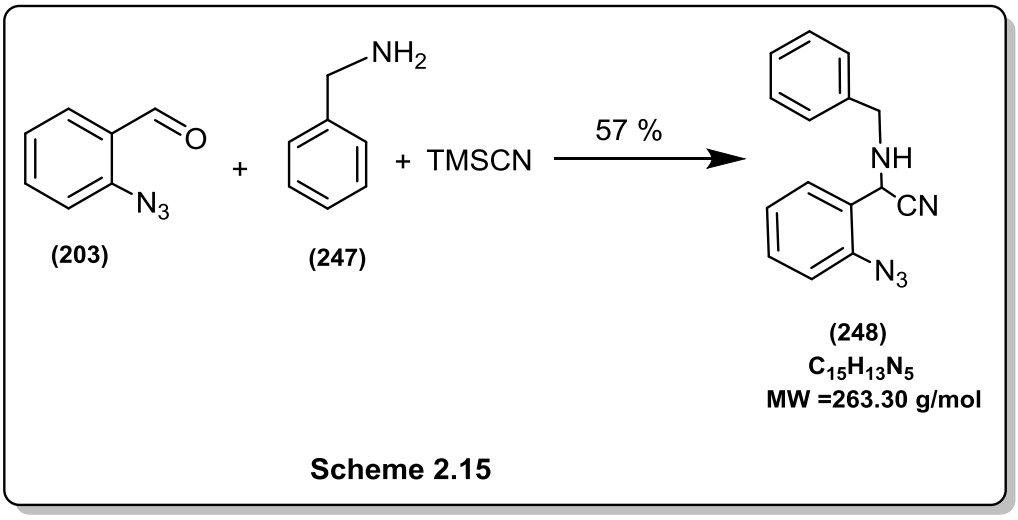


Scheme 2.13

As shown above in Scheme 2.13, this reaction might occur by loss of HCN, loss of N_2 and then nitrene formation and then nitrene insertion into the imine and to give compound (**250**)[181]. As this reaction looked to be interesting two other precursors were synthesised as shown below (Scheme 2.14 and Scheme 2.15):



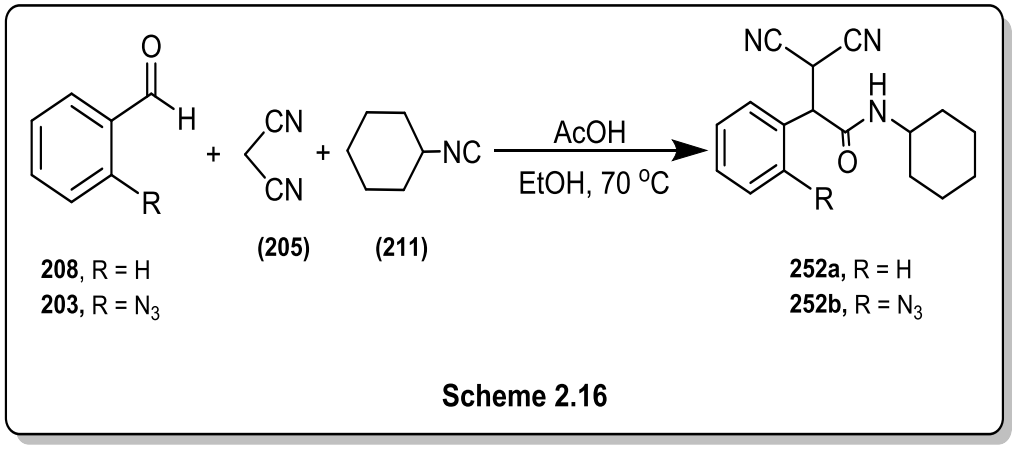
Scheme 2.14



Scheme 2.15

The structure of these products was confirmed by IR spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and mass spectrometry. The effects of heat on compounds (**248**) and (**245**) were investigated but neither of them formed an indazole or any other recognisable product.

2.2.5. 3,3-Dicyano-N-alkyl-2-arylpropanamide derivatives.



Scheme 2.16

The Ugi reaction of isocyanide, aldehyde, acetic acid, and malononitrile gave 3,3-dicyano-N-alkyl-2-arylpropanamide derivatives in good yield in ethanol as a solvent at 70^{o}C. Two carbon-carbon bonds and one amide group were formed by this reaction. In the literature[182], the role of the carboxylic acid in this reaction is to trap the nitrilium intermediate, and to activate the aldehyde and intermediate alkene toward nucleophilic attack as shown in Figure 2.1. The literature reaction (R=H) was repeated to make sure that the chemistry worked before

trying it with the azide (R=N_3). Compound (**252a**) was successfully synthesised in 71 % yield with data identical to that reported in the literature.[182]

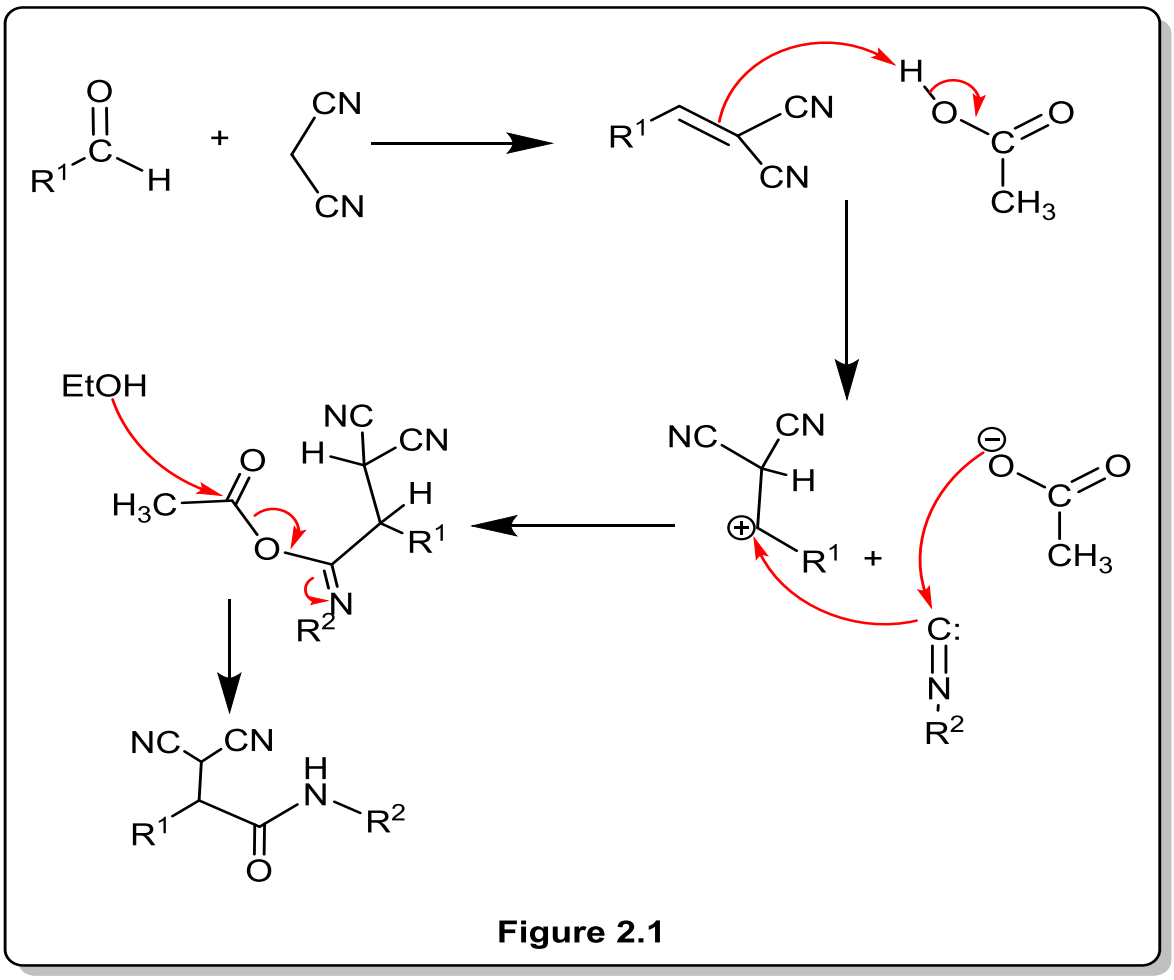
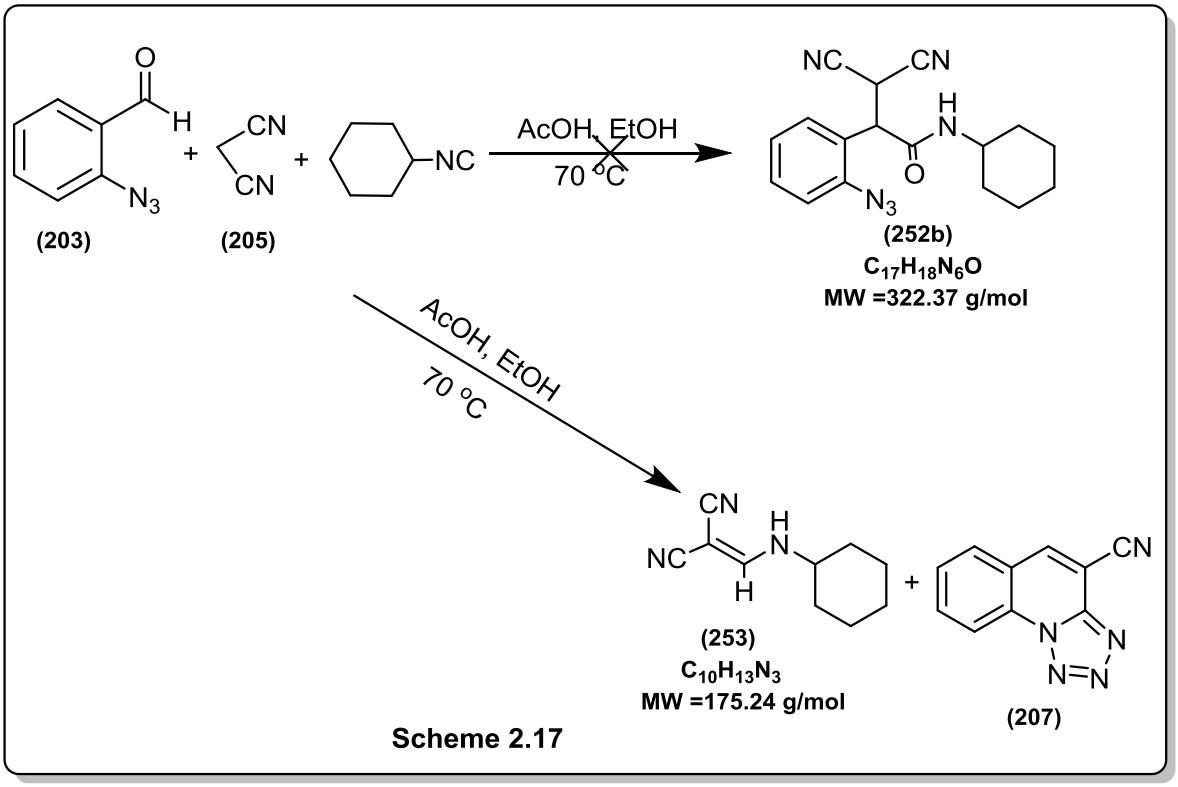


Figure 2.1

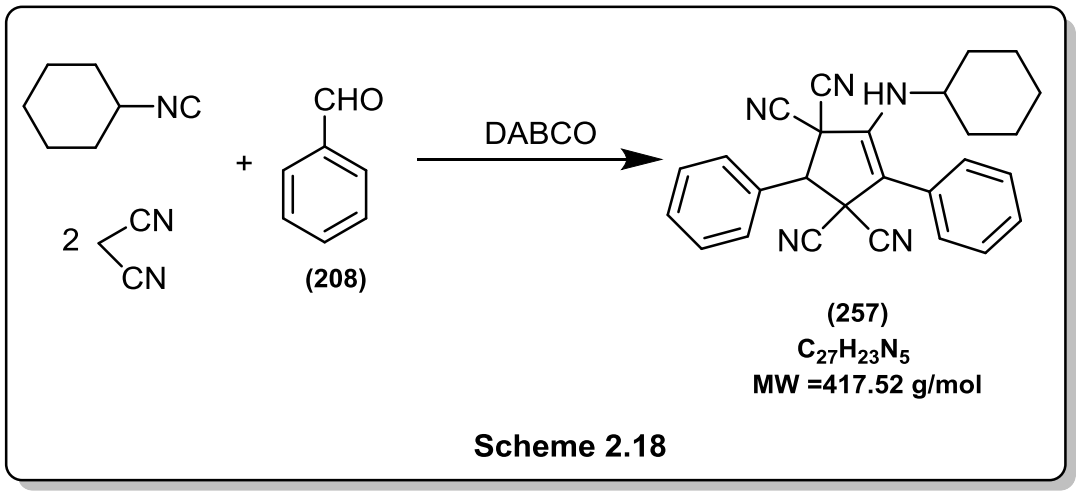
This reaction was repeated with 2-azidobenzaldehyde but was unsuccessful. The reaction was monitored by TLC at regular intervals and a different product (**253**) was identified, along with the aldehyde condensation then cycloaddition product (**207**) (see Scheme 2.17).



Scheme 2.17

It was also found that compound (**253**) could be formed by leaving out the aldehyde. The structure of compound (**253**) was deduced from its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum, and mass spectrometry. Molecular ion peak at 198.1008 g/mol ($M+Na^{+}$) was displayed by the mass spectrum of this compound as expected. In the ^{1}H NMR spectrum, there was a singlet for the alkene proton (7.41 ppm), a multiplet for the C-NH (6.99-7.05 ppm) and a multiplet for the cyclohexyl ring protons at around 1.13-1.95 ppm. In the ^{13}C NMR spectrum, the most deshielded peak was observed for the alkene carbon at 158.88 ppm. In the IR spectrum, the absorption band at 3277.2 cm^{-1} indicated the formation of the new NH group in the product and the CN group appeared at 2204.4 cm^{-1}. Product **(253)** can be formed from attack of the anion of **(205)** on the isocyanide, protonation and then tautomerism to the conjugated **(253).**

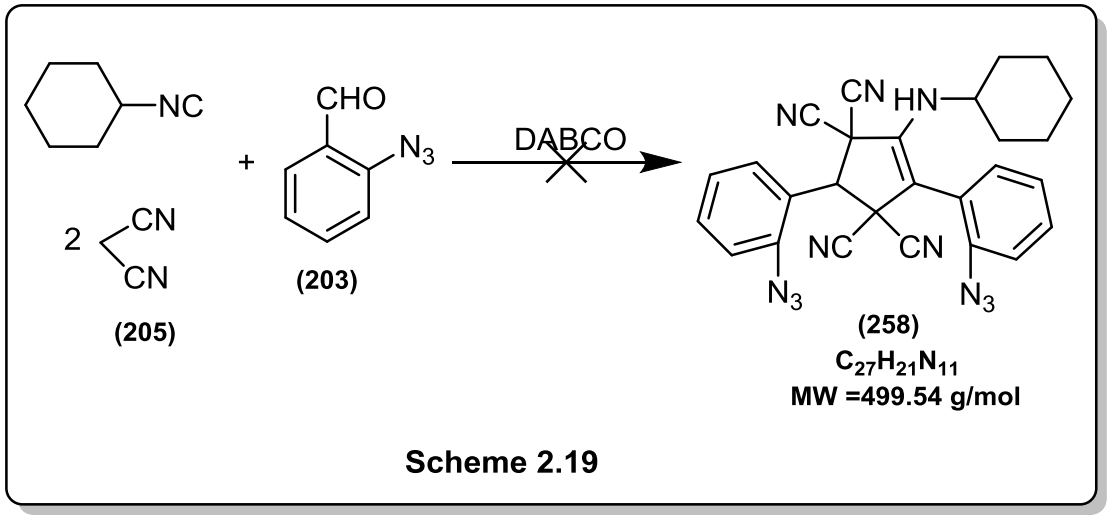
2.2.6. Synthesis of 4-(cyclohexylamino)-2,5-diphenylcyclopentane-1,1,3,3-tetracarbonitrile.



Scheme 2.18

The three component reaction of benzaldehyde, isocyanocyclohexane and malononitrile with DABCO as a catalyst proceeded as reported in the literature and gave the reported product (**257**) in 56 % yield, with melting point, IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry all in agreement with that reported in the literature[183] and entirely consistent with the structure.

We attempted the same reaction with *o*-azidobenzadehyde. The desired product (**258**, Scheme 2.19) could not be identified, and no other products could be identified.

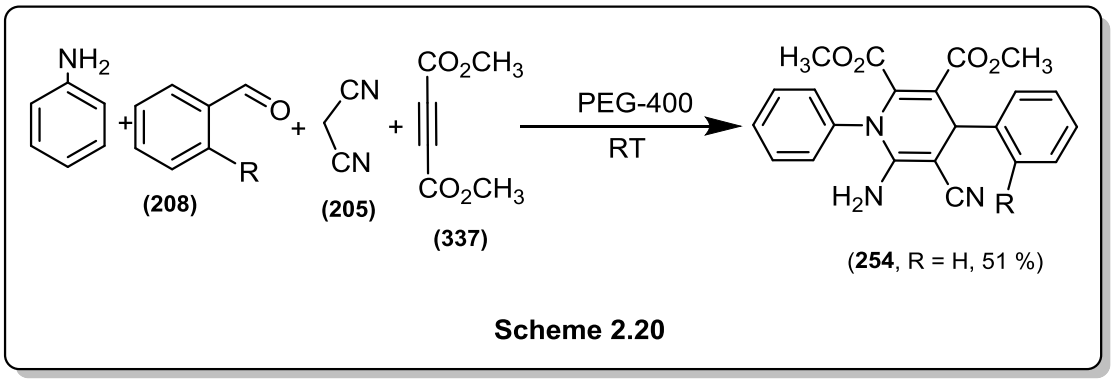


Scheme 2.19

2.3. The use of four component MCRs

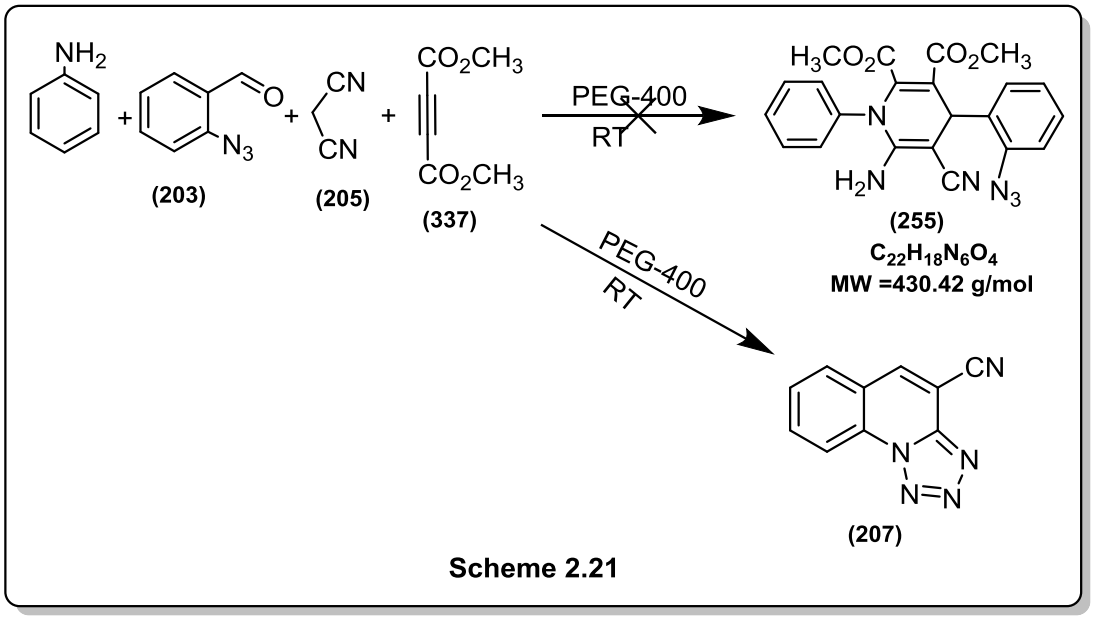
2.3.1. Dihydropyridine derivative.

The reaction of benzaldehyde (Scheme 2.20, R=H), aniline, dimethyl acetylene dicarboxylate and malononitrile gave dimethyl-6-amino-5-cyano-1,4-diphenyl-1,4-dihydropyridine-2,3-dicarboxylate in good yield. This was a literature reaction[184] that was repeated to confirm the chemistry before it was attempted with *o*-azidobenzaldehyde (R=N_3).



Scheme 2.20

When the reaction was attempted with 2-azidobenzaldehyde, it was unsuccessful. The reaction was monitored by TLC at regular intervals and a new product was identified, but was found (again) to be compound (**207**) which caused the reaction to stop before any MCR could take place, a reaction observed several times already in this chapter.



Scheme 2.21

Compound (**207**) did not react with aniline and dimethylacetylene dicarboxylate, the other components present in this reaction mixture.

2.4. Conclusions.

The formation of compound (**207**) proved to be a problem with respect to MCRs and this along with other priorities brought this part of the work to an end. The fact that azide to cyano cycloaddition to form (**207**) did occur was a good result, although other cyano-azides (when the MCR did work) did not cyclise. The unexpected indazole formation is being explored further. With these two exceptions, and despite having made some new azides using MCRs, the chemistry explored in this chapter proved unsuccessful in terms of post-MCR azide to nitrile cycloadditions.

Chapter 3:

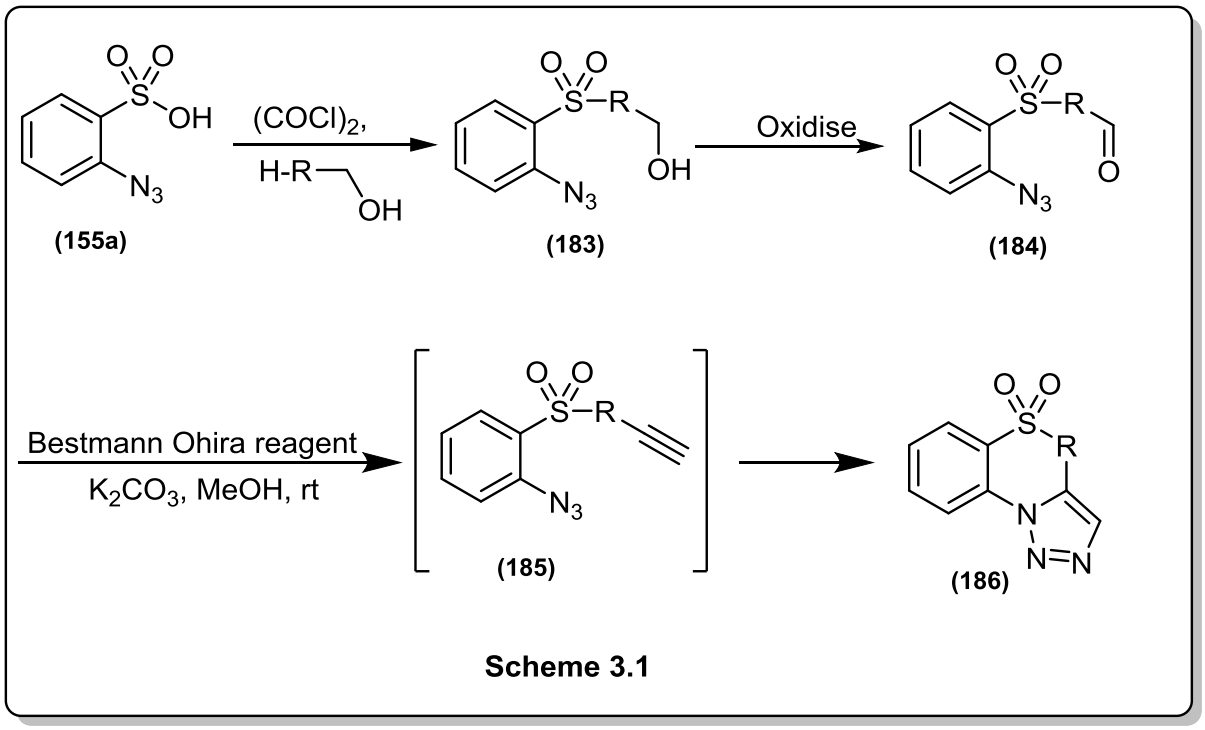
3. Results and Discussion: Triazolo and tetrazolobenzothiadiazepines and benzodiazepines.

In this section of the research the aim was to synthesise triazolo- and tetrazolo- benzothiadiazepines. These compounds were of great interest as synthetic targets due to their potential biological activity.

Our project investigated preparing triazolo and tetrazolo analogues via the intramolecular 1,3-dipolar cycloaddition between an azide moiety and an alkyne or nitrile.

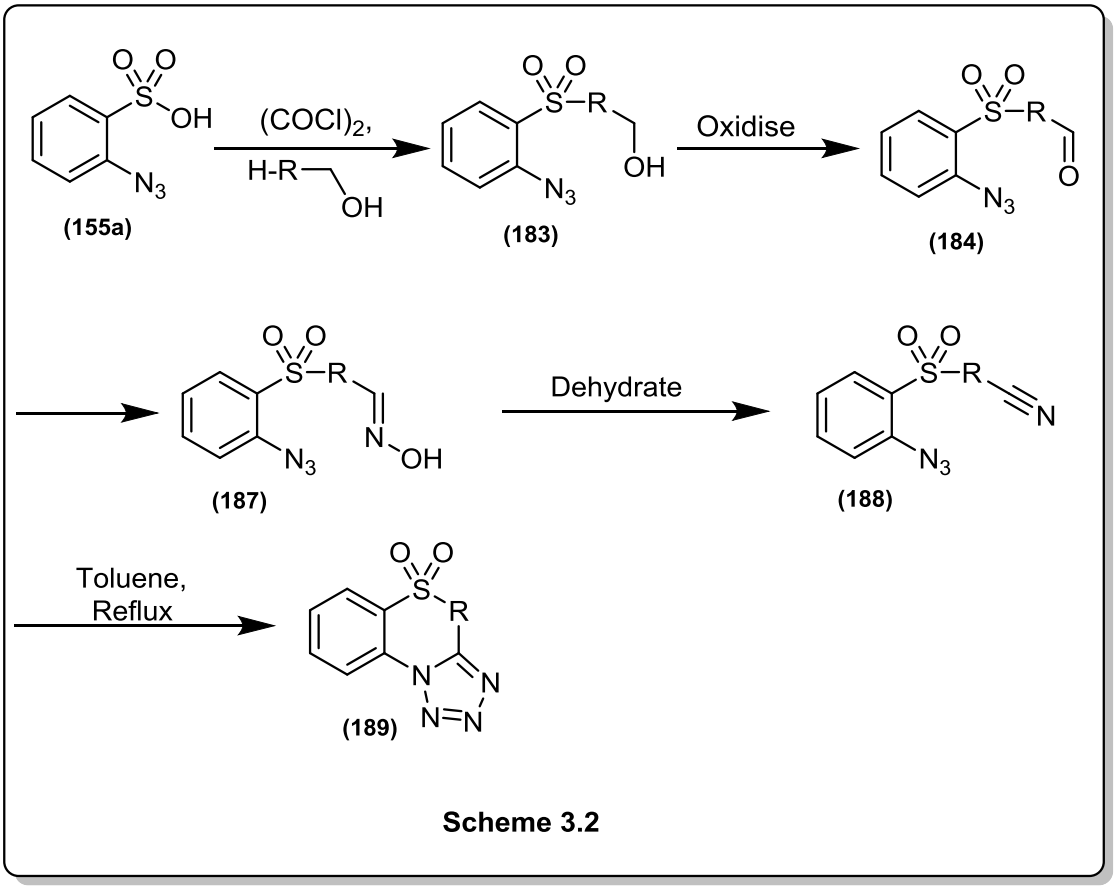
Schemes 3.1- 3.3 summarises the chemistry that will be presented in this chapter, with Section 3.1.1 looking at triazoles and Section 3.1.2 at tetrazoles.

In Scheme 3.1, the aldehydes (**184**) are to be converted to alkynes (**185**) using the Bestmann – Ohira reagent and then cyclised to the triazoles (**186**).



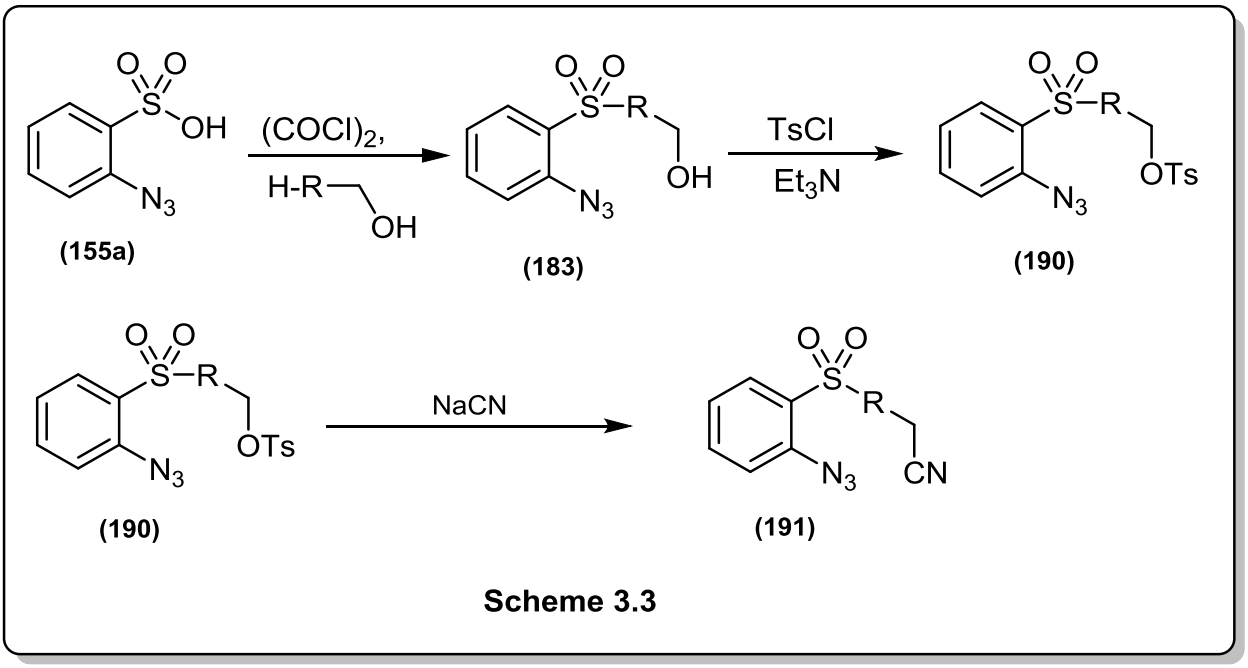
Scheme 3.1

In Scheme 3.2, aldehydes (**184**) are to be converted into oximes (**187**) and then are to be converted into nitrile compounds (**188**) via dehydration. 1,3-Dipolar cycloaddition of the azide group and nitriles could then be explored.



Scheme 3.2

The convertion of the alcohols (**183**) into tosylates and then into nitriles **(191)** by reaction with sodium cyanide, allowing further azide to nitrile reactions, as shown in Scheme 3.3. will also be discussed.

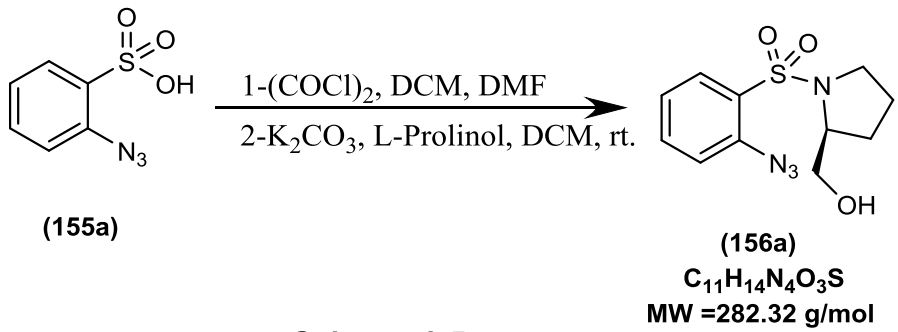


Scheme 3.3

3.1. The synthesis of triazolobenzothiadiazepines.

3.1.1. Synthesis of triazolopyrrolobenzothiadiazepine.

3.1.1.1. (*S*)-[1-(2´-Azidobenzenesulfonyl)pyrrolidin-2-yl] methanol.



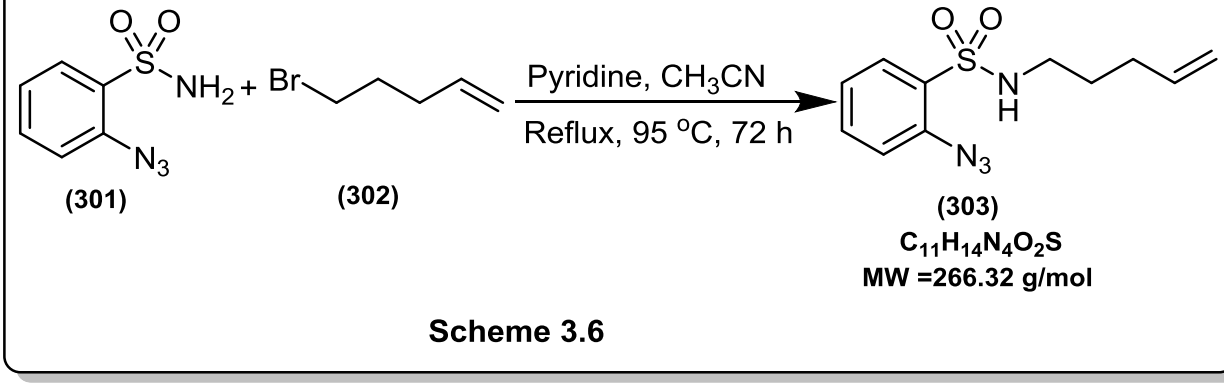
Scheme 3.5

This route started by the reaction of L-prolinol with the 2-azidobenzenesulfonyl chloride. The sulfonic acid[185] (**155a**) was synthesised and converted to the sulfonyl chloride by heating at reflux with ($COCl_2$) in DCM and DMF.[186] The sulfonyl chloride was coupled with prolinol in an aqueous solution of potassium carbonate as the base giving the alcohol **(156a)** in good yield (72 %).

The structure of the product (**156a**) was confirmed by its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry, and was identical to that synthesised by this same route in the group previously.[160] A sample of compound **(156a)** was required in order to compare it to the same alcohol made by another (novel) route as discussed in the next section.

3.1.1.2. An Alternative Method for the Synthesis of Alcohol (298).

3.1.1.2.1. Synthesis of 2-azido-*N*-(pent-4-en-1-yl)benzenesulfon-amide.



Scheme 3.6

The sulfonamide[161] **(301)** was treated with 5-bromo-1-pentene in MeCN in the presence of pyridine. The mixture was heated to reflux under a nitrogen atmosphere for 72 hours. The desired product was isolated in a low 8 % yield as a light yellow oil. Attempts to improve the reaction yield were unsuccessful (MeCN, DMSO, Et_3N, DMAP in many combinations).

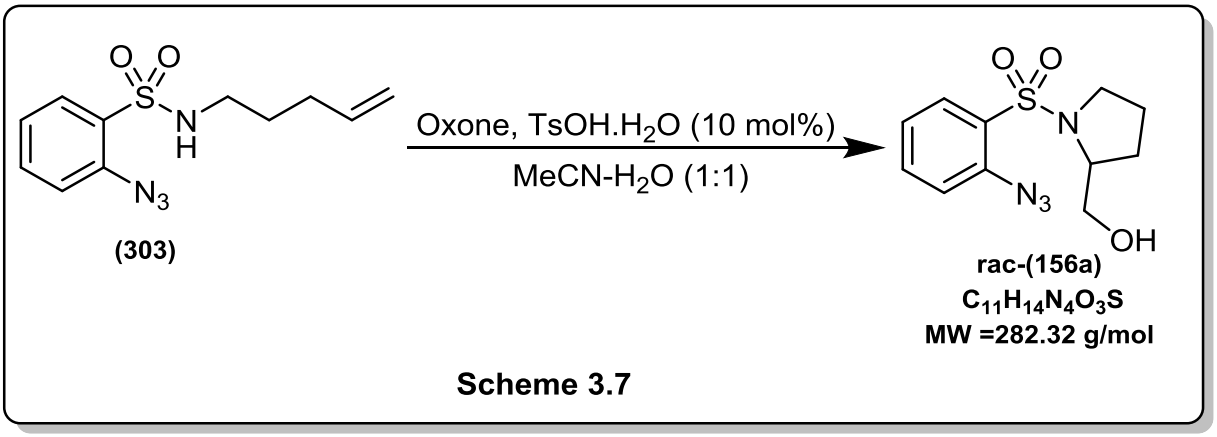
The structure of the product (**303**) was confirmed by spectroscopic analysis. The ^{1}H NMR spectrum showed the presence of the proton on the NH group in the compound at 4.88-4.96 ppm. The appearance of four downfield signals for four aromatic protons as a multiplet at 7.18-7.24 (2H) ppm, a triplet of doublets at 7.53 (1H) ppm and a doublet of doublets at 7.91 (1H) ppm indicated the presence of the aromatic ring. The six aliphatic protons were seen upfield as a quintet at 1.52 (2H), a quartet at 2.00 (2H) and a quartet at 2.83 ppm (2H). The alkene protons appeared downfield at 4.88-4.96 ppm for (=CH_2) and 5.59-5.70 ppm for (CH=).

The ^{13}C NMR (100 MHz) spectrum showed the three aliphatic CH_2 carbons at 28.66 (CH_2), 30.67 (CH_2) and 42.79 (CH_2) ppm. The appearance of five CH signals at 119.36, 124.91 130.76, 133.96 and 137.19 ppm and the sp^2 CH_2 carbon at 115.62 ppm confirmed the structural assignment.

It was determined that the product contained the NH stretching absorption peak at υ_{max} 3299.5 cm^{-1} in the infrared spectrum and the presence of the absorption peak at υ_{max} 2133.4 cm^{-1} for

N_3 group confirmed that the azide was still present. Mass spectrometry further supported the structure of product with measured mass of 289.0730 for the ion $[M+Na]^+$ for required mass of 289.0730.

3.1.1.2.2. Synthesis of {1-[(2-azidophenyl)sulfonyl]pyrrolidin-2-yl}methanol.



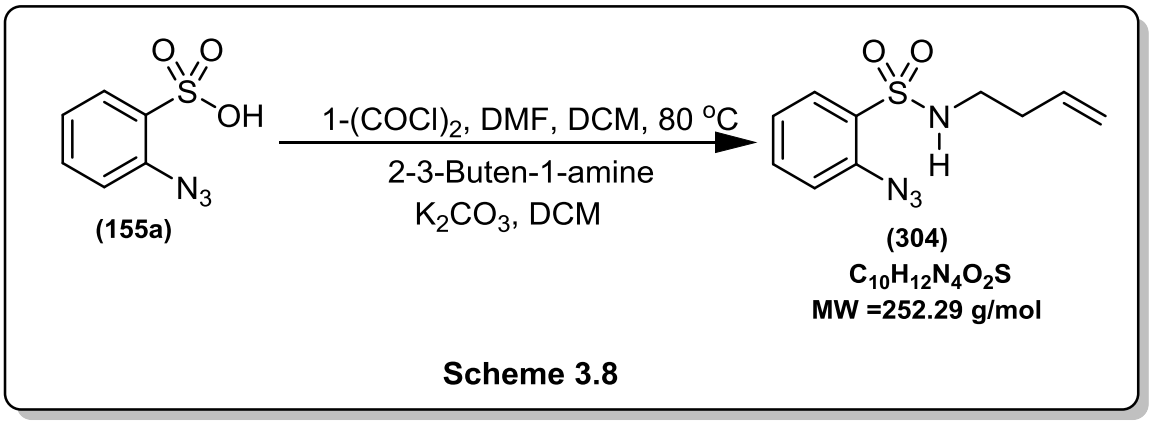
Scheme 3.7

The aim of this section was to investigate a new route to the alcohol (**156a**) using intramolecular aminohydroxylation of the *N*-alkenylsulfonamide via an inorganic oxidant under heavy metal-free conditions, a reaction that was reported in the recent literature with non-azide compounds.[187]

The *N*-alkenylsulfonamide was treated with Oxone ($KHSO_5$) in a mixture of MeCN and H_2O in the presence of TsOH-H_2O as Brønsted acid at room temperature. The desired product was obtained in excellent yield (95 %) as a yellow oil.

The structure of the product was confirmed by its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry, and the data was identical to that obtained from L-prolinol in the section above. The L-prolinol derived sample above is a single enantiomer. This sample is racemic.

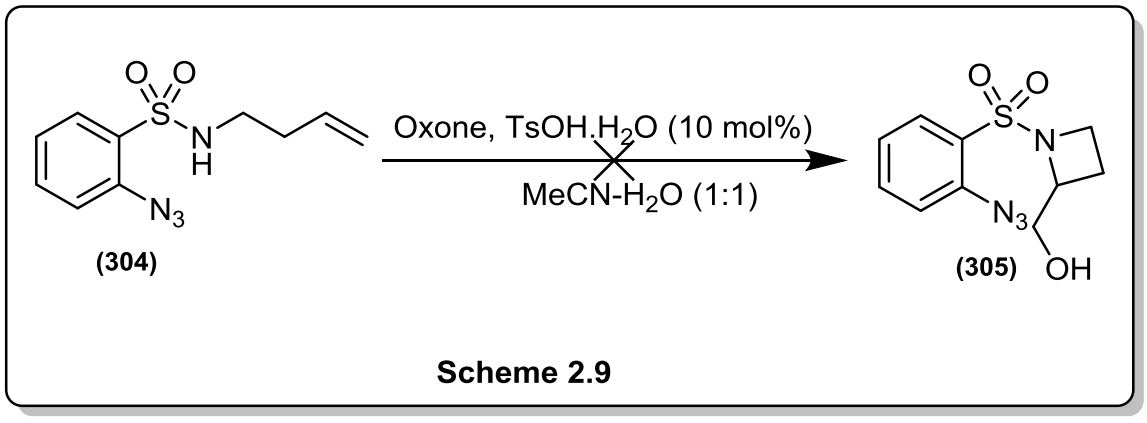
3.1.1.2.3. Synthesis of 2-azido-*N*-(but-3-en-1-yl)benzenesulfonamide.



Scheme 3.8

The reaction of 2-azidobenzenesulfonic acid with $(COCl)_2$ in DCM in the presence of DMF gave the sulfonyl chloride. The sulfonyl chloride was coupled with 3-buten-1-amine in a mixed phase reaction using K_2CO_3 as the base. The desired product (**304**) was isolated in 78 % as a pale yellow oil. The structure of the product was deduced from its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry, which were fully consistent with the assigned structure.

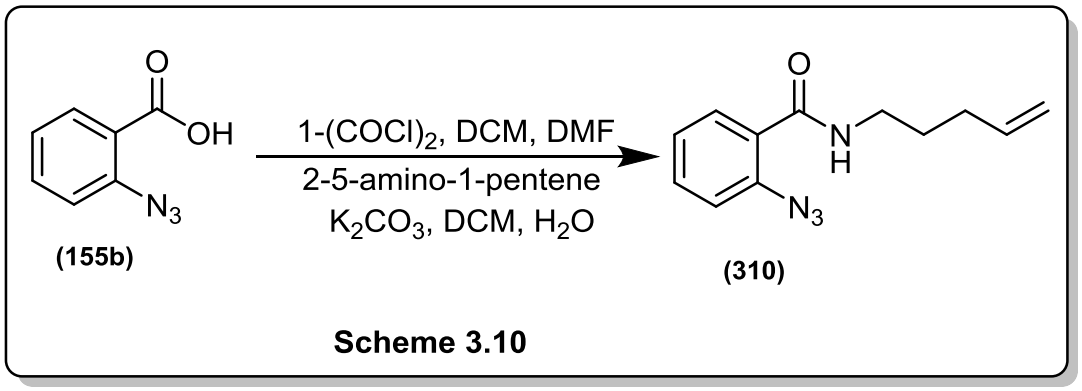
3.1.1.2.4. Attempted synthesis of {1-[(2-azidophenyl)sulfonyl]-azetidin-2-yl}methanol.



Scheme 2.9

The N-alkenylsulfonamide was treated with Oxone ($KHSO_5$) in a mixture of MeCN and H_2O in the presence of TsOH-H_2O as Brønsted acid at room temperature. The reaction was unsuccessful and no significant or identifiable product was obtained.

3.1.1.2.5. Synthesis of 2-azido-*N*-(pent-4-en-1-yl)benzamide.



Scheme 3.10

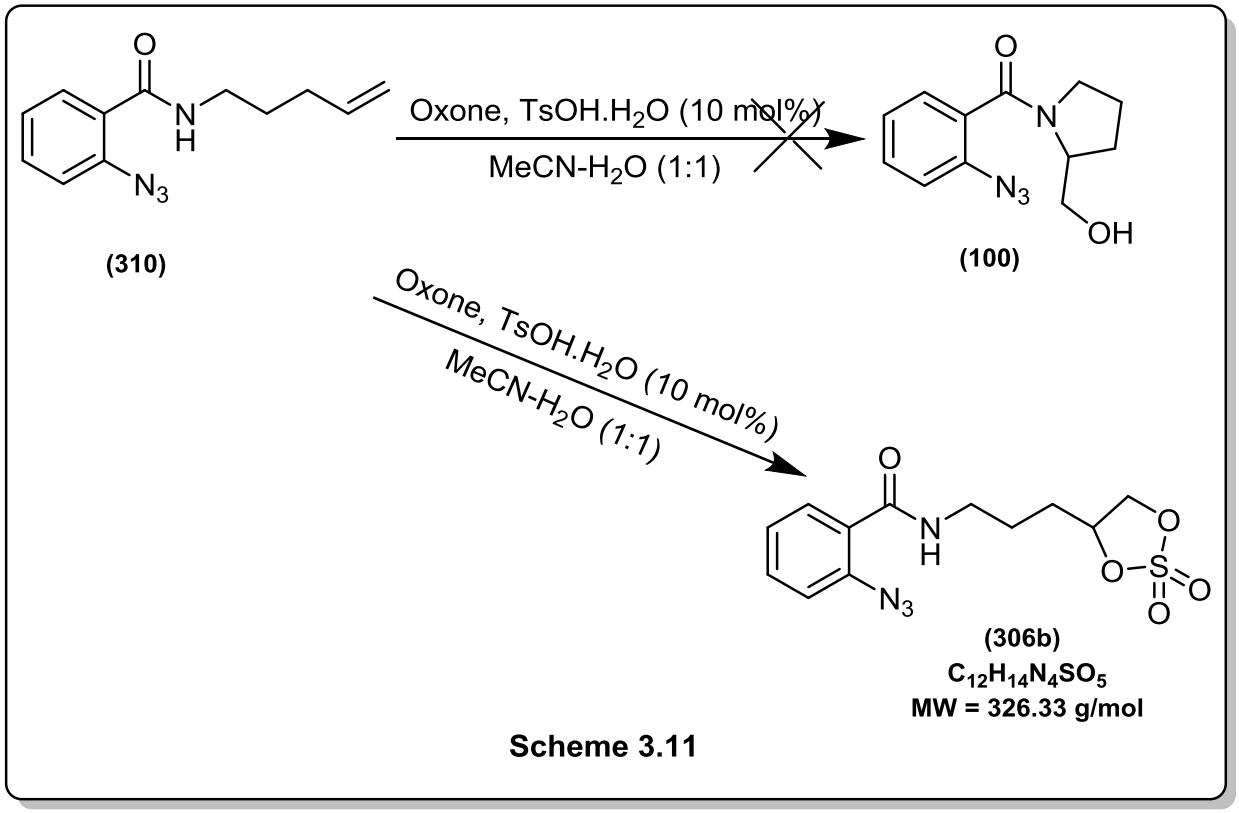
The reaction of 2-azidobenzenesulfonic acid with $(COCl)_2$ in DCM in the presence of DMF gave the acid chloride. The acid chloride was coupled with 5-amino-1-pentene[188] in a mixed phase reaction using K_2CO_3 as the base. The desired product (**310**) was isolated in 72 % as a yellow oil.

The structure of the product was deduced from its IR spectrum, ^{1}HNMR spectrum, ^{13}CNMR spectrum and mass spectrometry. In the ^{1}H NMR spectrum, the four aromatic protons showed as a doublet of doublets at 7.10 (1H) ppm, a triplet of doublets at 7.14 (1H) ppm and a triplet of doublets at 7.40 (1H) ppm which confirmed the 1,2-disubstitution pattern on the benzene ring system. The NH was found at 8.04 ppm. The six aliphatic protons appeared upfield as a quintet at 1.66 (CH_2), quartet at 2.09 (CH_2) and a multiplet at 3.37-3.42 (2H). The alkene protons were seen downfield at 4.92 ppm for (=C**H**H), 4.99 ppm for (=CH**H**) and 5.70-5.82 ppm for (CH=).

In the ^{13}C NMR (100 MHz) spectrum, the three aliphatic CH_2s carbons showed at 28.64 (CH_2), 31.25 (CH_2) and 39.54 (CH_2) ppm and showed the appearance of the carbonyl carbon at 164.58 ppm. The appearance of five CH signals at 118.37 (CH), 125.17 (CH), 132.17 (CH), 132.19 (CH) and 137.79 (CH) ppm and the sp^2 CH_2 at 115.22 ppm completed the assignment.

It was determined that the product contained the NH stretching absorption peak at υ_{max} 3293.9 cm^{-1}, a peak at υ_{max} 1712.4 cm^{-1} for C=O and a peak at υ_{max} 2124.9 cm^{-1} for the N_3 group in the IR spectrum. Mass spectrometry further supported the structure of product with a measured mass of 231.1238 for the ion $[M+H]^+$ for a required mass of 231.1240.

3.1.1.2.6. Attempted synthesis of (2-azidophenyl)(2-(hydroxymethyl) pyrrolidin-1-yl)methanone.



Scheme 3.11

The *N*-alkenylcarbonamide (**310**) was treated with Oxone ($KHSO_5$) in a mixture of MeCN and H_2O in the presence of TsOH-H_2O as Brønsted acid at room temperature.

The reaction mixture was purified by using column chromatography. Instead of the desired product (**100)**, compound (**306b)** was isolated in reasonable yield (60 %) as a yellow oil. This is the product of alkene reaction with oxone and not aminohydroxylation.

The structure of the product (**306b**) was implied by its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry. The ^{1}H NMR spectrum showed the eight upfield aliphatic CH_2 protons at 1.50-1.99 (4H) and 3.32-3.56 (4H) and the single CH at 3.76-3.83 ppm. The presence of the proton on NH was noted at 7.51 ppm. The aromatic protons were downfield at 7.12 (1H), 7.16 (1H), 7.42 (1H) and 8.03 (1H) giving a pattern of d, dd, dd and d consistent with a 1,2-disubstituted benzene ring system. The disappearance of the alkene protons present in compound (**310)** was also noted.

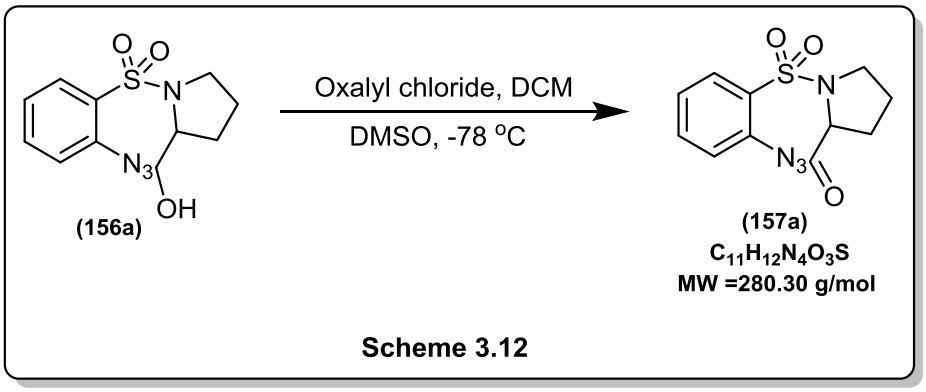
The ^{13}C NMR spectrum showed the four (CH) aromatic carbons downfield at 118.42, 125.22, 132.17 and 132.37 ppm. The presence of four aliphatic CH_2 at 25.93, 32.12, 50.24 and 67.04

(O-$\mathbf{C}H_2$) together with the CH at 58.24 ppm supported the structural assignment. The IR spectrum showed a peak at υ_{max} 2125.8 cm^{-1} for N_3 stretch. The NH stretching absorption peak appeared at υ_{max} 3360.0 cm^{-1}. The correct measured mass 326.0378 for the ion $[M]^+$ gives further evidence for the structure.

It should be noted that a genuine sample of compound (**100**) was made from 2-azidobenzoyl chloride and proline and this give very different spectroscopic data to that seen for compound (**306b**)

3.1.1.3. (*S*)-[1-(2´-Azidobenzenesulfonyl)pyrrolidin-2yl]carbaldehyde.

Chambers[160,163] had already converted enantiopure (**156a**) into **(157a)** and then into the alkyne and triazole. We repeated this with the racemic sample in order that both were available for biological testing.



Scheme 3.12

The alkyl alcohol was converted to the aldehyde by oxidation reaction under nitrogen to yield the aldehyde. This reaction worked in 96 % yield.

This method was that of the Swern oxidation[189] which uses $(COCl)_2$ and DMSO, for which the mechanism is given below.

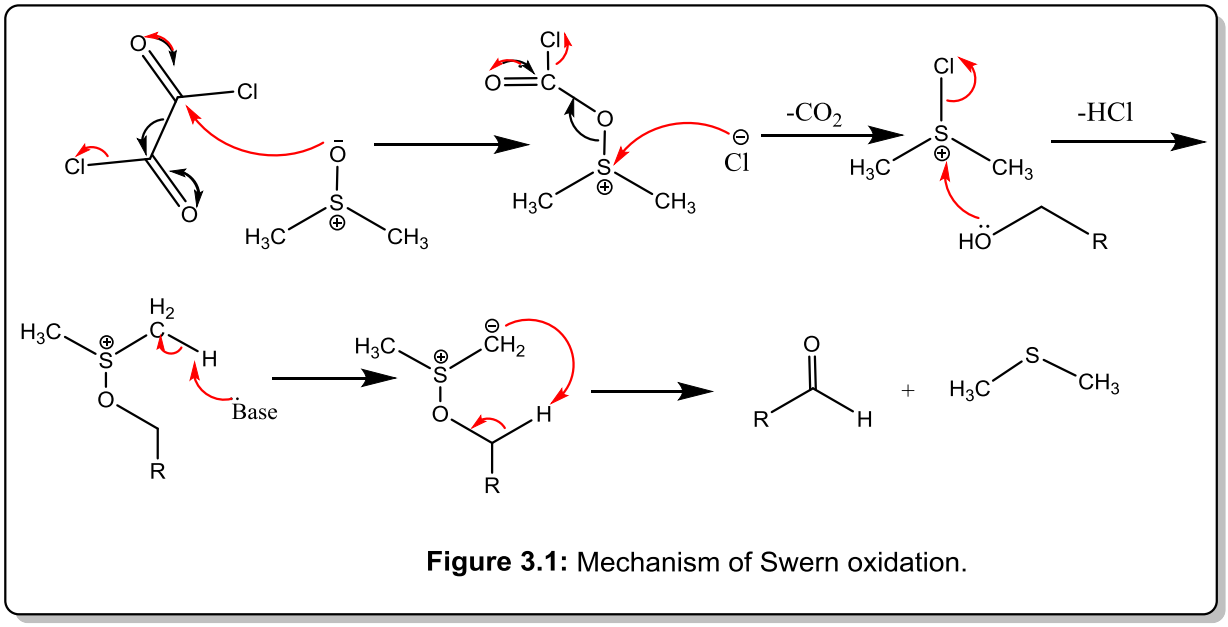
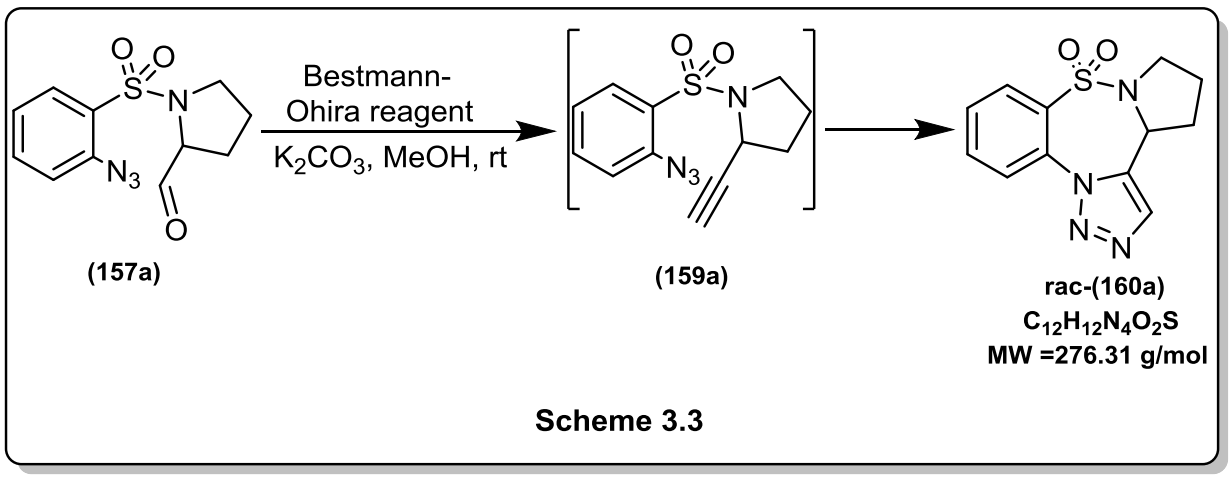


Figure 3.1: Mechanism of Swern oxidation.

The structure of compound **(157a)** was deduced from its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry, and was identical to that reported previously in the group by Chambers[160].

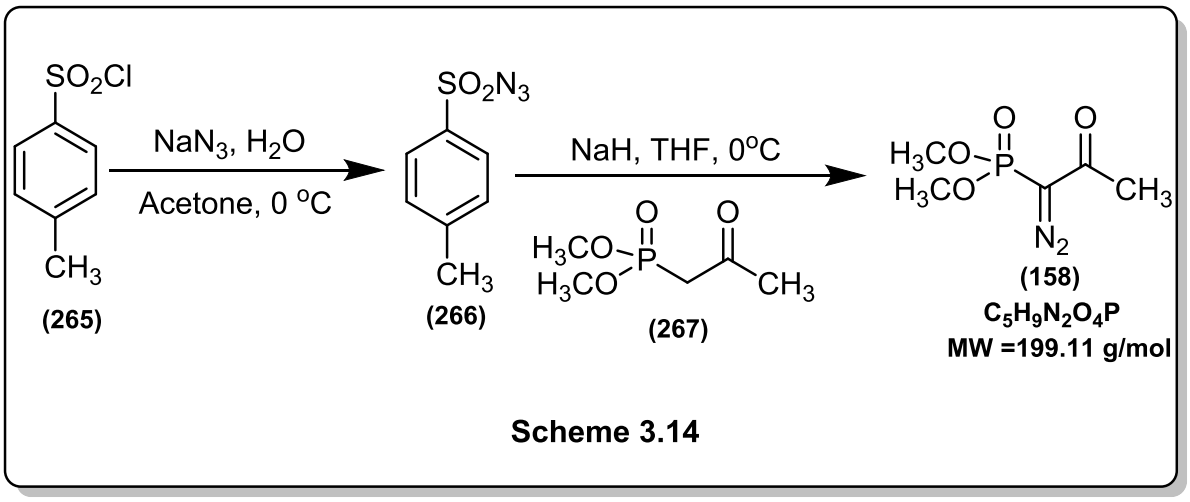
3.1.1.4. Pyrrolo[1,2-*b*][1,2,3]triazolo[5,1-*d*][1,2,5]benzothiadiazepine 8,8-dioxide.



Scheme 3.3

The next reaction in the synthesis was to convert the aldehyde **(157a)** into the triazole **(160a)**. This reaction was performed using the Bestmann-Ohira reagent which was prepared freshly in two steps.

To make the Bestmann-Ohira reagent tosyl chloride was reacted with sodium azide (forming in-situ the sulfonyl azide) and then reacted with dimethyl (2-oxopropyl) phosphonate to give the Bestmann-Ohira reagent as shown in Scheme 3.14. All spectroscopic data for this reagent agreed with the literature[190].



Scheme 3.14

The reagent was reacted with the aldehyde and converted it into the alkyne by reaction in a basic solution of potassium carbonate in methanol.

The proposed mechanism for the formation of the alkyne[191] moiety is shown in Figure 3.2.

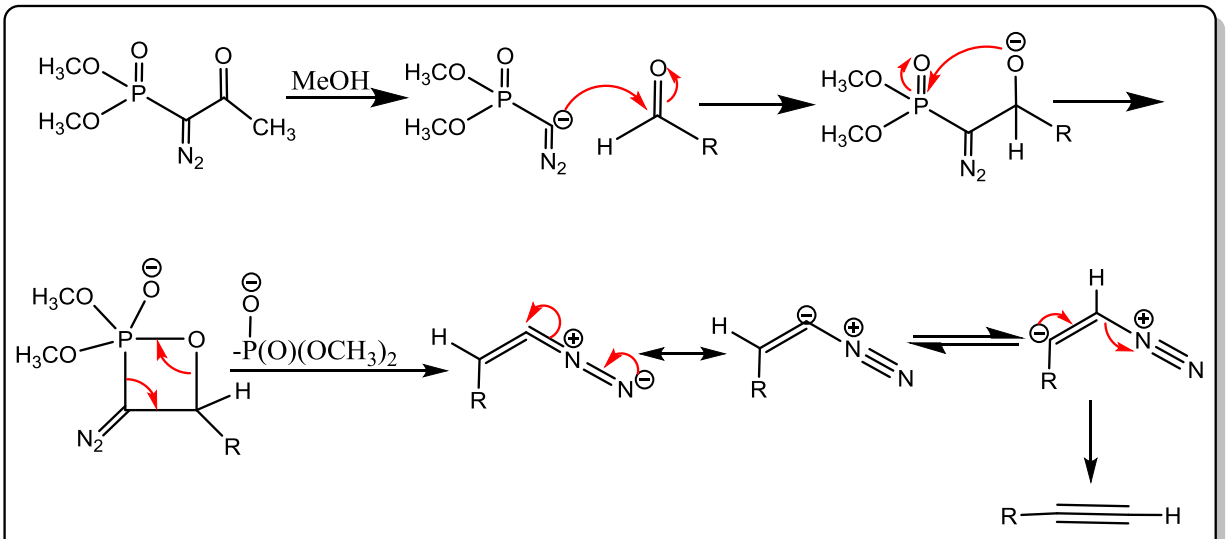


Figure 3.2: Mechanism for alkyne formation.

In our case, as with Chambers,[160,163] the alkyne product (**159a**) was not isolated. The alkyne reacted with the azide and underwent a 1,3-dipolar cycloaddition to form the desired triazole product (**160a**) in 70 % yield.

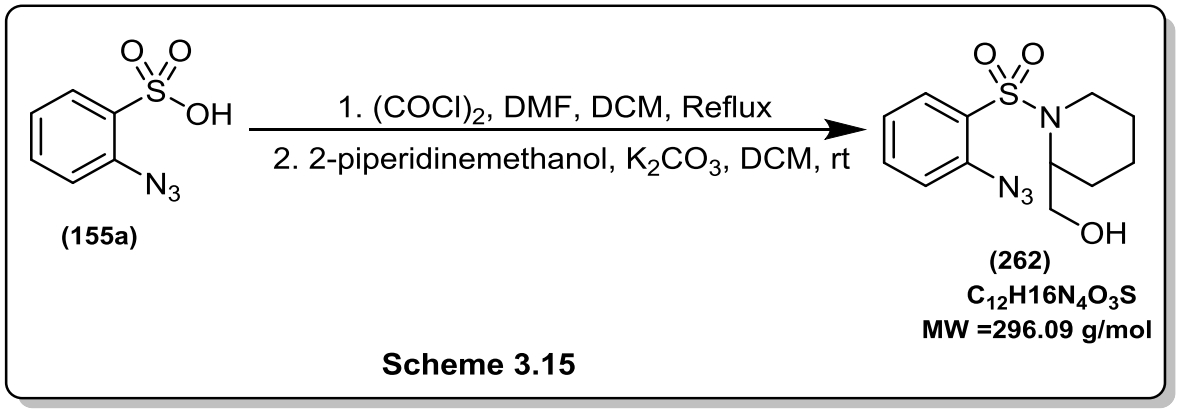
The structure of compound **(160a)** was deduced from its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry, and was identical to that reported by Chambers in the group previously.

Again, it is worth noting that the Chambers sample was derived from L-proline and was enantiopure. Triazole (**160a**) here is racemic. The synthesis of this was useful for biological testing and was useful as a test reaction before looking at some new molecules.

3.1.2. The synthesis of other triazolobenzothiadiazepines.

3.1.2.1. Coupling of the sulfonic acid with secondary amine alcohols.

Having successfully repeated Chambers' work, the scope of the intramolecular azide – alkyne 1,3-dipolar cycloaddition was next explored. This started with some other secondary amino alcohols. Chambers had only looked at other naturally occurring amino acid derived systems.[160,163]



Scheme 3.15

The reaction of 2-azidobenzenesulfonic acid (**155a**) with oxalyl chloride in DCM in the presence of a drop of DMF gave a sulfonyl chloride which was coupled with the 2-piperidine methanol in a mixed phase reaction using potassium carbonate as the base. The isolated product was the alcohol **(262)** in 85 % yield.

The structure of compound **(262)** was deduced from its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry.

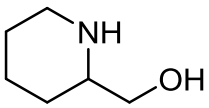
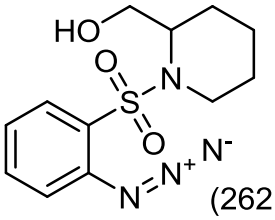
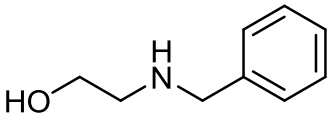
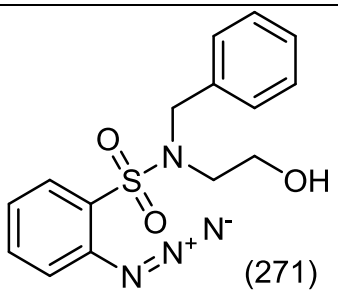
It was determined that the compound contained a hydroxyl group from the peak at υ_{max} 3521.2 cm^{-1} and a peak at υ_{max} 2097.7 cm^{-1} confirmed the azide group in the IR spectrum.

The ^{1}H NMR spectrum showed a multiplet at 4.04-4.09 ppm for the hydroxyl group and the alcohol methylene was found at 3.77-3.88 ppm. The four aromatic protons were downfield at 7.22 (1H), 7.29 (1H), 7.57 (1H) and 7.99 (1H) ppm giving a pattern of dd, d, dd and d consistent with a 1,2-disubstituted benzene ring system. The eight aliphatic CH_2 protons were upfield at 1.69-1.59 (5H), 1.69 (1H), 3.10 (1H) and 3.55-3.61 (1H) and the single CH was seen at 2.41 ppm.

The ^{13}C NMR (100 MHz) spectrum showed the six aromatic carbons at 119.95 (CH), 124.63 (CH), 130.90 (qC), 131.48 (CH), 133.87 (CH) and 137.83 (qC) and the four CH_2 and single CH in piperidine ring system were upfield at 18.95 (CH_2), 24.91 (CH_2), 25.29 (CH_2), 41.30 (CH_2) and 54.38 (CH).

The correct measured mass 297.1024 for the ion $[M+H]^+$ gives further proof for the structure.

The same strategy was next applied to other secondary amino alcohol derivatives, and the structures and yields are summarised in Table 3.1 with spectroscopic data summarised in Table 3.2.

No	Secondary amine alcohol	Products	Appearance	%, Yield
1	 2-piperidinemethanol	 (262)	yellow oil	85
2	 2-(benzylamino)ethanol	 (271)	brown solid, (93-95 ^{o}C)	88

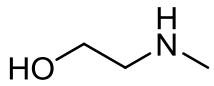
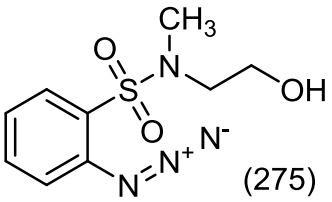
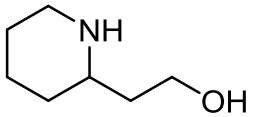
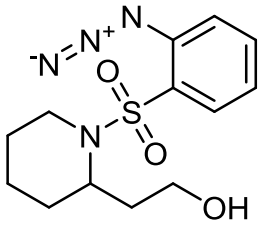
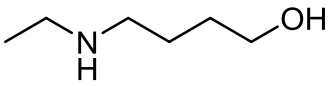
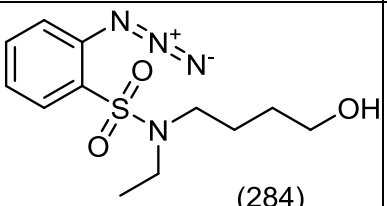
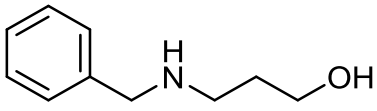
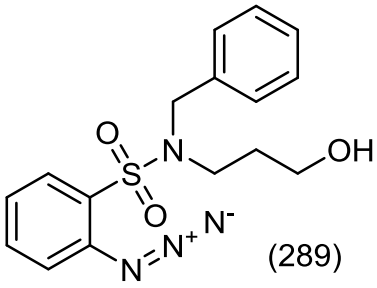
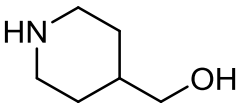
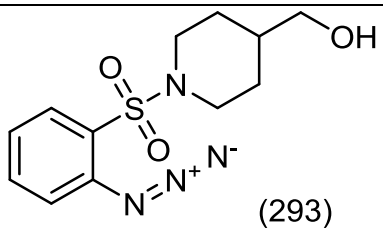
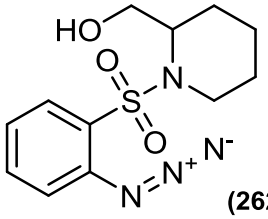
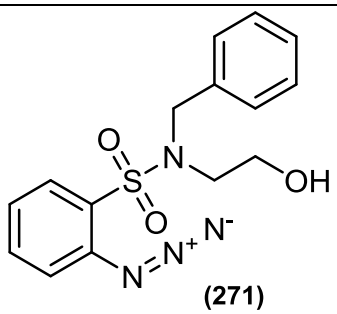
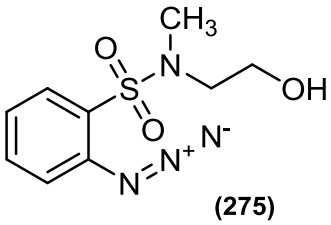
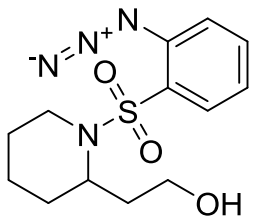
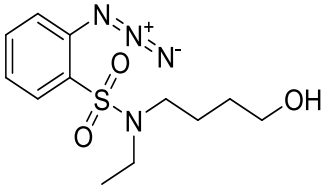
3	 2-(methylamino)ethanol	 (275)	yellow oil	90
4	 2-piperidineethanol	 (279)	orange oil	82
5	 4-(ethylamino)-1-butanol	 (284)	brown oil	75
6	 3-(benzylamino)-1-propanol	 (289)	dark brown oil	86
7	 4-piperidinemethanol	 (293)	brown oil	70

Table 3.1: Synthesis of sulfonamides with primary alcohol substituents.

No.	Products	NMR (400 MHz, $CDCl_3$, ppm)			IR (cm^{-1})		HRMS
		^{1}H NMR		^{13}CNMR			
		O***H***	**C*H*$_2$OH**	**C**H$_2$OH	**N_3**	**OH**	
1	 **(262)**	2.41	3.77-3.88 (m)	60.53	2097.7	3521.2 (bs)	297.1024 $[M+H]^+$ [Calc.= 297.1016]
2	 **(271)**	2.22 (bs)	3.49 (br.s)	60.74	2101.1	3359.0 (bs)	333.1016 $[M+H]^+$ [Calc.= 333.1016]
3	 **(275)**	2.19 (br.s)	3.71 (t)	60.43	2099.4	3516.1	257.0703 $[M+H]^+$ [Calc.= 257.0703]
4	 **(279)**	2.84 (br.s)	3.63-3.73 (m)	58.58	2097.4	3537.1	311.1167 $[M+H]^+$ [Calc.= 311.1172]
5	 **(284)**	2.23-2.33 (m)	3.56-3.58 (m)	60.07	2098.4	3527.0	299.1166 $[M+H]^+$ [Calc.= 299.1172]

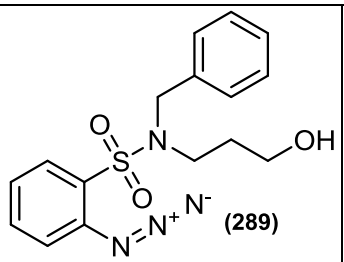
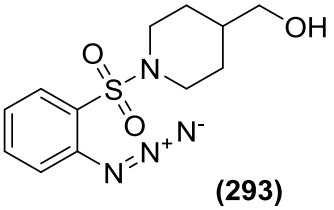
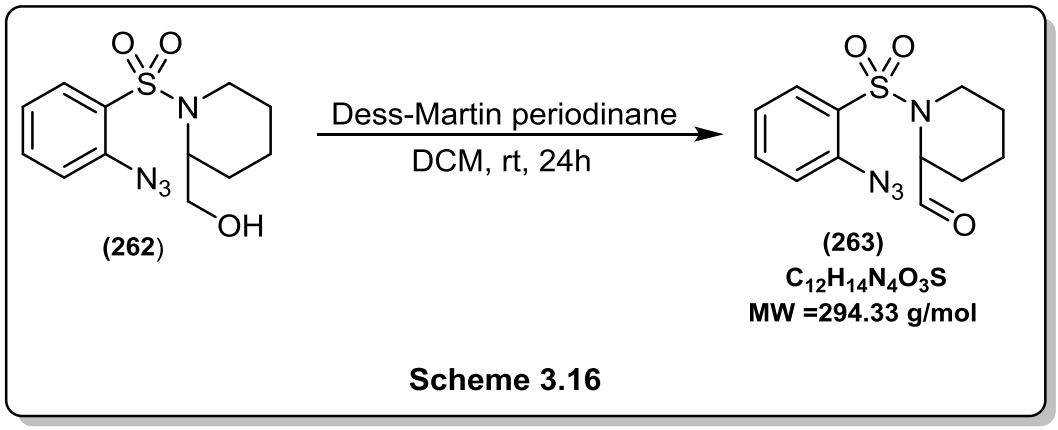
6	 (289)	2.18 (bs)	3.55-3.57 (m)	58.75	2101.2	3542.4	347.1166 $[M+H]^+$ [Calc.= 347.1172]
7	 (293)	2.68 (bs)	3.81 (d)	66.83	2127.6	3517.0	297.1026 $[M+H]^+$ [Calc.= 297.1016]

Table 3.2: Charateristic spectroscopic data for the primary alcohols.

3.1.2.2. Synthesis of the aldehydes.



Scheme 3.16

The alcohols in Tables 3.1 and 3.2 were converted into the aldehydes by oxidation reaction under nitrogen. Although many oxidation methods are known, our attempts used the Dess-Martin periodinane reagent[192] and the Swern oxidation.

All oxidation reactions were successful and yields and key spectroscopic data are recorded in Table 3.3 and 3.4, respectively. The mechanism[193] of the Dess-Martin process is given in Figure 3.3. The Swern mechanism was done above in Figure 3.1.

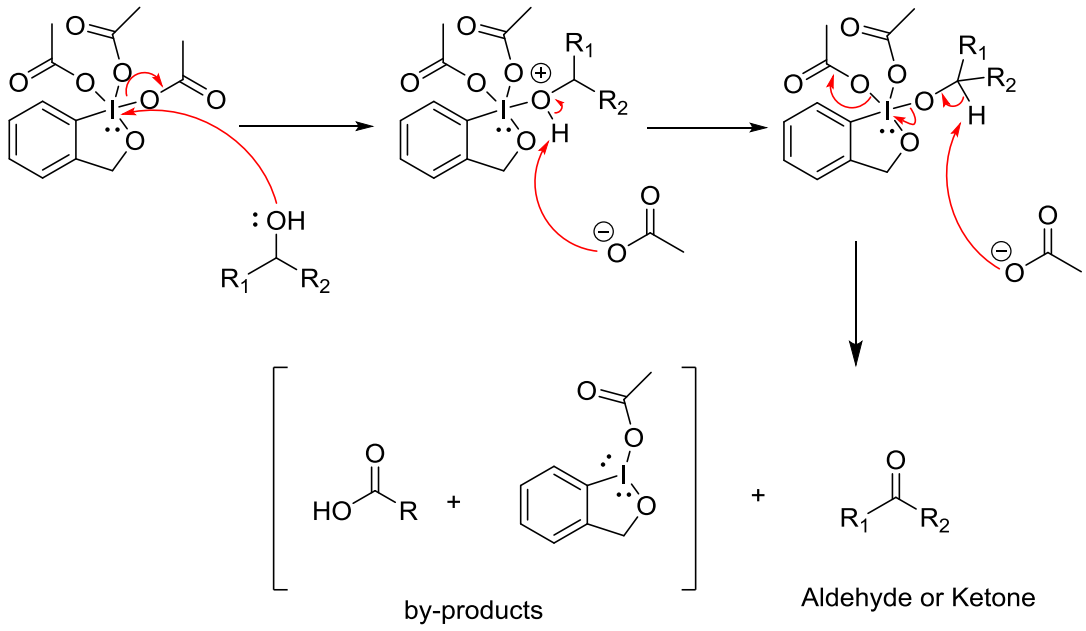
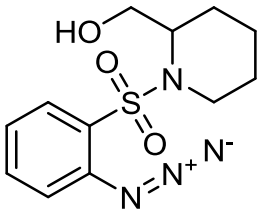
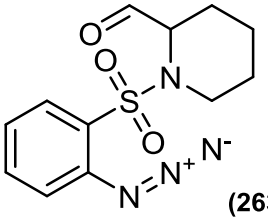
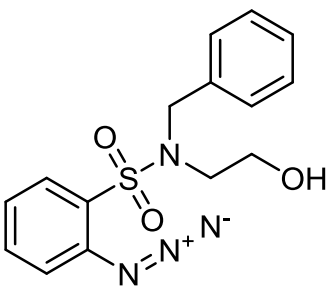
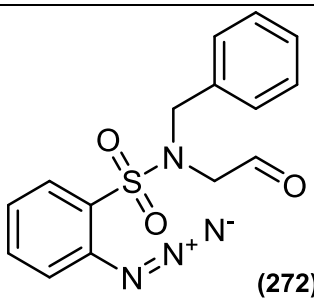


Figure 3.3

No	Starting material	Products	Appearance	%, Yield
1		 **(263)**	Orange oil	76
2		 **(272)**	White solid, (m.p.=111-113 ^{o}C)	83

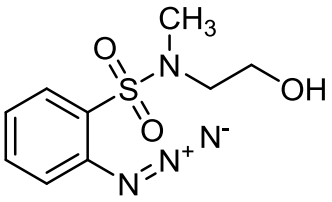
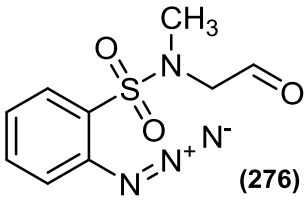
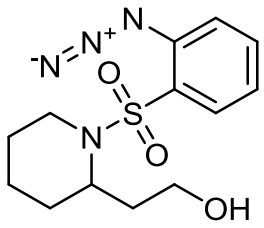
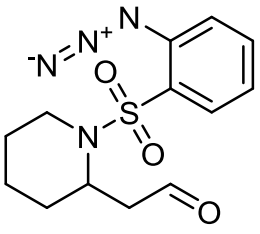
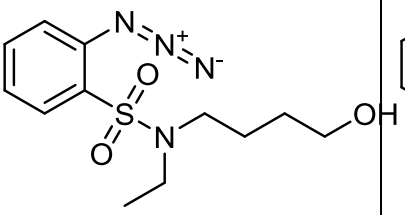
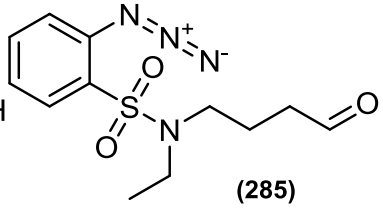
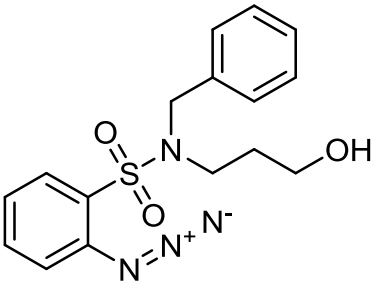
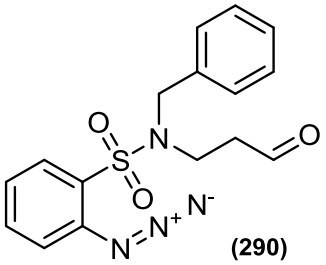
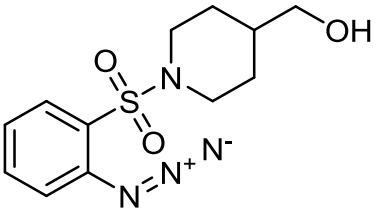
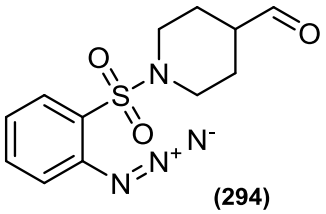
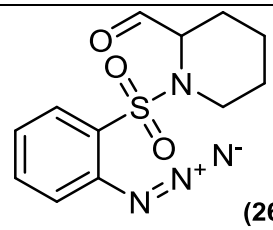
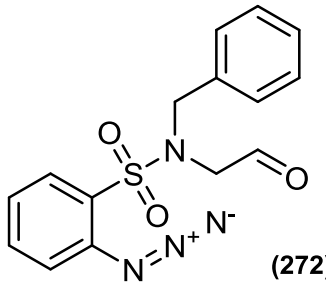
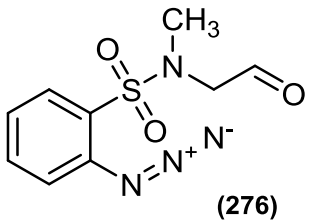
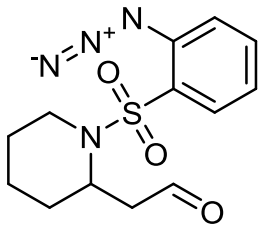
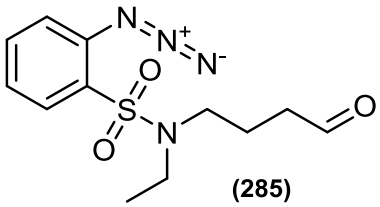
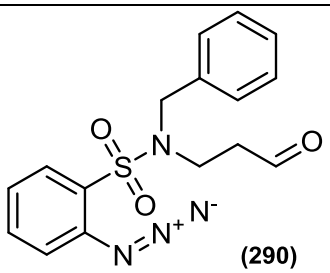
3		 **(276)**	deep brown oil	76
4		 **(280)**	Light yellow oil	81
5		 **(285)**	light yellow oil	76
6		 **(290)**	light yellow oil	77
7		 **(294)**	Yellow oil	92

Table 3.3: Yield and appearance of the aldehydes.

No.	Products	NMR (400 MHz, ppm)		IR		HRMS
		^{1}HNMR	^{13}CNMR			
		C**H**O	**C**HO	**N_3**	**CHO**	
1	 **(263)**	9.66 (s) **($CDCl_3$)**	200.94 **($CDCl_3$)**	2098.8	1731.8	317.0680 $[M+H]^+$ [Calc.= 317.0679]
2	 **(272)**	9.34 (s) **($CDCl_3$)**	197.87 **($CDCl_3$)**	2102.1	1715.6	369.0420 $[M+K]^+$ [Calc.= 369.0418]
3	 **(276)**	9.61 (s) **($CDCl_3$)**	197.73 **($CDCl_3$)**	2100.3	1731.1	277.0373 $[M+Na]^+$ [Calc.= 277.0366]
4	 **(280)**	9.62 (t) **($CDCl_3$)**	199.87 **($CDCl_3$)**	2099.4	1721.0	331.0832 $[M+Na]^+$ [Calc.= 331.0825]
5	 **(285)**	9.79 (s) **($CDCl_3$)**	201.42 **($CDCl_3$)**	2098.1	1720.1	297.1009 $[M+H]^+$ [Calc.= 297.1016]
6	 **(290)**	9.53 (s) **($CDCl_3$)**	200.12 (DMSO-d6)	2100.0	1722.0	345.1012 $[M+H]^+$ [Calc.= 345.1016]

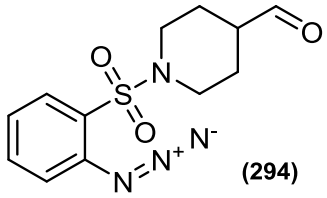
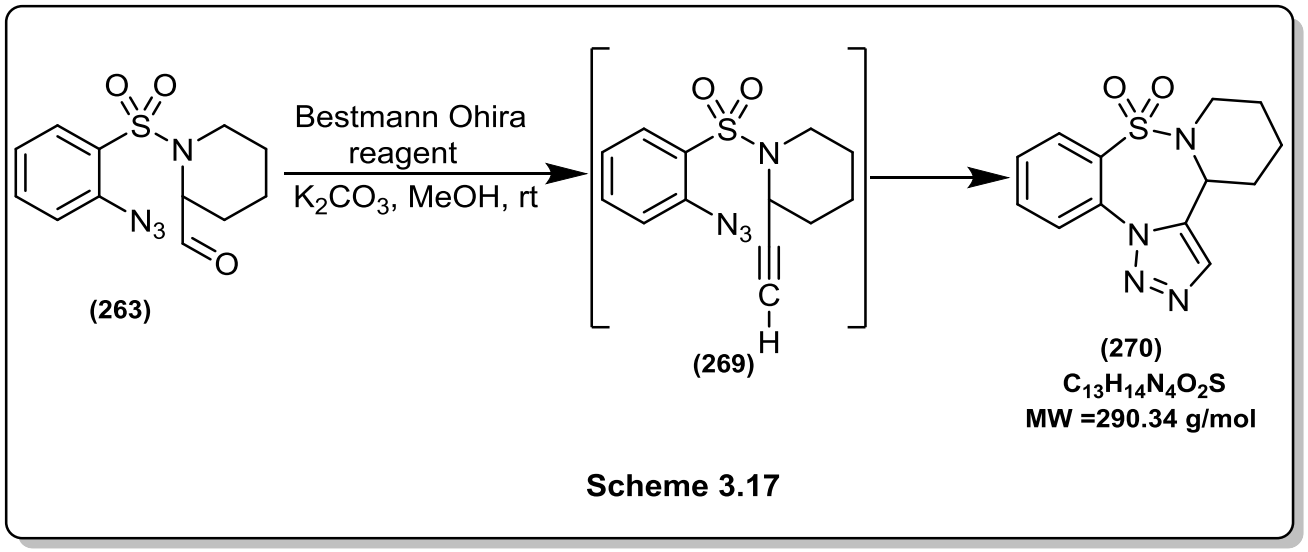
7	 (294)	9.58 (s) **($CDCl_3$)**	202.44 **($CDCl_3$)**	2098.6	1723.0	295.0856 $[M+H]^+$ [Calc.= 295.0859]

Table 3.4: Spectroscopic data summary for the aldehydes.

3.1.2.3. Reaction of the aldehydes with Bestmann-Ohira reagent and attempted triazole formation.

The next set of reactions conducted was to convert the aldehyde moiety into the triazole via the alkyne. These reactions were performed using the Bestmann-Ohira reagent.

In the case of aldehyde (**263**), the alkyne product was not isolated as the intermediate alkyne (**269**) underwent a spontaneous 1,3-dipolar cycloaddition to form the desired triazole product (**270**) in 71 % yield.



Scheme 3.17

The structure of compound **(270)** was deduced from its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry.

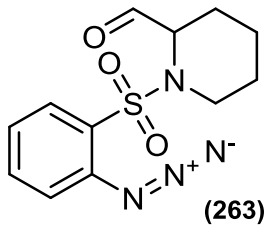
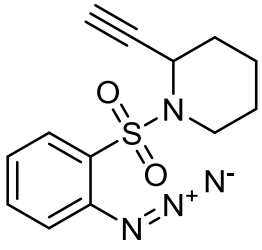
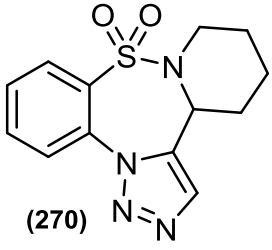
The ^{1}H NMR spectrum showed the disappearance of the CHO proton at 9.66 ppm. The piperidine ring CH_2 protons showed upfield at 1.33-1.45 (1H), 1.60-1.79 (2H), 1.87-1.92 (1H), 2.02-2.15 (2H), 3.73 (1H) and 3.86-3.89 (1H). The aromatic protons appeared as a

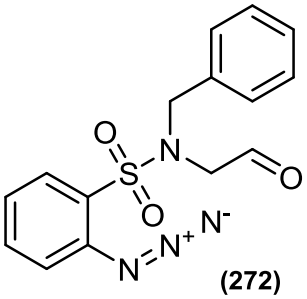
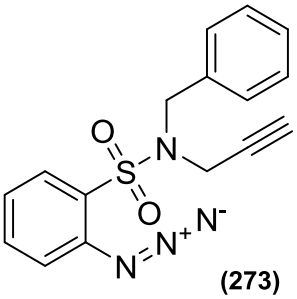
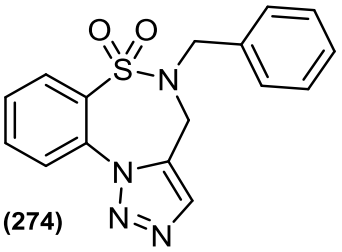
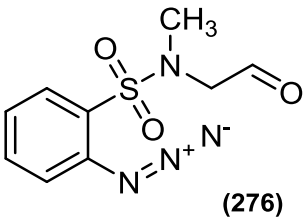
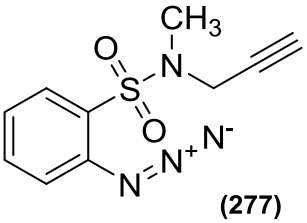
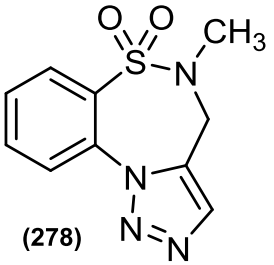
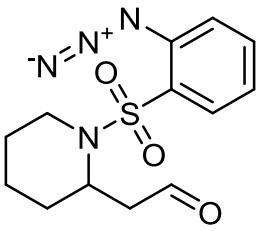
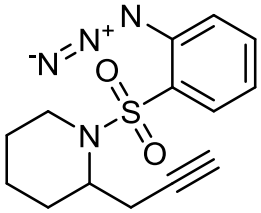
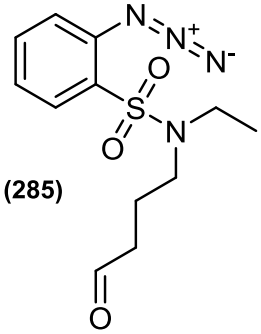
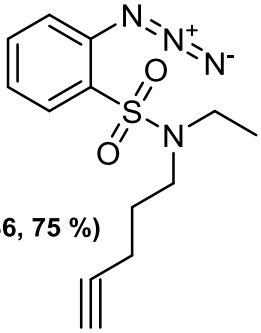
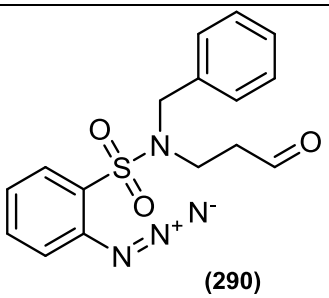
triplet of doublets (td) at 7.58 (1H) ppm, a broad signal (br.s) at 7.68 (1H) ppm, a doublet of doublets (dd) at 7.75 (1H) ppm and a doublet of doublets (dd) at 7.93 (1 H) ppm which showed the 1,2-substitution pattern on the aromatic ring system. The appearance of a new aromatic proton was seen downfield as a doublet (d) at 9.97 (1H) ppm and consistent with triazole formation.

The ^{13}C NMR spectrum showed no carbon for the aldehyde carbonyl at 200.94 ppm. The appearance of five aromatic CH signals confirmed an extra aromatic CH carbon from the triazole formation with peaks at 125.02 (CH), 127.96 (CH), 129.70 (CH), 132.86 (CH) and 134.48 (CH) ppm. The four CH_2 and the CH of the piperidine ring system appeared upfield at 23.67 (CH_2), 25.07 (CH_2), 29.42 (CH_2), 48.80 (CH_2), 52.25 (CH) ppm. Infrared spectral data proved that the azide was absent and also confirmed the disappearance of the carbonyl group peak at υ_{max} 1731.8 cm^{-1}.

Further evidence for the structure was given by the HRMS for the measured ion $[M+H]^+$ was consistent at 291.0910.

The reaction of aldehydes **(272)** and **(276)** with the Bestmann-Ohira reagent gave the alkynes and again these reacted with the azide. The isolated products were the desired triazole products (**274)** and (**278)** (Table 3.5, below) in good yields of 73 % and 68 %, respectively. However, the reaction of aldehydes (**280), (285)** and (**294)** with Bestmann-Ohira reagent gave the three alkynes (**281)**, **(286)** and (**295)** showing in these cases that the alkynes did not react with the azide to form the desired triazole product. The aldehyde (**290)** did not react with Bestmann-Ohira reagent and did not give the alkyne. Table 3.5 summaries the syntheses of triazolobenzothiadiazepines attempted in this thesis, and Table 3.6 summaries the spectroscopic data for compound (**270)**, (**274)** and (**278)**.

No	Starting material	Intermediate products	Desired products	%
1	 (263)	 (269)	 (270)	71

2	 (272)	 (273)	 (274)	73
3	 (276)	 (277)	 (278)	68
4	 (280)	 (281, 66 %)	No	0
5	 (285)	 (286, 75 %)	No	0
6	 (290)	No	No	0

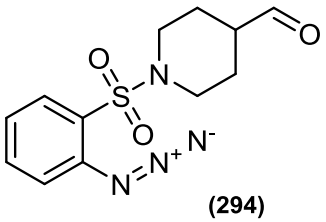
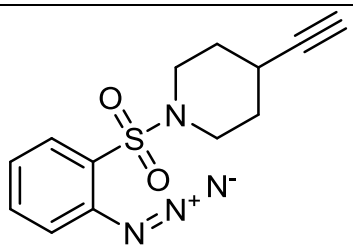
7	 **(294)**	 **(295, 64 %)**	No	0

Table 3.5: Summary of Triazolobenzothisdiazepine reaction.

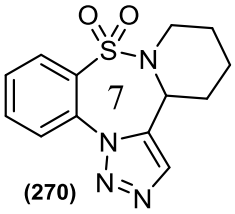
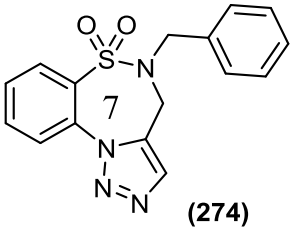
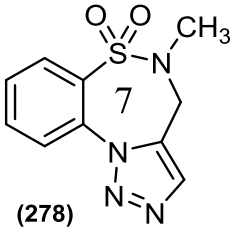
Entry	**Desired Products**	**NMR (400 MHz, $CDCl_3$, ppm)**		**HRMS**
		^{1}H NMR	**^{13}C NMR**	
		N-C**H**=C	N-CH=**C**	
1	 **(270)**	7.68 (br.s)	136.53	291.0909 $[M+H]^+$ [Calc.= 291.0910]
2	 **(274)**	7.54 (m)	134.41	327.0905 $[M+H]^+$ [Calc.= 327.1091]
3	 **(278)**	7.68 (s)	133.15	251.0612 $[M+H]^+$ [Calc.= 251.0597]

Table 3.6: Summary of Triazolobenzothiazepine data.

Table 3.7 summarises the data obtained for the alkynes (**281**), (**286**) and (**295**). It is interesting that azide to alkyne cycloadditions only occurred in cases where 7-membered rings could

result. Alkynes **(281)** and **(286)** would give 8- and 9-membered rings and **(295)** would give a bridged 9-membered ring. It is possible that spontaneous 8- and 9- membered ring formation is not as favoured as 7-membered ring formation.

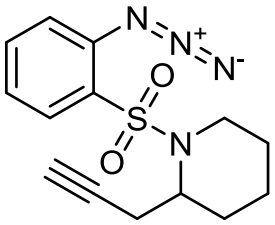
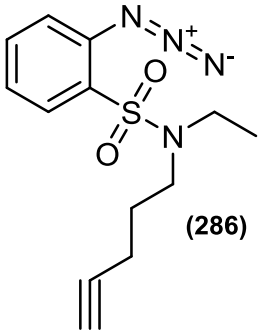
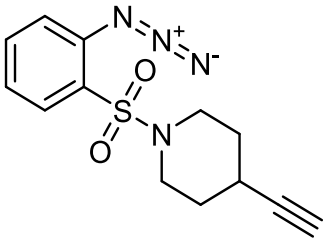
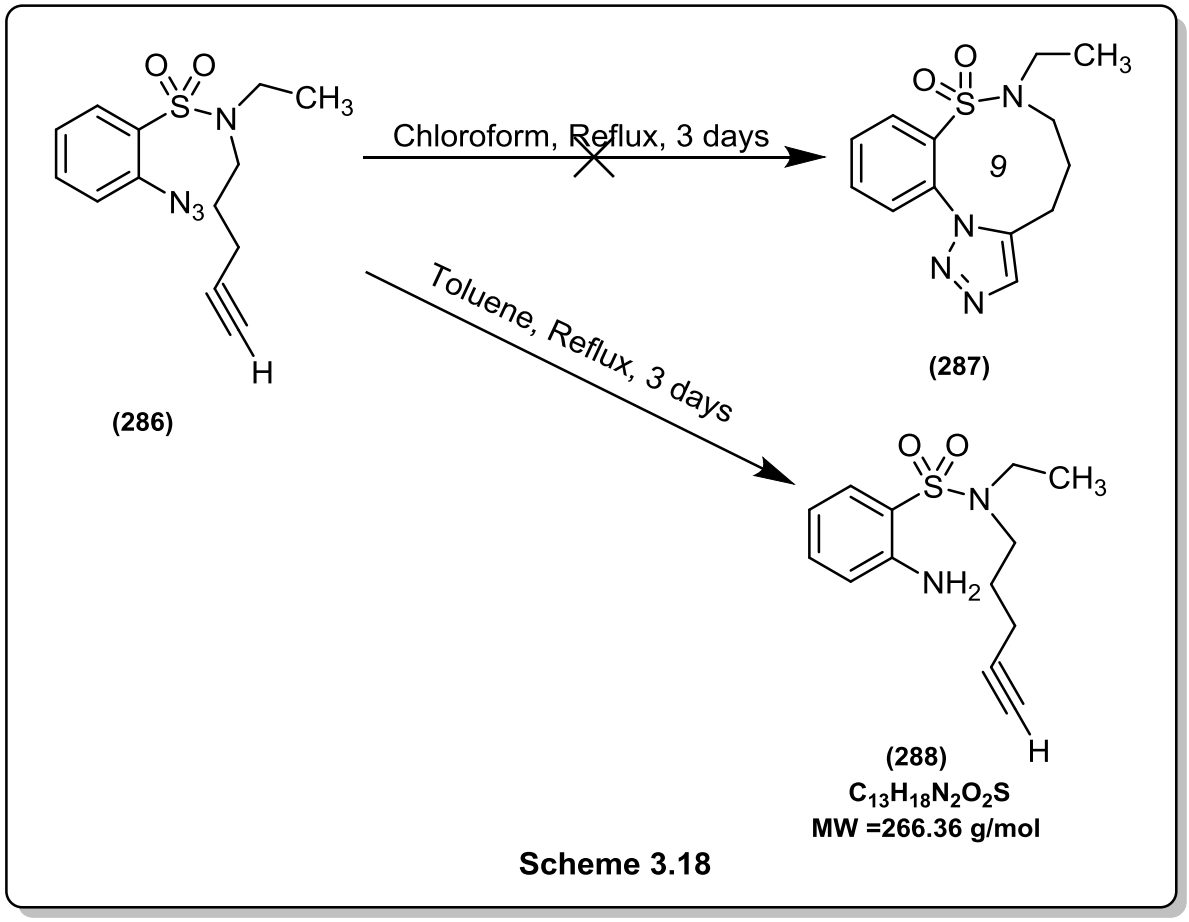
No	Products	**NMR** (400 MHz, $CDCl_3$, ppm)			**IR (cm^{-1})**		**HRMS**
		^{1}H NMR	**^{13}C NMR**				
		-CC**H**	-C**C**H	-**C**CH	**N_3**	-CCH	
4	 **(281)**	1.84 (bs)	70.44	80.81	2099.6	3307.6	305.1062 $[M+H]^+$ [Calc.= 305.1067]
5	 **(286)**	1.87 (bs)	68.98	83.18	2101.1	3281.9	293.1064 $[M+H]^+$ [Calc.= 293.1067]
7	 **(295)**	2.03(bs)	70.23	85.55	2099.1	3270.0	291.0910 $[M+H]^+$ [Calc.= 291.0910]

Table 3.7: Summary of spectroscopic data for compounds **281, 286** and **295.**

3.1.2.4. Attempted cyclization reaction with heating.



Scheme 3.18

In a further attempt to perform intramolecular cyclization of the alkynes (**281**), (**286**) and (**295**), compound (**286**) was heated to reflux in anhydrous chloroform for 3 days under a nitrogen atmosphere whilst being monitored by TLC which showed no change. The solvent was replaced with dry toluene and heated to reflux for 3 days. A different product was identified. Instead of the desired triazole product (**287**) the amine (**288**) (Scheme 3.18) was isolated: this is the product of azide reduction.

The structure of compound (**288**) was deduced by its infrared spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR spectrum and mass spectrometry.

The ^{1}H NMR spectrum showed the presence of the characteristic amine NH_2 proton signal as a broad singlet at 4.95 ppm while the alkyne CH proton was seen at 1.87 ppm.

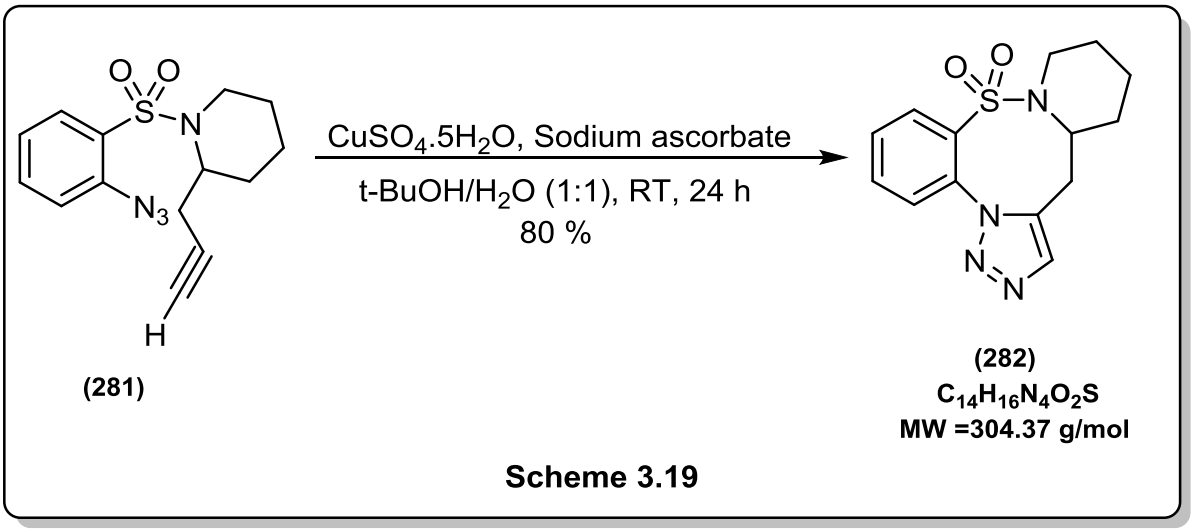
The ^{13}C NMR (100 NMR) spectrum showed the presence of the alkyne carbons at 68.97 (C**CH**) and 83.28 (**C**CH) ppm.

The infrared spectrum showed the disappearance of the azide stretch at υ_{max} 2101.1 cm^{-1} and also showed the appearance of the NH_2 group at υ_{max} 3375.7-3485.8 cm^{-1}. The alkyne (CH) absorption was present at υ_{max} 2304.1 cm^{-1}.

Mass spectrometry further supported the structure of product with measured mass of 267.1167 for the ion $[M+H]^+$ for required mass of 267.1162.

Attempts to thermally cyclise alkynyl azides (**281)** and (**295)** were also attempted but were unsuccessful.

3.1.2.5. Cyclisation reaction under "click" conditions.



(281)

(282)
$C_{14}H_{16}N_4O_2S$
MW =304.37 g/mol

Scheme 3.19

One final attempt was made to cyclise the alkynyl azides (**281)**, **(286)** and (**295)**.

In this attempt, the alkyne azides were treated with a solution of $CuSO_4.5H_2O$ in the biphasic system t-BuOH/H_2O as a solvent in the presence of sodium ascorbate.[194] This method is that used for copper catalysed alkyne-azide cycloaddition (CuAAC) for which the mechanism[195] is given below. This reaction is the well-known azide-alkyne "click" process.

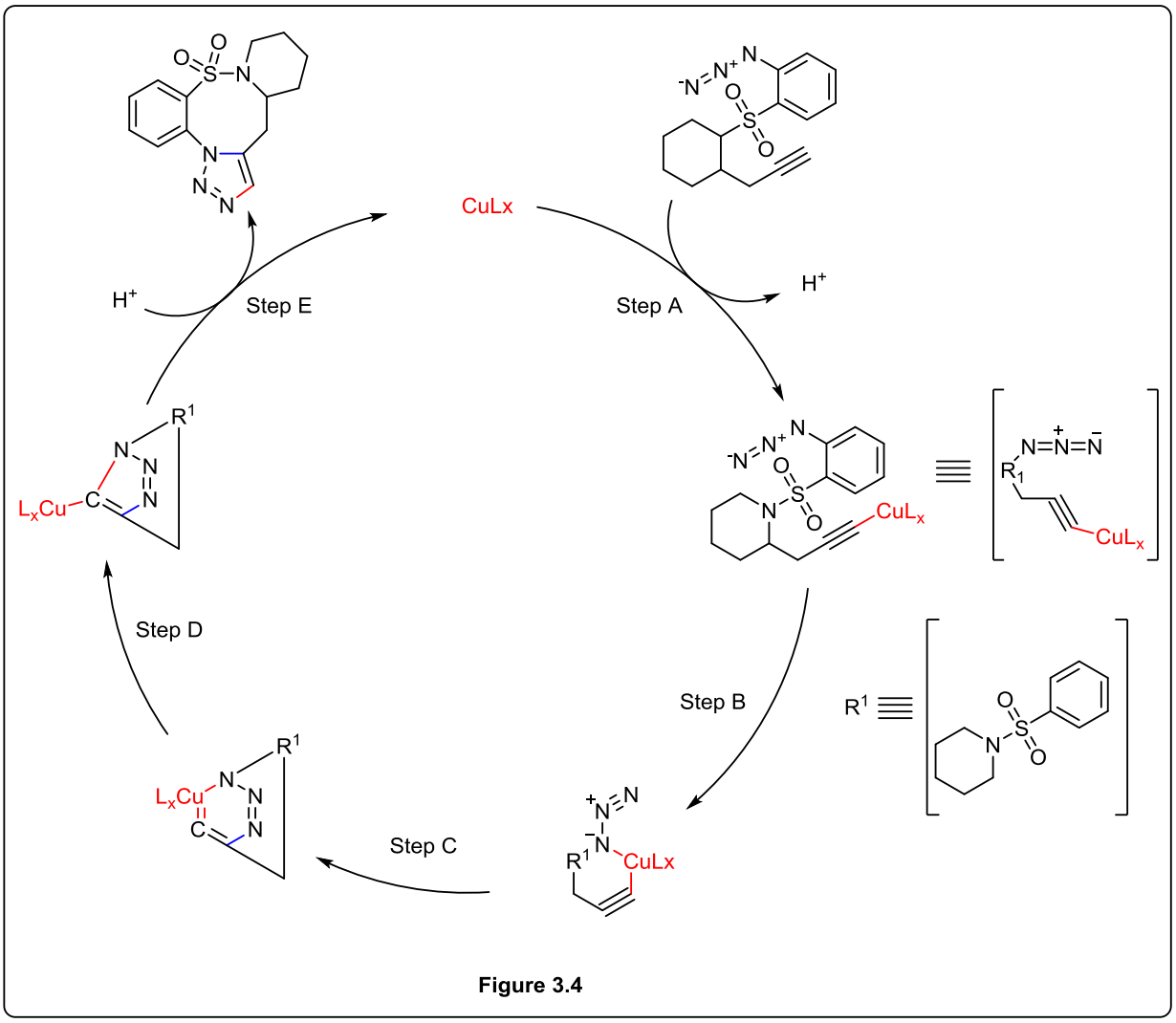


Figure 3.4

The reaction was successful with compound (**281**) and gave the benzothiazocine **(282)** in 80 % yield. Alkynylazides **(286)** and **(295)** did not react.

The structure of the product (**282**) was confirmed by IR spectroscopy, its ^{1}H NMR (400 MHz) spectrum, and ^{13}C NMR (100MHz) spectrum and by mass spectrometry.

The ^{1}H NMR (400 MHz) spectrum showed the disappearance of the alkyne proton at 1.84 ppm. The appearance of five aromatic protons confirmed an extra aromatic proton from the triazole with peaks as a multiplet at 7.55-7.59 (2H), a doublet at 7.63 (1H), a triplet of doublets at 7.68 (1H) and a doublet at 8.03 (1H) ppm. The piperidine ring CH_2 protons showed upfield at 1.18-1.69 (6H, 3 x C**H$_2$**), 3.51 (1H, NC**H**H) and 4.03-4.12 (1H, NCH**H**) and the CH in the piperidine ring system appeared at 2.68-2.71 ppm. The remaining (diazocine) CH_2 was seen as two signals at 1.87/2.28 ppm.

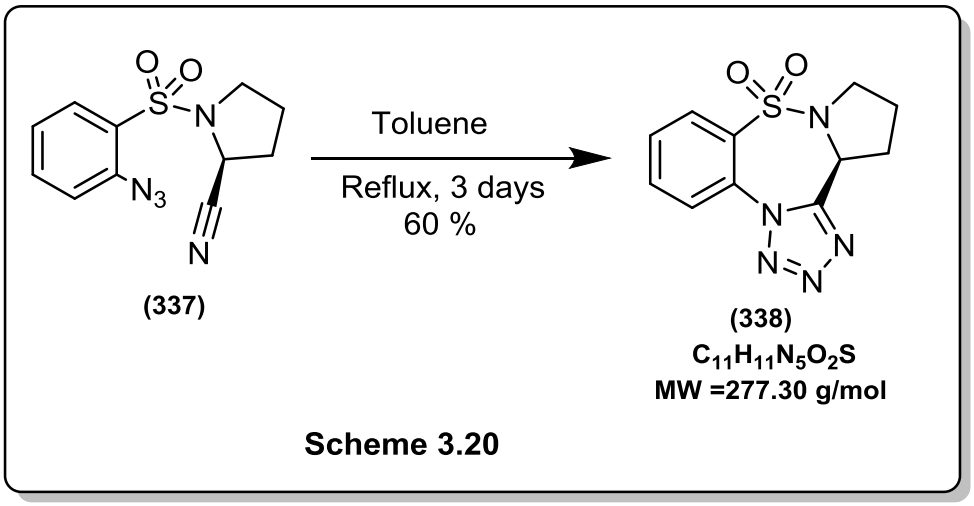
The ^{13}C NMR (100 MHz) spectrum showed the disappearance of the two alkyne carbons at 70.44 (C**CH**) and 80.81 (**C**CH) ppm. The presence of five aromatic CH signals confirmed an extra aromatic (CH) carbon from the triazole formation in the ^{13}C NMR spectrum with peaks at 127.65 (CH), 130.01 (CH), 130.30 (CH), 131.70 (CH) and 133.87 (CH) ppm. The extra aromatic quaternary carbon was seen at 133.93 ppm. The five CH_2 and the CH signal were upfield at 18.32 (CH_2), 23.07 (CH_2), 24.79 (CH_2) 32.38 (CH_2), 41.22 (CH_2) and 54.68 (CH) ppm. The infrared spectrum data proved that the azide absorption peak was absent and also confirmed the disappearance of the alkyne group absorption.

Further evidence for the structure was given by the HRMS for the measured ion $[M+H]^+$ at 305.1063.

3.2. The Synthesis of tetrazolobenzothiadiazepines.

3.2.1. Synthesis of tetrazolopyrrolobenzothiadiazepine.

3.2.1.1. (*S*)-Pyrrolobenzo[1,2-*b*]tetrazolo[5,1-*d*][1,2,5]thiadiazepine 9,9-dioxide.



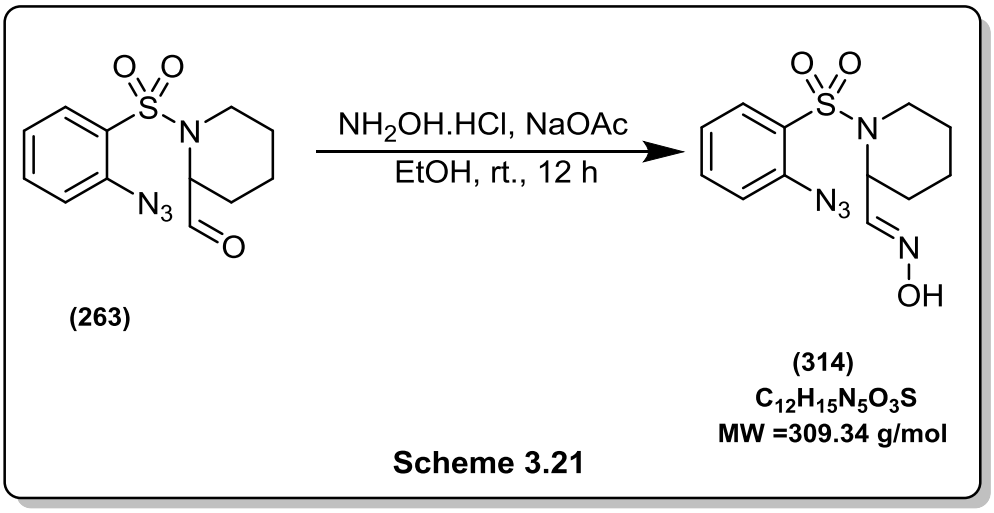
Scheme 3.20

The nitrile[186] (**337**) was synthesised as described by Chambers[160] in the group previously and was cyclised to give the tetrazole as also shown by Chambers. The synthesis and cyclisation of compound **(337)** were repeated to establish the process before moving onto new systems. Compound (338) was successfully formed in 60 % yield.

3.2.2. The synthesis of new tetrazolobenzothiadiazepines.

The nitriles were made by oxime dehydration where the oximes came, in turn, from the aldehydes we had already synthesised, as discussed above.

3.2.2.1. Conversion of the aldehydes into the oximes.



Scheme 3.21

Scheme 3.21 shows a typical example of this reaction. Oximes can exist as two stereo isomers, syn (Z) and anti (E) as shown[196] in Figure 3.5.

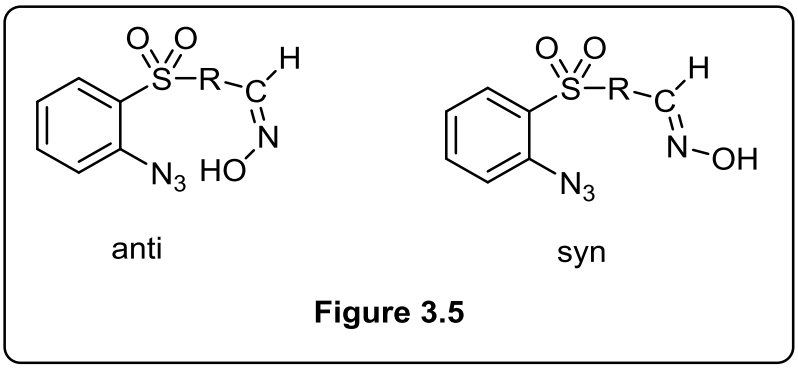


Figure 3.5

Scheme 3.21 shows a typical example of this reaction. The mechanism[197] is illustrated below (Figure 3.6), and involves first addition of the aldehyde or ketone to hydroxylamine to form an unstable intermediate[198]. In the second step, the intermediate decomposes by loss of H_2O giving the oxime.

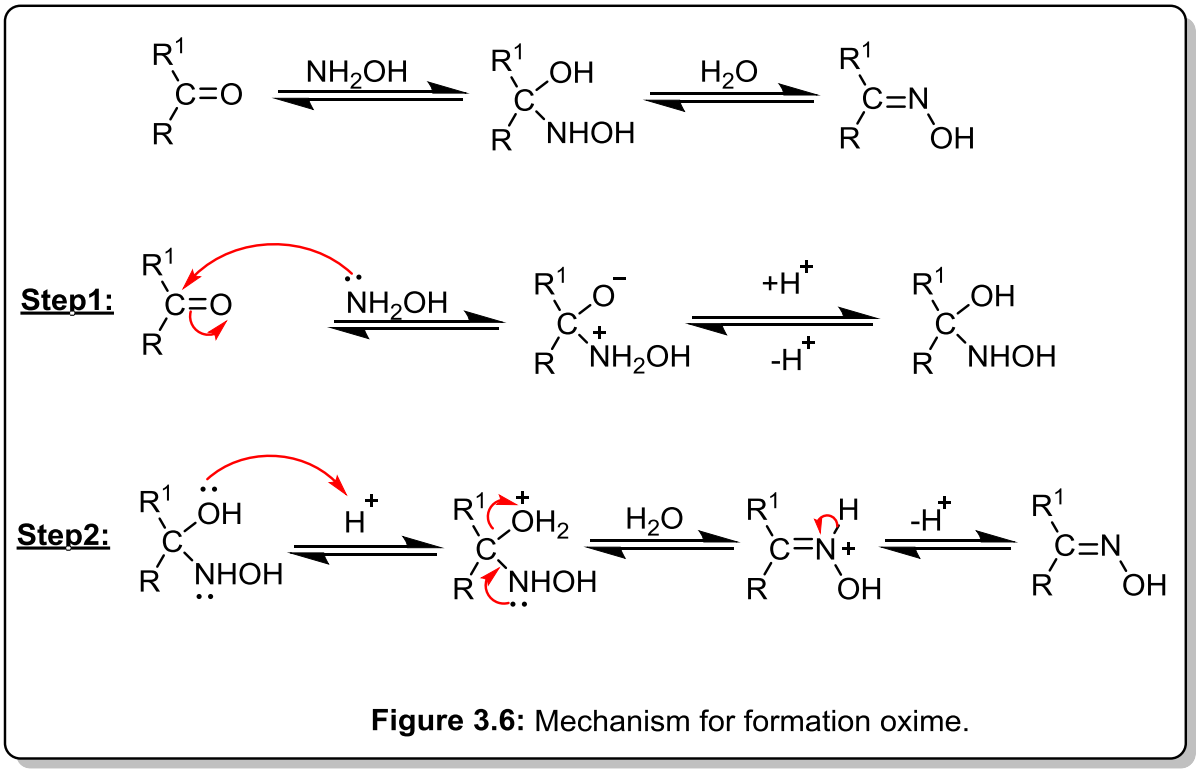
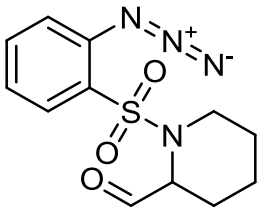
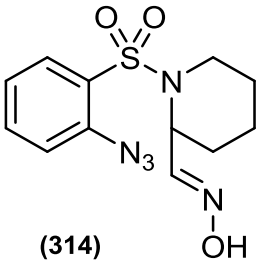
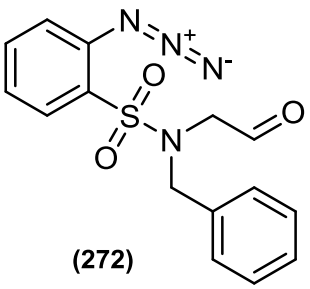
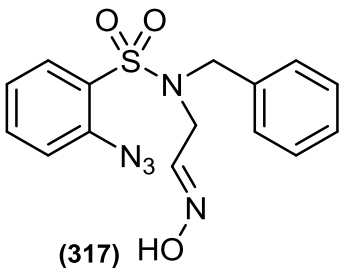


Figure 3.6: Mechanism for formation oxime.

The oximes synthesised in our work by reaction of aldehydes with hydroxylamine are summarised in Table 3.8.

No	Starting material	Products	Appearance/m.p	Yield %
1	 (263)	 (314)	Light yellow oil	68
2	 (272)	 (317)	White solid (m.p.=129-131 ^{o}C)	96

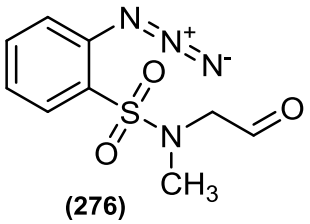
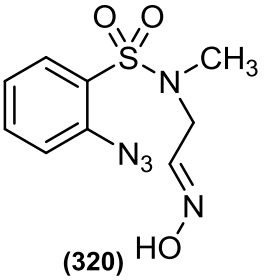
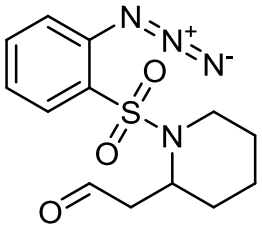
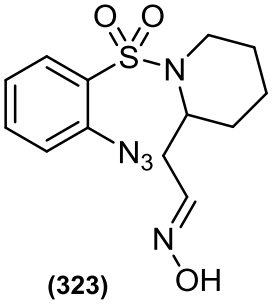
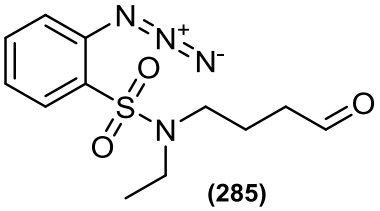
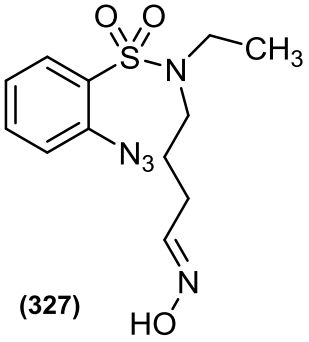
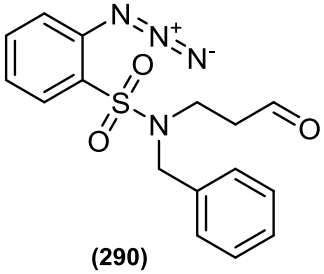
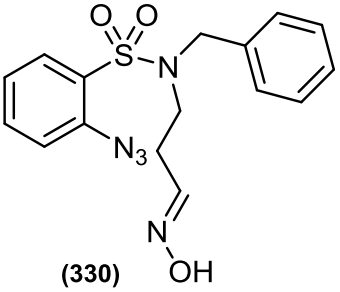
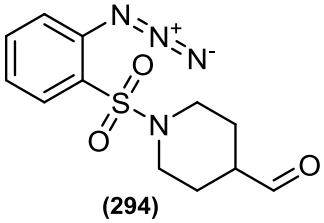
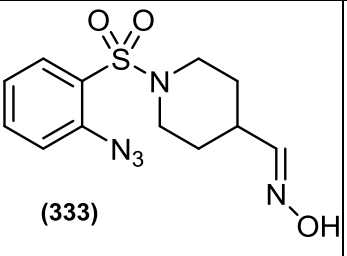
3	 **(276)**	 **(320)**	Light yellow oil	78
4	 (280)	 **(323)**	Light yellow oil	88
5	 **(285)**	 **(327)**	light yellow oil	92
6	 **(290)**	 **(330)**	yellow oil	93
7	 **(294)**	 **(333)**	White solid (m.p.= 151-153 ^{o}C)	85

Table 3.8: Oximes synthesis in this work

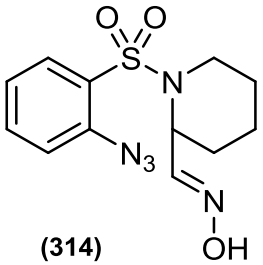
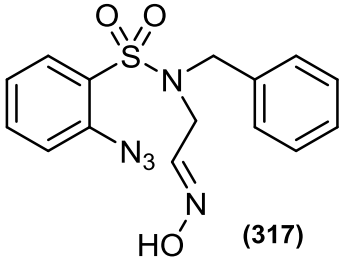
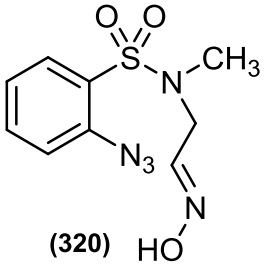
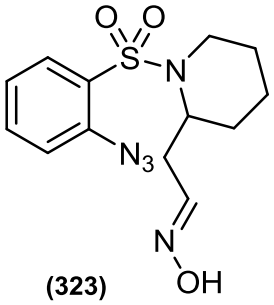
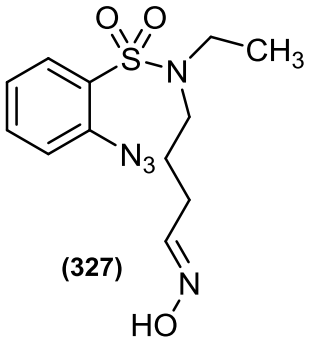
The structures of all oxime products were confirmed by spectroscopic means. The ^{1}H NMR (400 NMR) spectrum of compound (**314**), for example, showed the absence of the characteristic aldehyde CH proton signal. The presence of the broad signal OH proton downfield at 9.01 ppm gave further evidence for the success of the conversion of the aldehyde to the oxime and also seen was the appearance of the C**H**=N proton as a doublet at 6.84 ppm. The appearance of four aromatic protons downfield as a doublet of doublets at 7.21(1H) ppm, a doublet at 7.28 (1H) ppm, a doublet of doublet of doublets at 7.57 (1H) and doublet of doublets at 7.96 (1H) ppm showed the expected pattern of a 1,2-disubstituted benzene ring system. The eight upfield aliphatic CH_2 protons showed at 1.26 (1H), 1.36-1.42 (1H), 1.54-1.62 (1H), 1.66-1.74 (3H), 2.12 (1H) and 3.16 (1H) ppm and the single CH proton in the ring system appeared at 3.93 (1H) ppm.

The ^{13}C NMR spectrum confirmed that the carbonyl carbon had disappeared from 200.94 ppm and the new CHN signal appeared at 149.71 ppm. The presence of four aromatic CH signals at 119.85, 124.57, 131.42 and 134.02 ppm confirmed the structural assignment.

The infrared spectrum showed the presence of the broad OH stretch at υ_{max} 3244.5 cm^{-1} and showed the presence of the CH=N group at υ_{max} 1471.5 cm^{-1}. The azide was present at υ_{max} 2100.3 cm^{-1} and also noted was the disappearance of the carbonyl group peak at υ_{max} 1731.8 cm^{-1}.

Further evidence for the structure was given by the HRMS for the measured ion $[M+Na]^{+}$ which was consistent at 332.0788.

The data for the oximes produced is shown in Table 3.9 in summary form.

No	Products	NMR (400 MHz, ppm)			IR (cm^{-1})		Mass
		^{1}H NMR		^{13}C NMR			
		C**H**=N	O**H**	**C**HN	**N_3**	**OH**	
1	 (314)	6.84 (d), ($CDCl_3$)	9.01 (bs)	149.71 ($CDCl_3$)	2100.3	3244.5 (br.)	332.0788 $[M+H]^+$ [Calc.= 332.0788]
2	 (317)	6.43 (dd) (DMSO-d6)	11.14	147.42, (DMSO-d6)	2098.5	3213.7	346.0970 $[M+H]^+$ [Calc.= 346.0968]
3	 (320)	7.31 (t), ($CDCl_3$)	8.77	147.22 ($CDCl_3$)	2129.7	3427.0	270.0659 $[M+H]^+$ [Calc.= 270.0655]
4	 (323)	6.55 (t), ($CDCl_3$)	8.75	148.79 ($CDCl_3$)	2098.7	3247.6	324.1120 $[M+H]^+$ [Calc.= 324.0625]
5	 (327)	7.34 (t), ($CDCl_3$)	8.26	150.30 ($CDCl_3$)	2098.5	3446.4	312.1124 $[M+H]^+$ [Calc.= 312.1125]

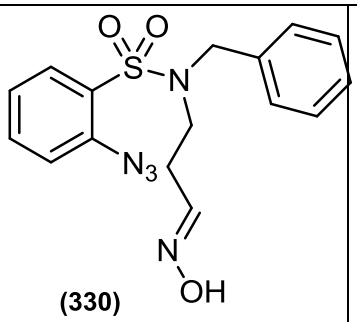
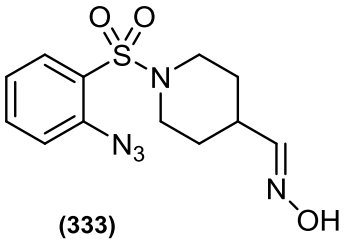
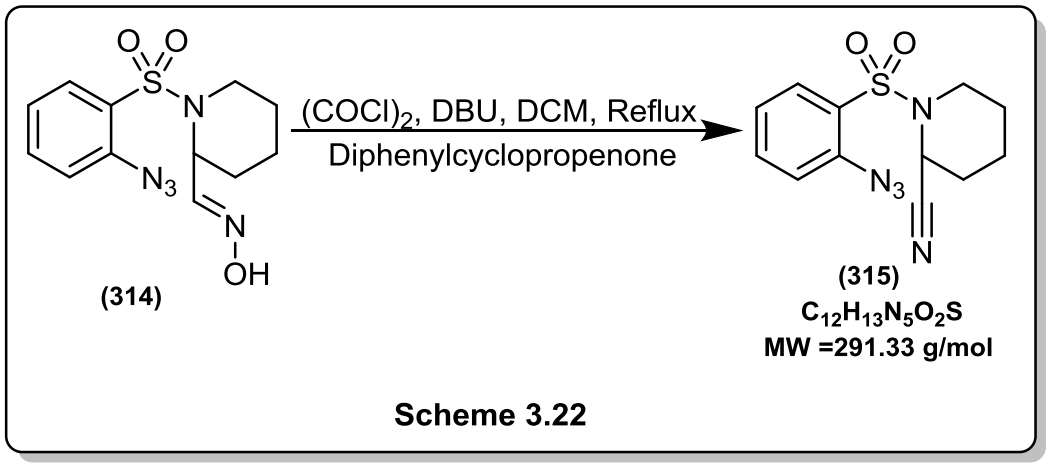
6	 **(330)**	7.02 (t), ($CDCl_3$)	9.41	148.49 ($CDCl_3$)	2101.2	3258.9	360.1120 $[M+H]^+$ [Calc.= 360.01125]
7	 **(333)**	7.27 (d), ($CDCl_3$)	9.58	153.69 ($CDCl_3$)	2097.8	3255.6	310.0967 $[M+H]^+$ [Calc.= 310.0968]

Table 3.9: Summary of oxime spectroscopic data.

3.2.2.2. Conversion of the oximes into the nitriles.



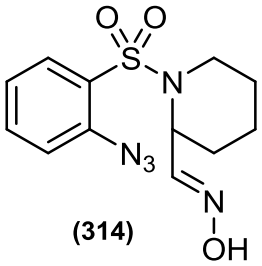
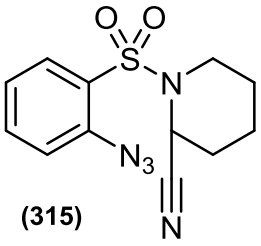
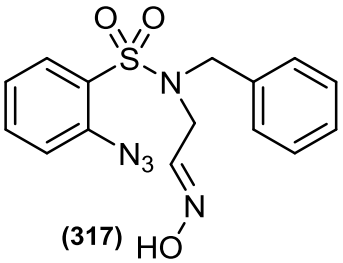
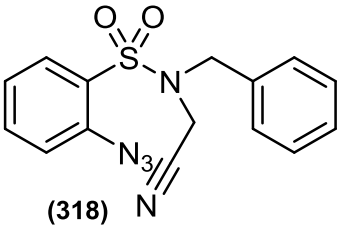
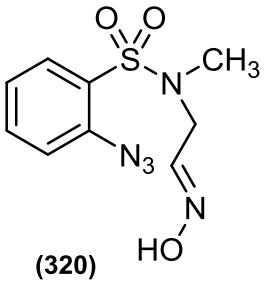
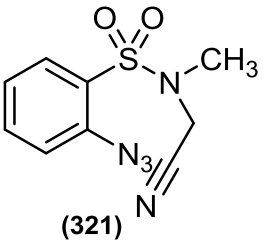
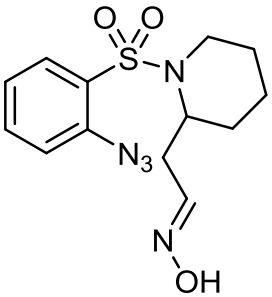
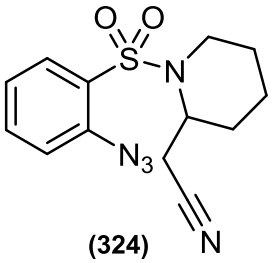
Scheme 3.22

In the next reaction, nitriles were synthesised by the dehydration of the oximes. Many reagents are available for this process and an example is the use of BOP in combination with DBU.[199,200]

In our work, the oxime was reacted with $(COCl)_2$ in the DCM in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base. The mixture was heated to reflux while monitoring by TLC and the nitrile was isolated from the reaction by extraction with DCM.

The reaction was performed using diphenylcyclopropenone as a catalyst, and is based on interest in our group and others[201] in the development of diphenylcyclopropenone as a reagent and catalyst.

In this case, the nitriles **(315), (318), (321), (324), (328), (331)** and **(334)** were synthesised with yields shown in Table 3.10.

No	Starting material	Products	Appearance-m.p.	Yield %
1	 (314)	 (315)	Dark brown oil	86
2	 (317)	 (318)	Light yellow solid (m.p.=107-109 ^{o}C)	84
3	 (320)	 (321)	Yellow oil	71
4	 (323)	 (324)	Light yellow oil	81

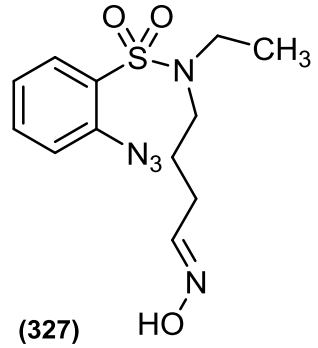
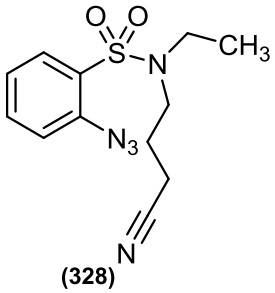
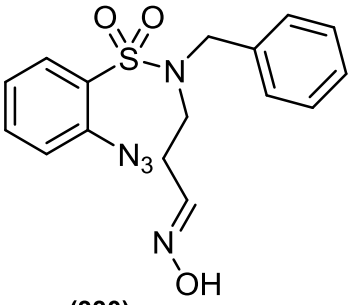
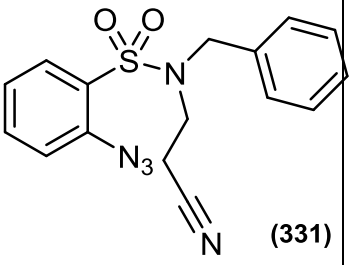
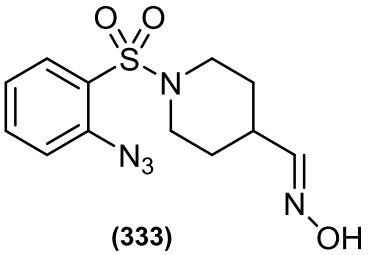
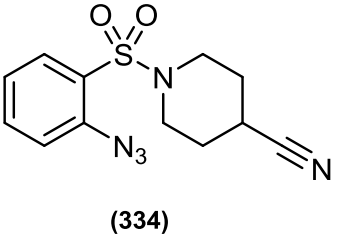
5	 (327)	 (328)	light yellow oil	92
6	 (330)	 (331)	Bronze coloured solid (m.p.=78-80 ^{o}C)	77
7	 (333)	 (334)	Light yellow oil	85

Table 3.10: Synthesis of nitriles from oximes.

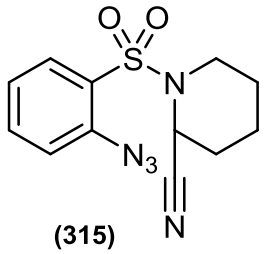
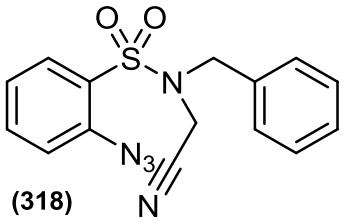
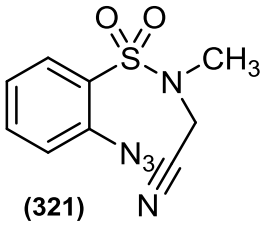
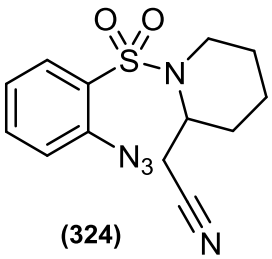
All the nitriles gave consistent spectroscopic data. With compound **(315)**, for example, the ^{1}H NMR spectrum showed the absence of the characteristic oxime hydroxyl OH proton and the disappearance of the CH=N proton. The eight upfield aliphatic CH_2 protons showed at 1.46-1.59 (1H), 1.61-1.71 (2H), 1.78-1.87 (2H), 1.91-1.96 (1H), 2.91 (1H) and 3.77 (1H) ppm and the single CH proton in the ring system appeared at 5.09 ppm. The presence of four aromatic protons downfield as a doublet of doublet of doublets at 7.18 (1H) ppm, a doublet at 7.25 (1H) ppm, a doublet of doublet of doublets at 7.54 (1H) and a doublet at 7.87 (1H) ppm confirmed that the 1,2-disubstituted benzene ring system was still present.

The ^{13}C NMR spectrum showed the presence of the (CN) as a new quaternary carbon at 116.35 ppm and confirmed that the CH=N signal had disappeared. The presence of four aromatic CH signals at 120.05, 124.05, 131.55 and 134.70 ppm and four aliphatic CH_2 carbons and the CH carbon at 20.01 (CH_2), 24.93 (CH_2), 29.63 (CH_2), 43.49 (CH_2) and 46.16 (CH) ppm confirmed the assignment.

The infrared spectrum showed the disappearance of the broad OH stretch at υ_{max} 3244.5 cm^{-1} and showed the absence of the CH=N group at υ_{max} 1471.5 cm^{-1}. The azide absorption was present at υ_{max} 2100.4 cm^{-1} and further proof came from a υ_{max} of 2257.0 cm^{-1} for (CN).

Mass spectrometry further supported the structure of the product with a measured mass of 309.1140 for the ion $[M+NH_4]^+$ for required mass of 309.1128.

The IR spectra, ^1H NMR spectra, ^{13}C NMR spectra, and mass spectrometry identified the other products, and the data obtained is summarised in Table 3.11.

No	**Products**	**^{13}C NMR (400 MHz, $CDCl_3$, ppm)**	**IR (cm^{-1})**		**HRMS**
		CN	**N_3**	**CN**	
1	 **(315)**	116.35	2100.4	2257.0	309.1140 $[M+NH_4]^+$ [Calc.= 309.1128]
2	 **(318)**	114.29	2104.9	2248.8	350.0685 $[M+Na]^+$ [Calc.= 350.0682]
3	 **(321)**	114.50	2125.2	2261.1	269.0812 $[M+NH_4]^+$ [Calc.= 269.0815]
4	 **(324)**	117.34	2098.5	2253.7	323.1294 $[M+NH_4]^+$ [Calc.= 323.1284]

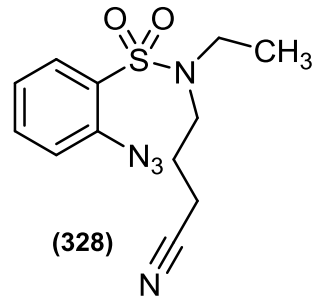
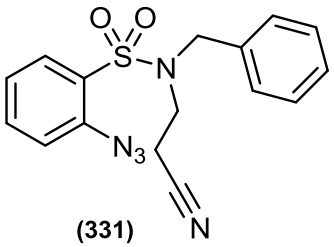
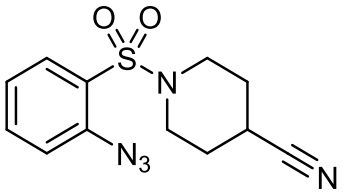
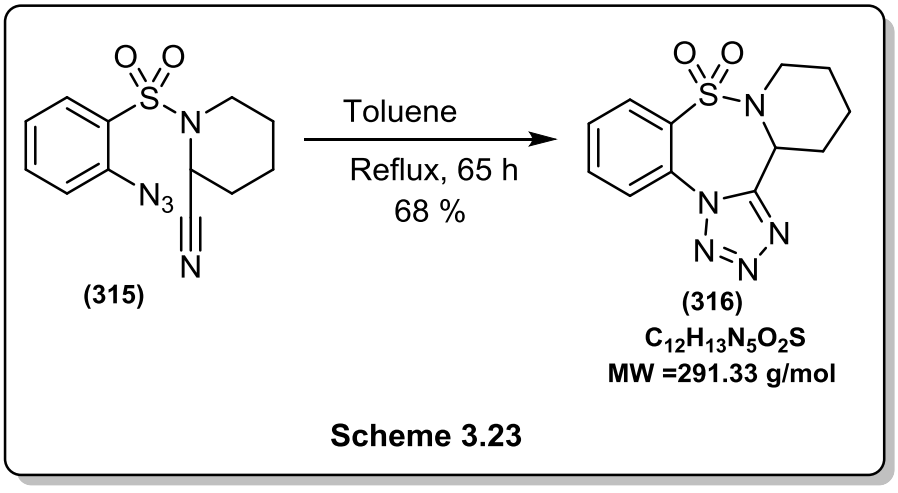
5	 (328)	119.21	2099.0	2246.5	311.1286 $[M+NH_4]^+$ [Calc.= 311.1285]
6	 (331)	117.34	2102.2	2250.7	364.0836 $[M+Na]^+$ [Calc.= 364.0839]
7	 (334)	120.58	2098.6	2254.0	292.0857 $[M+H]^+$ [Calc.= 292.0863]

Table 3.11: Summary of spectroscopic data for nitriles.

3.2.2.3. Cycloaddition of the nitriles with azides.

The intramolecular azide to nitrile reaction is shown in the following example:



Scheme 3.23

This method is one of the most important synthesis routes to tetrazoles, as shown in figure 3.7.

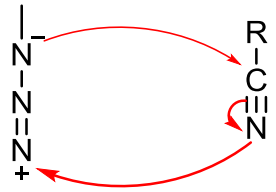
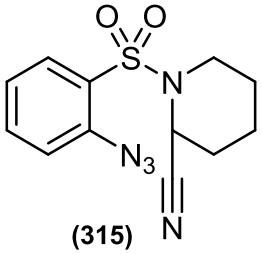
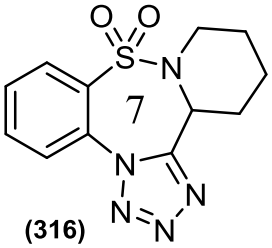
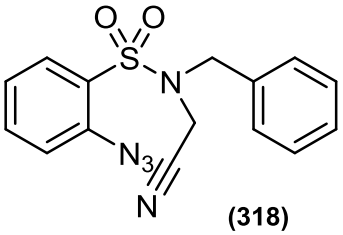
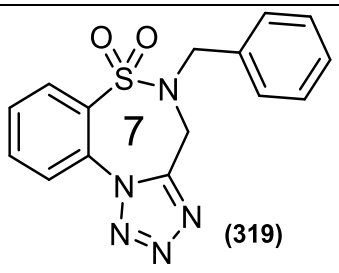


Figure 3.7: 1,3-dipolar cycloaddition between the azide and nitrile

The reaction mechanism is a straightforward [2+3] cycloaddition of nitrile to form a five membered tetrazole ring.

With the azides (**315**), (**318**) and (**321**) expected benzothiazepine products (**316, 319** and **322**) were isolated in 68 %, 78 % and 89 %, respectively. However, none of the desired products could be identified and only starting material (**324, 328, 331** and **334**) could be identified in the other reactions attempted, as summarised in Table 3.12.

No	Starting material	Products	Appearance/m.p.	%
1	 (315)	 (316)	White solid (m.p.= 179-181 ^{o}C)	68
2	 (318)	 (319)	Light yellow oil	78

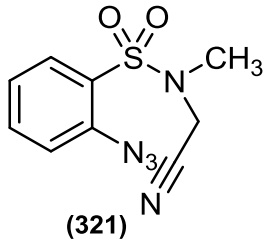
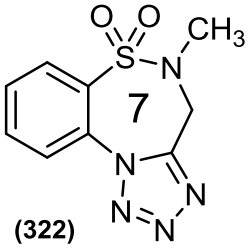
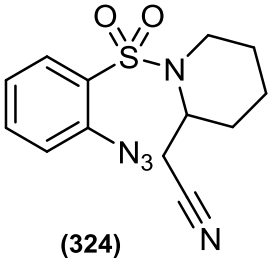
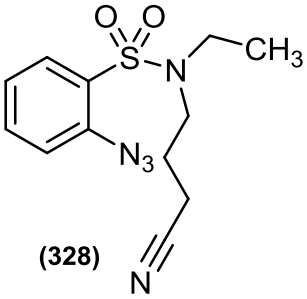
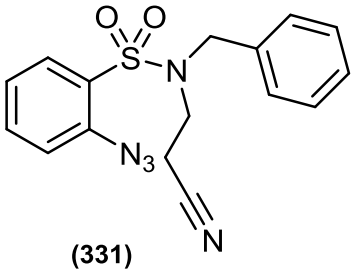
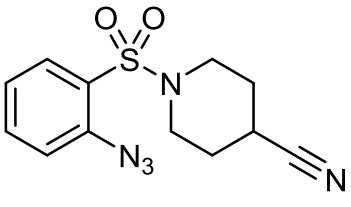
3	 (321)	 (322)	Yellow oil	89
4	 (324)	No	No	0
5	 (328)	No	No	0
6	 (331)	No	No	0
7	 (334)	No	No	0

Table 3.12: Synthesis of Tetrazoles.

The structures of the products (**316)**, (**319**) and (**322**) were confirmed through spectroscopic analysis.

The ^{1}H NMR spectrum of compound (**316**), for example, showed the eight upfield CH_2 protons at 1.43-1.50 (1H), 1.66-1.85 (3H), 2.24-2.32 (1H), 2.71-2.82 (2H) and 3.35-3.39 (1H) ppm and the single CH proton in the thiadiazepine ring system at 5.23 (1H) ppm. The

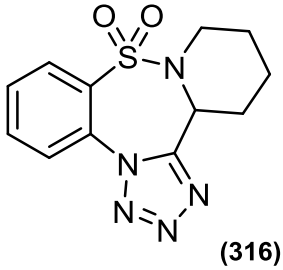
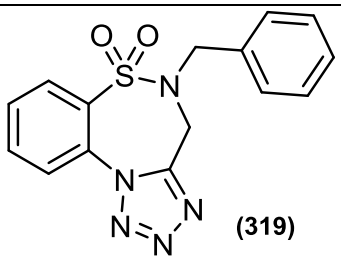
presence of four aromatic protons at 7.67 (1H) ppm, 7.84 (1H) ppm, 8.16 (1H) and 8.47 (1H) ppm confirmed the 1,2-disubstituted benzene ring system.

The ^{13}C NMR spectrum showed the absence of the (CN) carbon at 116.35 ppm and the appearance of seven aromatic carbon signals confirmed the extra sp^2 carbon of the tetrazole ring with signals at 124.48 (CH), 129.46 (CH) 129.74 (CH), 130.37 (qC), 130.67 (qC), 134.64 (CH) and 154.24 (qC) ppm while the four aliphatic CH_2 carbon signals and CH carbon signal of the piperidine ring system appeared at 20.62 (CH_2), 24.27 (CH_2), 28.97 (CH_2), 45.37 (CH_2) and 51.81 (CH) ppm.

The IR spectrum confirmed the loss of the azide group at υ_{max} 2100.4 cm^{-1} and the absence of the nitrile group at υ_{max} 2257.0 cm^{-1}.

Mass spectrometry further supported the structure of product with a measured mass of 292.0866 for the ion $[M+H]^+$ for a required mass of 292.0863.

The other structures were confirmed in the same manner with IR spectroscopy, ^1H NMR spectra, ^{13}C NMR spectra and mass spectrometry all being consistent (Table 3.13).

No.	**Products**	**^{13}C NMR (400 MHz, $CDCl_3$, ppm)**	**Mass**
		C=N	
1	 **(316)**	154.24	292.0866 $[M+H]^+$ [Calc.= 292.0863]
2	 **(319)**	151.75	328.0866 $[M+H]^+$ [Calc.= 328.0863]

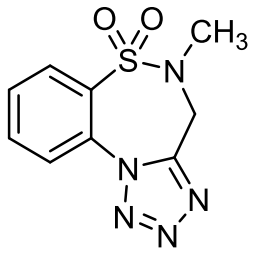
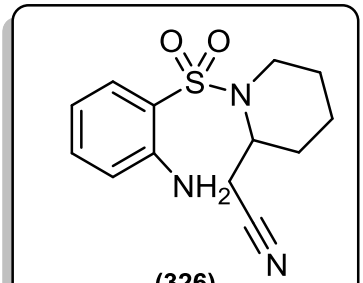
3	 **(322)**	151.72	252.0555 $[M+H]^+$ [Calc.= 252.0550]

Table 3.13: Summary of the Tetrazole Data.

All attempts to cyclise compound, **(324)**, **(328)**, **(331)** and (**334**) were unsuccessful, again showing that the formation of 8- and 9-membered rings, this time using azide to nitrile cycloadditon, is not favoured. Compound (**324**) gave the amine (**326**) when heated in xylene for 3 days, but no other reactions gave any products.

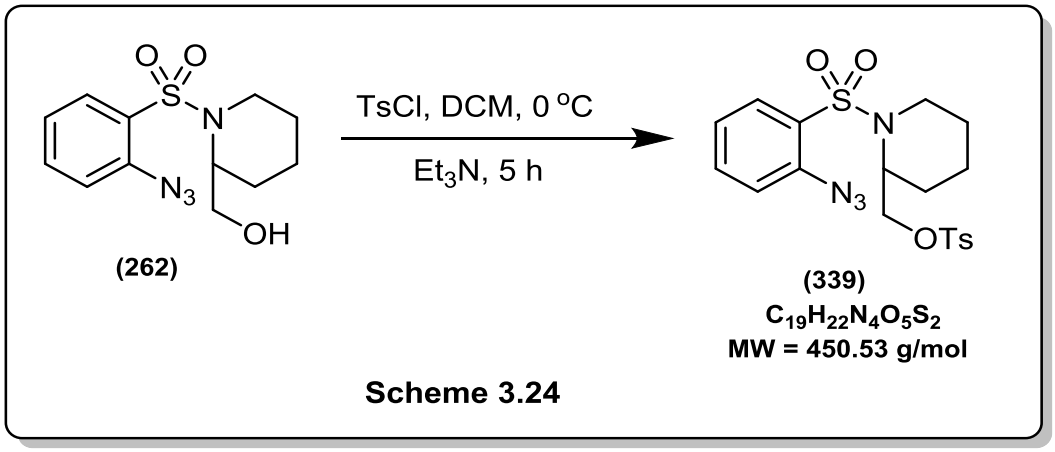


(326)
$C_{13}H_{17}N_3O_2S$
MW =279.10 g/mol

Figure 3.8

3.2.3. Attempted synthesis of tetrazolobenzothiadiazepine analogues via tosylates.

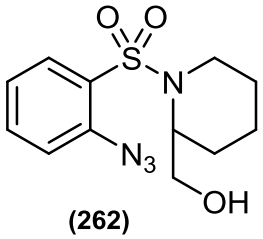
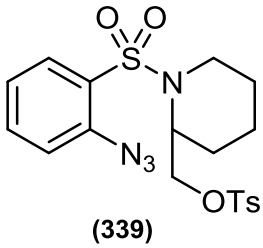
3.2.3.1. Tosylation of the alcohol.

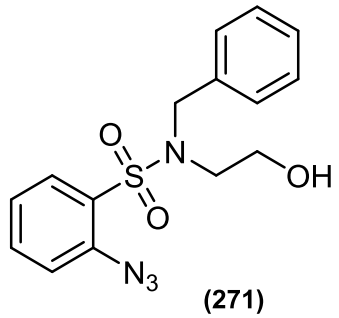
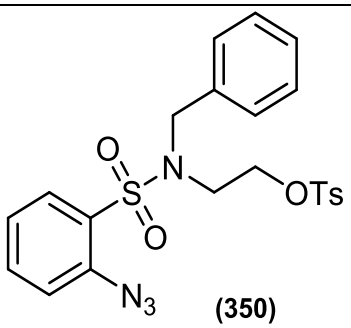
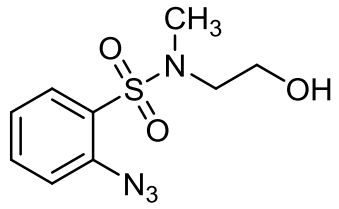
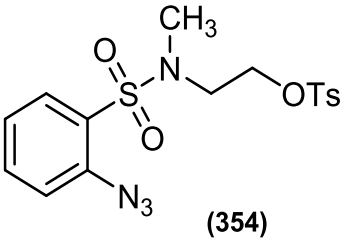
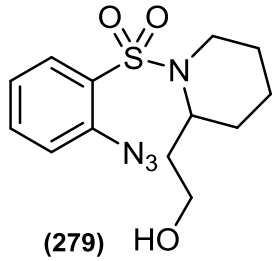
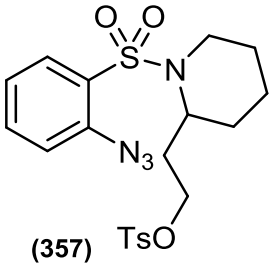
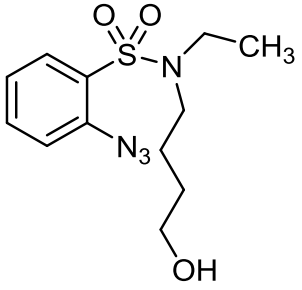
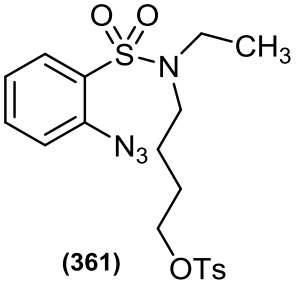
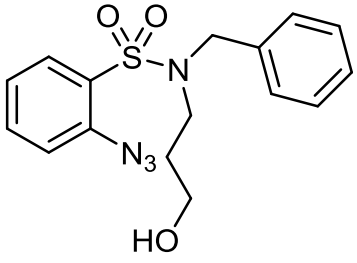
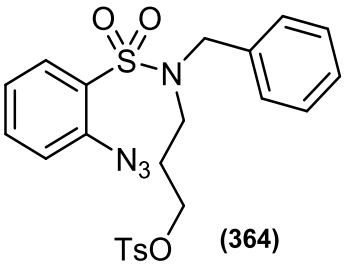
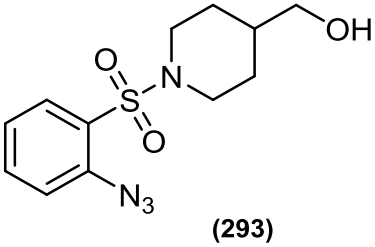
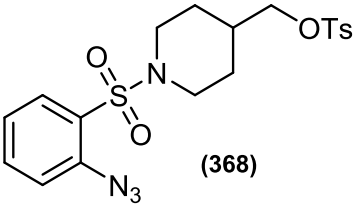


Scheme 3.24

As well as making nitriles by oxime dehydration, we also made them by nucleophilic substitution of tosyl by cyanide. The tosylates were made from the alcohols made above.

Thus the alcohols were converted into tosylates using p-toluenesulfonyl chloride and base.[202] The alcohol was treated with p-toluenesulfonyl chloride in the presence of Et_3N as a base in DCM and the mixture stirred for 5 hours at room temperature. The desired products (**339, 350, 354, 357, 361, 364, 368** and **346**) were synthesised with the yields and appearance shown in Table 3.14.

No.	Starting material	Desired products	Appearance	Yield %
1	 (262)	 (339)	Yellow oil	98

2	 **(271)**	 **(350)**	Light yellow solid (m.p.=92-94 ^{o}C)	98
3	 **(275)**	 **(354)**	Yellow oil	88
4	 **(279)**	 **(357)**	Light yellow oil	84
5	 **(284)**	 **(361)**	Deep brown oil	97
6	 **(289)**	 **(364)**	Brown oil	89
7	 **(293)**	 **(368)**	Brown oil	89

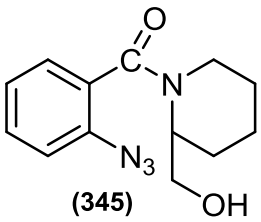
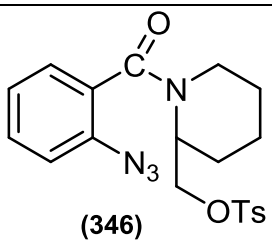
8	 **(345)**	 **(346)**	Light yellow oil	94

Table 3.14: Sythesis of tosylates**.**

The structures of the tosylates were confirmed by IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

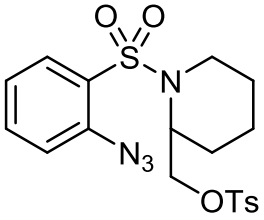
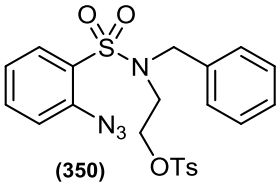
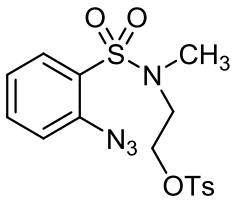
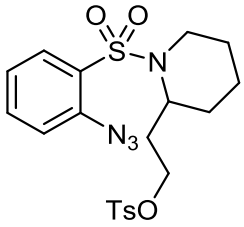
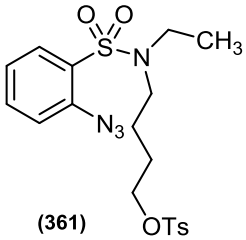
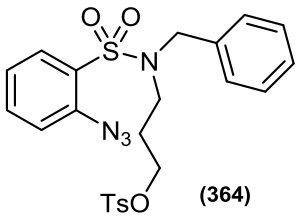
The ^{1}H NMR spectrum of compound (**339**), for example, showed the three CH_3 protons from the tosylate group as a singlet at 2.34 (3H) ppm while the absence of the OH proton signal gave further evidence for the success of the tosylation. The distinct signals of the p-tosyl aromatic ring protons confirmed the tosylation.

The ^{13}C NMR spectrum showed the aromatic CH carbons downfield at 120.10, 124.44, 127.83, 129.97, 131.05 and 133.89 ppm and the four aliphatic CH_2 carbons and CH in the piperidine ring system were found at 18.24 (CH_2), 24.89 (CH_2), 24.92 (CH_2), 41.97 (CH_2) and 50.58 (CH) ppm. The p-totyl methyl was seen at 21.63 ppm.

IR spectroscopy showed the azide group at υ_{max} 2099.0 cm^{-1} and the disappearance of the broad peak at υ_{max} 3359.0 cm^{-1} for OH stretching.

Mass spectrometry further supported the structure of the product with a measured mass of 468.1365 for the ion $[M+NH_4]^+$ for a required mass of 468.1370.

The structures of the other tosylates were confirmed in the same manner with IR spectroscopy, ^{1}H NMR spectra, ^{13}C NMR spectra, mass spectrometry and the key data is shown in Table 3.15.

No.	Tosylate	NMR (400 MHz, $CDCl_3$, ppm)		IR (cm^{-1})		HRMS
		^{1}H NMR	^{13}C NMR			
		CH_3	CH_3	N_3	C-O	
1	 (339)	2.34 (bs)	21.63	2099.0	1159.2	468.1365 $[M+NH_4]^+$ [Calc.= 468.1370]
2	 (350)	2.47 (bs)	21.68	2129.5	1159.4	509.0910 $[M+Na]^+$ [Calc.= 509.0924]
3	 (354)	2.42 (s)	21.65	2100.5	1157.7	428.1063 $[M+NH_4]^+$ [Calc.= 428.1057]
4	 (357)	2.36 (bs)	21.65	2098.1	1157.0	465.1269 $[M+H]^+$ [Calc.= 465.1261]
5	 (361)	2.46 (bs)	21.66	2129.0	1155.9	453.1264 $[M+H]^+$ [Calc.= 453.1261]
6	 (364)	2.45 (s)	21.66	2128.0	1157.0	501.1266 $[M+H]^+$ [Calc.= 501.1261]

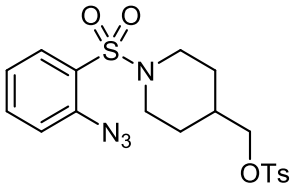
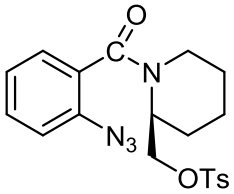
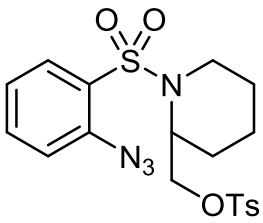
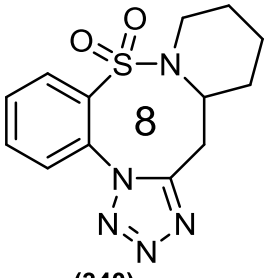
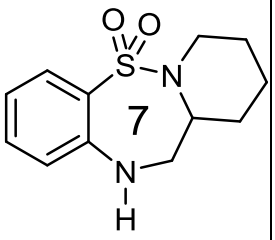
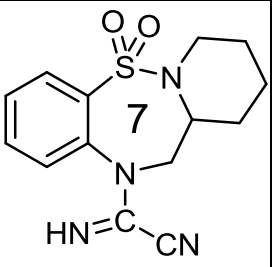
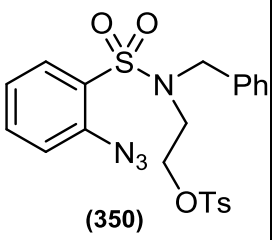
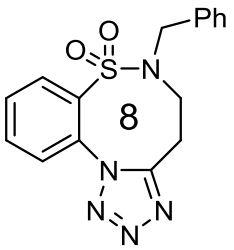
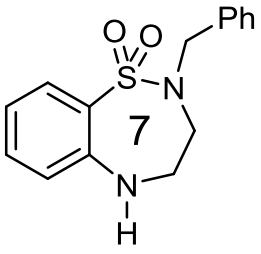
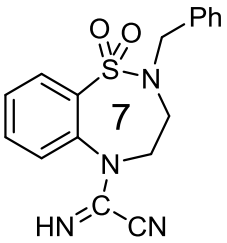
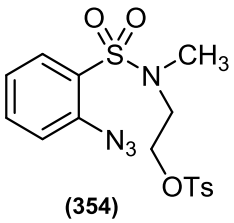
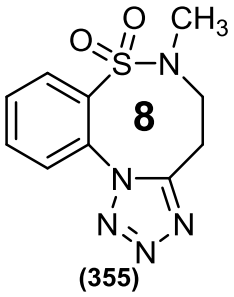
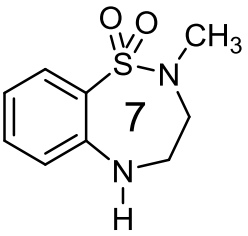
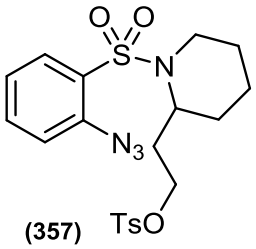
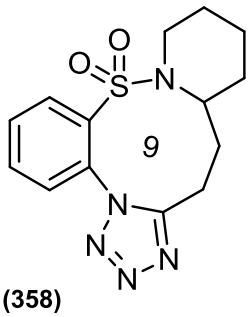
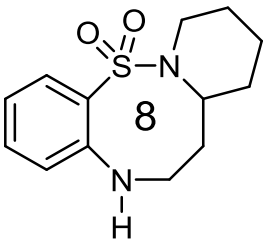
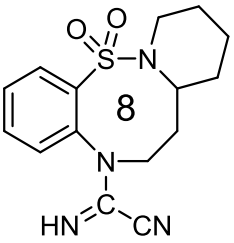
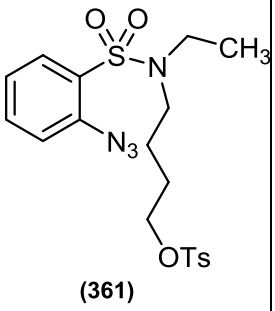
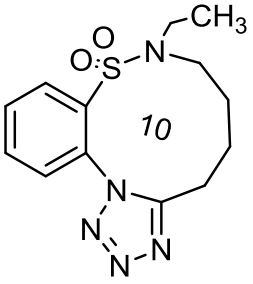
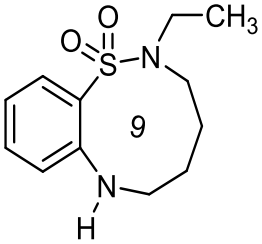
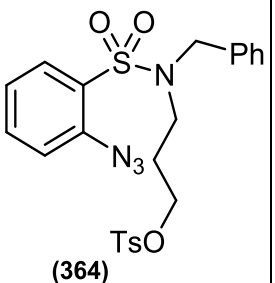
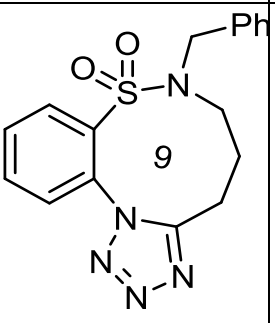
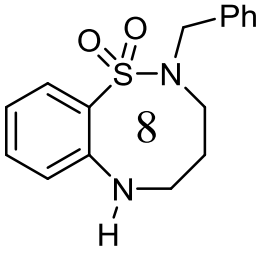
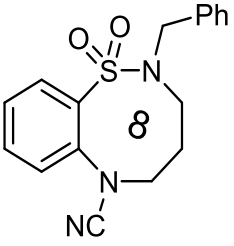
7	 (368)	2.35 (s)	21.64	2130.6	1173.8	451.1108 [M+H]+ [Calc.= 451.1104]
8	 (346)	2.26 (bs)	21.46	2120.5	1147.4	437.1237 $[M+Na]^+$ [Calc.= 437.1254]

Table 3.15: Summary of spectroscopic Data for the Tosylates.

3.2.3.2. Reactivity of tosylate with sodium cyanide.

The next step was the displacement of the tosylate with cyanide anion. [203] The tosylates were treated with NaCN in dry DMSO. The mixture was heated at 70 ^{o}C under a nitrogen atmosphere for 12 h. Under these conditions, the expected nitriles were never isolated. Instead a mixture of saturated 7, 8- and 9-membered rings were formed [product (1) in Table 3.16] together with some additional cyanide addition products [product **(2)** in Table 3.16].

No.	**Tosylate**	**Desired product**	**Product obtained (1)**	**Product obtained (2)**
1	 **(339)**	 **(340)**	 **(341,** 63 %)	 **(342,** 31 %)

2	 **(350)**	 **(351)**	 (**352**, 84 %)	 **(353,** 9 %)
3	 **(354)**	 **(355)**	 **(356,** 87 %)	None
4	 **(357)**	 **(358)**	 **(359,** 61 %)	 **(360,** 29 %)
5	 **(361)**	 **(362)**	 **(363,** 60 %)	None
6	 **(364)**	 **(365)**	 **(366,** 80 %)	 **(367, 17 %)**

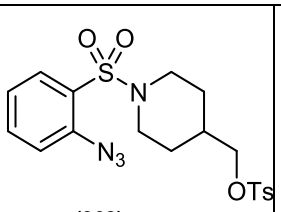
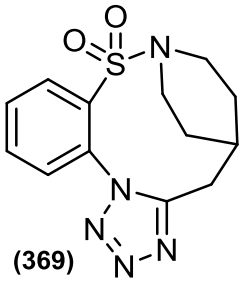
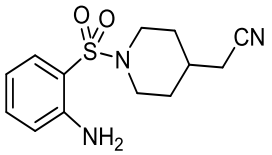
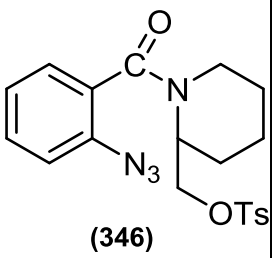
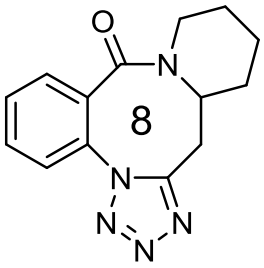
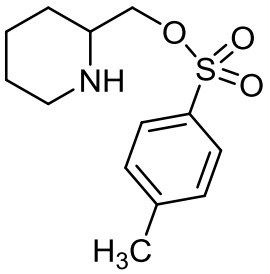
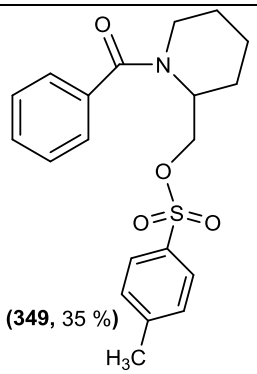
7	 **(368)**	 **(369)**	 **(370,** 57 %**)**	None
8	 **(346)**	 **(347)**	 **(348,** 31 %**)**	 **(349,** 35 %**)**

Table 3.16: The results of attempted nitrile to azide cycloadditions.

The structures of these products were confirmed by their infrared spectra, ^{1}H NMR spectra, ^{13}C NMR spectra, mass spectrometry and (in the case of (**342**)) by X-ray crystallography.

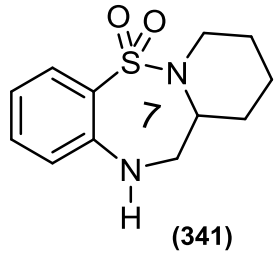
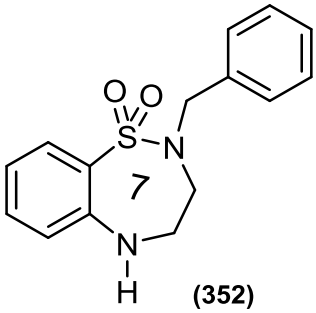
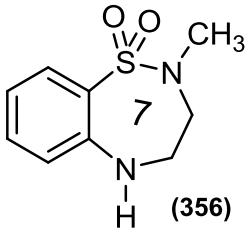
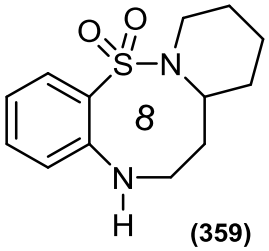
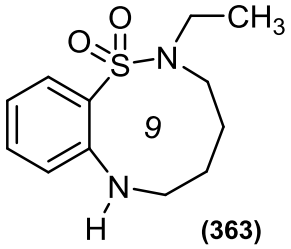
The ^{1}H NMR spectrum of compound (**356**), for example, showed the presence of the secondary amine NH proton signal as a broad singlet at 4.38 ppm and the appearance of the three CH_3 protons as a singlet at 2.82 (3H) ppm. The presence of four aromatic protons at 6.89 (1H) ppm, 7.01 (1H) ppm, 7.33 (1H) and 7.85 (1H) ppm confirmed the 1,2-disubstituted benzene ring system.

The ^{13}C NMR spectrum showed the $2CH_2$ carbons and the CH_3 carbon upfield at 35.73 (CH_3), 42.64 (CH_2) and 52.41 (CH_2) ppm. The four aromatic CH signals were found at 120.97 (CH), 121.10 (CH), 130.33 (CH) and 133.35 (CH) ppm.

The IR spectrum showed the presence of the NH stretch at υ_{max} 3370.5 cm^{-1}. The azide absorption peak had disappeared from υ_{max} 2100.5 cm^{-1} and the C-N stretch peak at υ_{max} 1148.7 cm^{-1} was also seen. No nitrile was present.

Further evidence for the structure was given by the HRMS for the measured ion $[M+H]^{+}$ was which consistent at 213.0694.

For the other cyclised examples (**341, 352, 359, 363** and **366**), the structures were confirmed in the same manner with IR spectroscopy, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry. The data for these compounds is summarised in Table 3.17.

No.	Product (1)	^{1}H NMR (400 MHz, $CDCl_3$, ppm)	IR (cm^{-1})		HRMS
		N-**H**	**N-H**	**C-N**	
1	 **(341)**	4.47 (bs)	3348.1	1153.2	252.0931 $[M]^+$ [Calc.= 252.0932]
2	 **(352)**	4.32 (bs)	3370.8	1152.8	289.1007 $[M+H]^+$ [Calc.= 289.1005]
3	 **(356)**	4.38 (bs)	3370.5	1148.7	213.0694 $[M+H]^+$ [Calc.= 213.0692]
4	 **(359)**	4.20 (bs)	3365.0	1150.0	267.1167 $[M+H]^+$ [Calc.= 267.1162
5	 **(363)**	4.79 (bs)	3409.9	1146.1	255.1165 $[M+H]^+$ [Calc.= 255.1162]

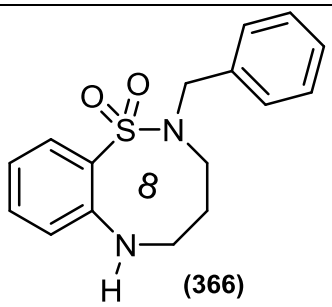
6	 (366)	5.07 (bs)	3368.7	1150.1	303.1157 $[M+H]^+$ [Calc.= 303.1162]

Table 3.17: Summary of spectroscopic data for products formed from amine displacement of tosyl.

The structure of compound **(342)** was established by X-ray crystallography and also gave fully consistent spectroscopic data. This allowed the structures of the other products (**353, 360** and **367**) to be confirmed with IR spectroscopy, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry, as all showed similar features to those noted for compound (**342**), summarised in Table 3.18.

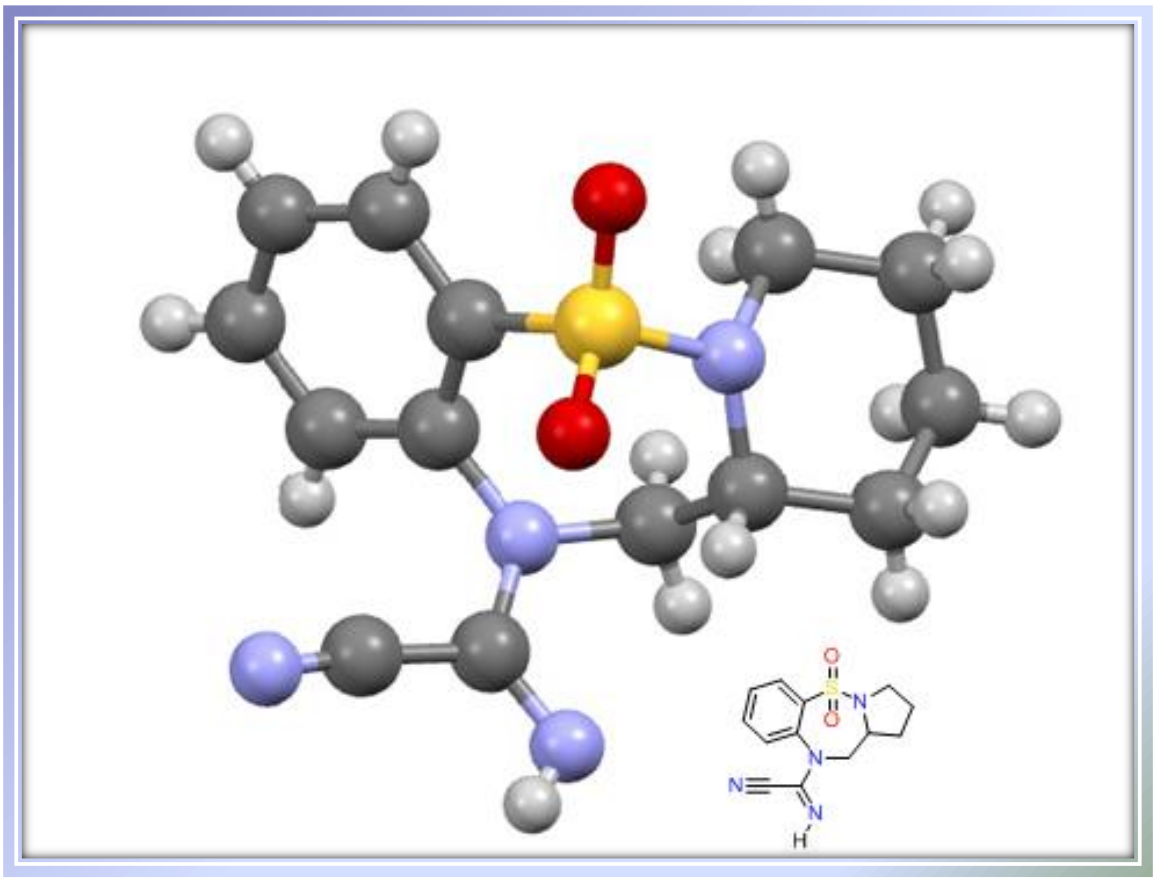


Figure 3.9: Crystal structure of the compound **(342)**

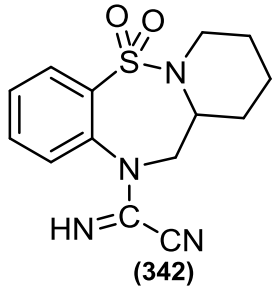
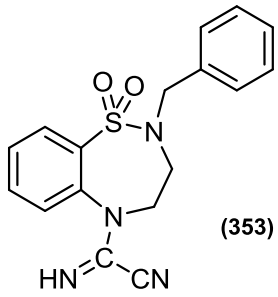
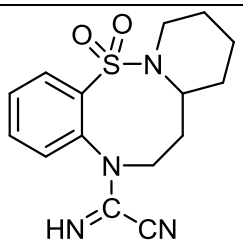
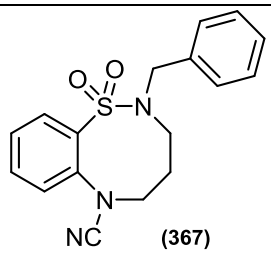
No	Product (2)	NMR (400 MHz, $CDCl_3$, ppm)			IR (cm^{-1})		HRMS
		^{1}H NMR	^{13}C NMR				
		N**H**	**C**=N	**C**N	**NH**	**CN**	
1	 **(342)**	8.22 (bs)	141.06	110.36	3346.4	2252.6	304.0998 $[M]^+$ [Calc.= 304.0994]
2	 **(353)**	8.20 (bs)	146.20	110.37	3378.1	2248.7	341.1065 $[M+H]^+$ [Calc.= 341.1067]
3	 **(360)**	8.09 (bs)	158.19	110.76	3314.0	2255.2	319.1228 $[M+H]^+$ [Calc.= 319.1223]
4	 **(367)**	No	No	114.73	No	2216.5	327.1040 $[M]^+$ [Calc.= 327.1041]

Table 3.18: Summary of data for nitriles **(342), (353), (360) and (367).**

The mechanism for the reaction is proposed (Scheme 3.10, below) to be nitrene formation and conversion of the nitrene to an amine or attack of the azide by cyanide[204-208] followed by nitrogen loss. The amine could then displace tosylate to give products (**341**), (**352**), (**350**), (**359**), (**363**) and (**366**) [Table 3.17] or the cyano substituted amine anion could displace tosyl and then be further attacked by more cyanide to form compounds **(342**), (**353**) and (**360**)

[Table 3.18] or stop (no extra cyanide addition) to form compound (**367**) [Table 3.18]. Compound (**370**) [entry 7, Table 3.16] results from azide reduction and tosyl displacement by cyanide.

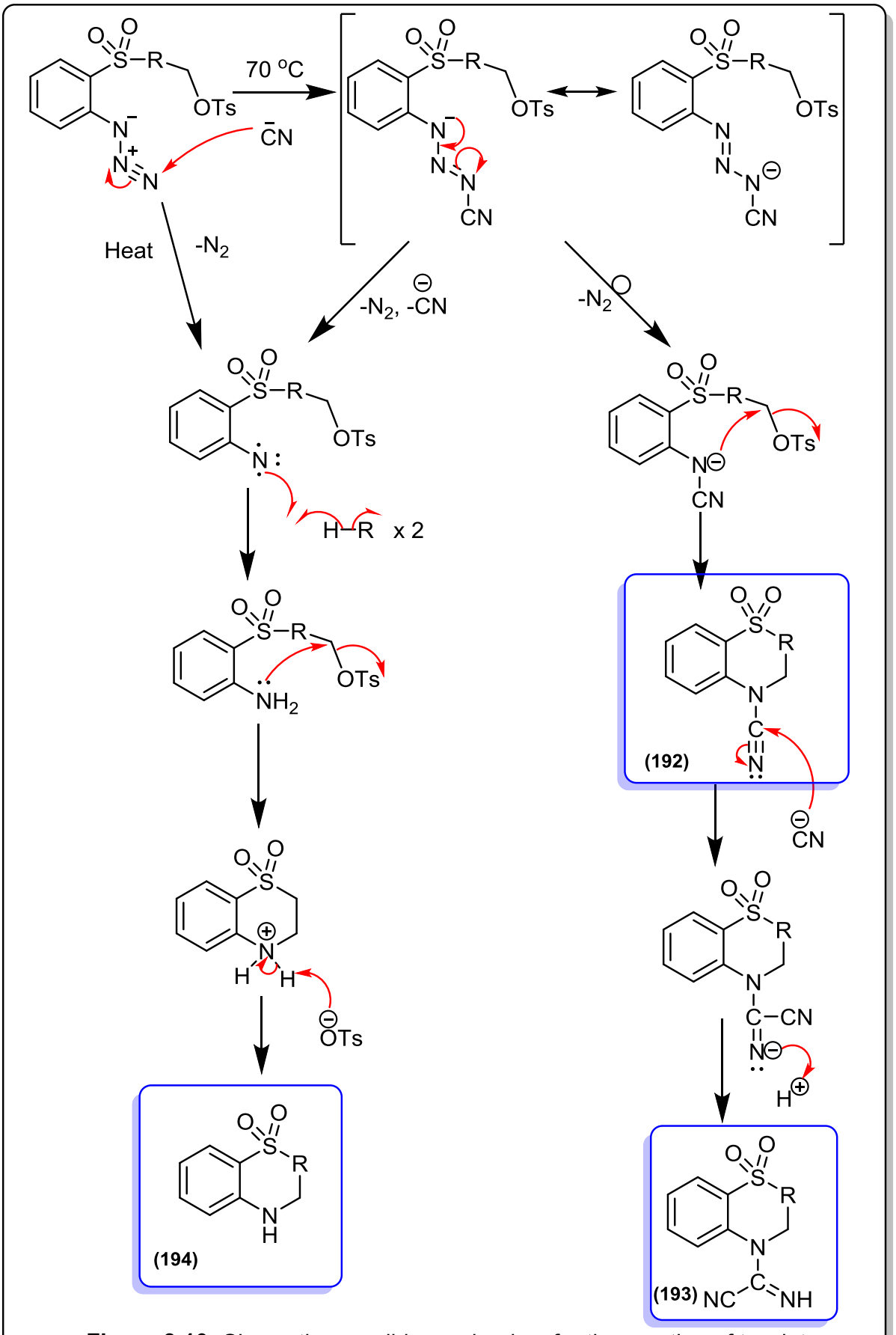
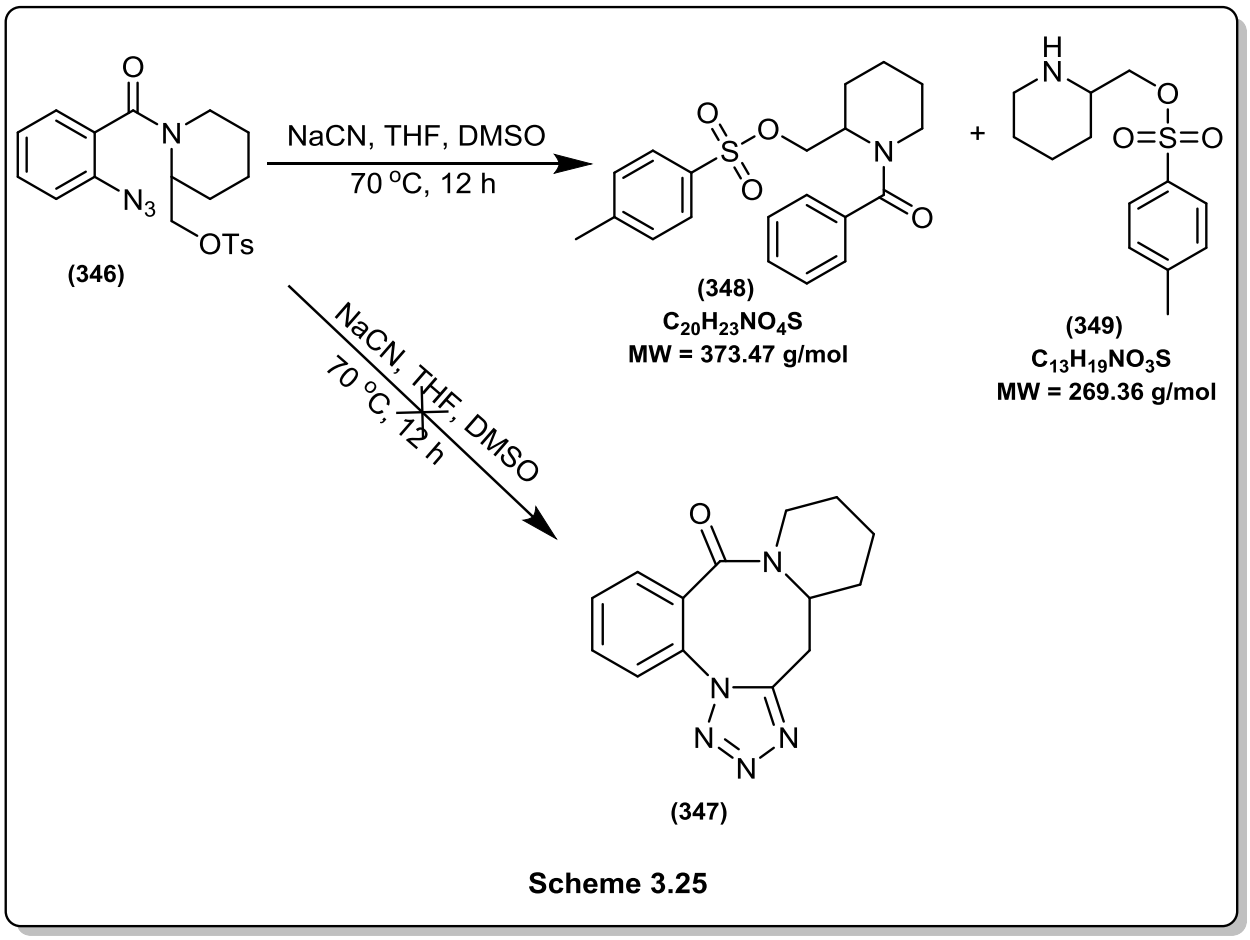


Figure 3.10: Shows the possible mechanism for the reaction of tosylate with cyanide

3.2.3.3. Reactivity of compound (346) with sodium cyanide.



Scheme 3.25

As implied in Table 3.16, tosylate **(346)** behaved differently when reacted with NaCN in the presence of dry DMSO. The mixture was heated at 70 ^{o}C under a nitrogen atmosphere for 12 h. Instead of the tetrazolo-product or other compounds just discussed above, products (**348** and **349**) were formed with yields of 31 % and 35 %, respectively. These unusual products were only seen with this one amide example (those above are all sulfonamides).

Spectroscopic analysis implied of the formation of product (**348).** The ^{1}H NMR spectrum showed the appearance of nine aromatic protons including the distinct tosyl doublets at 7.63 (2H) and 7.95 (2H) ppm. The eight upfield aliphatic CH_2 protons showed at 1.18-1.64 (6H), 3.73 (1H), and 4.22-4.29 (1H) ppm and the single CH proton in the ring system appeared at 3.05 (1H) ppm. The presence of three upfield CH_3 protons on the toluene was seen as a singlet at 2.28 (3H) ppm.

The ^{13}C NMR spectrum showed the aromatic CH carbons downfield at 126.91 (2 x CH), 128.36 (2 x CH), 129.65 (2 x CH), 129.79 (2 x CH), and 133.07 ppm and the four aliphatic

CH_2 carbons and CH in the piperidine ring system were found at 18.96 (CH_2), 24.42 (CH_2), 25.36 (CH_2), 41.30 (CH_2) and 51.11 (CH) ppm. There were three aromatic quaternary carbons plus one carbonyl. IR spectroscopy showed the presence of the carbonyl group at υ_{max} 1719.5 cm^{-1} and the disappearance of the broad peak at υ_{max} 2120.5 cm^{-1} for azide stretching. Mass spectrometry further supported the structure of the product with a measured mass of 396.1242 for the ion $[M+Na]^+$ for a required mass of 396.1240.

The structure of the product (**349**) was implied by its IR spectrum, ^1H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry. The ^1H NMR spectrum showed the eight aliphatic CH_2 protons at 1.18-1.53 (6H), 2.17 (1H), and 3.02 (1H) ppm and the single CH in the piperidine ring system was seen at 3.50 ppm. The four aromatic protons were downfield as a doublet at 7.22 ppm (2H) and as a doublet at 7.67 ppm (2H).

The ^{13}CNMR spectrum showed the CH aromatic carbons downfield at 126.99 (2 x CH) and 129.79 (2 x CH) ppm and and the four aliphatic CH_2 carbons and CH in the piperidine ring system were found at 19.15 (CH_2), 24.19 (CH_2), 24.77 (CH_2), 41.41 (CH_2) and 54.68 (CH) ppm. The CH_3 carbon on the tosylate appeared as a singlet at 21.53 ppm.

IR spectroscopy showed the absence of the carbonyl group seen in compound (**346**) at υ_{max} 1720.8 cm^{-1} and the disappearance of the broad peak at υ_{max} 2120.5 cm^{-1} for azide stretching.

The correct measured mass 270.1164 for the ion $[M+H]^+$ gives further evidence for the structure.

Compound (**349**) can be formed from cleavage of the amide bond present in starting material (**346**). Compound (**348**) is more difficult to explain but would arise from the de-azideation of the starting material (**346**)- a reaction never seen in our research group in many years of azide chemistry, and for which precedent could not be found in the literature.

Chapter 4:

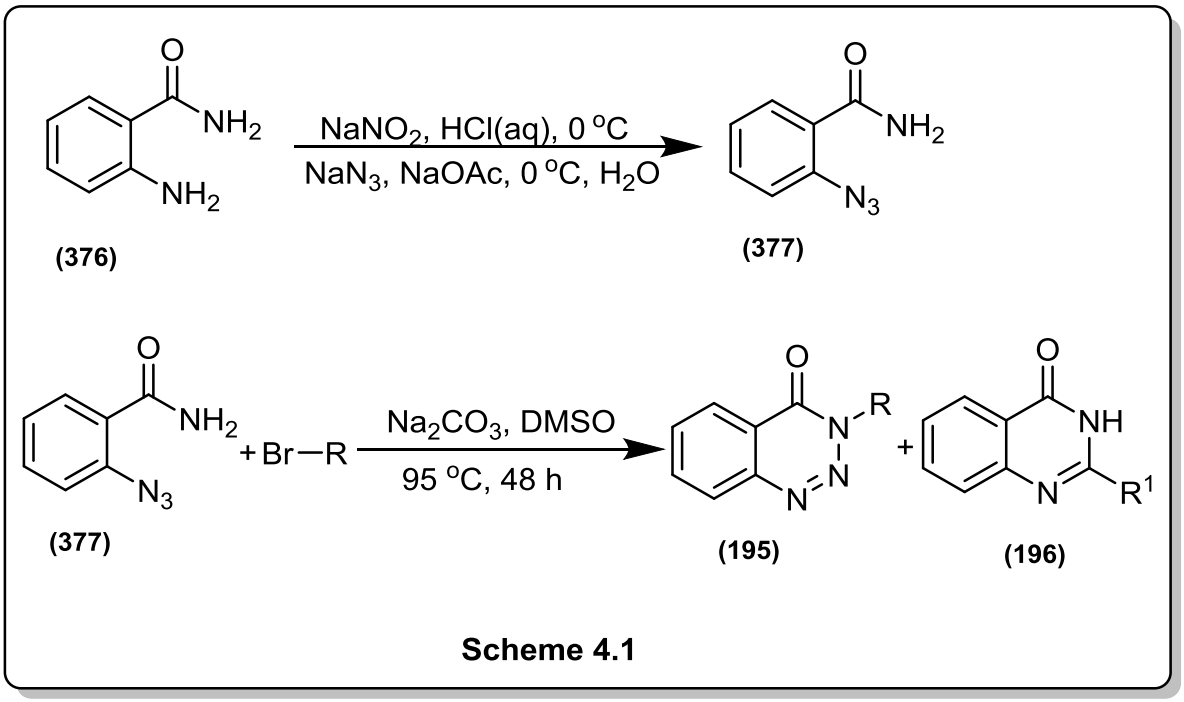
4. Results and Discussion: 1. Reactivity of 2-azidobenzamide.

This short section brings together some results that were obtained as part of an investigation into the reactivity of 2-azidobenzoic acid derivatives and of compounds derived from 2-azidobenzaldehyde.

4.1. Reactivity of 2-azidobenzamide

4.1.1. Summary.

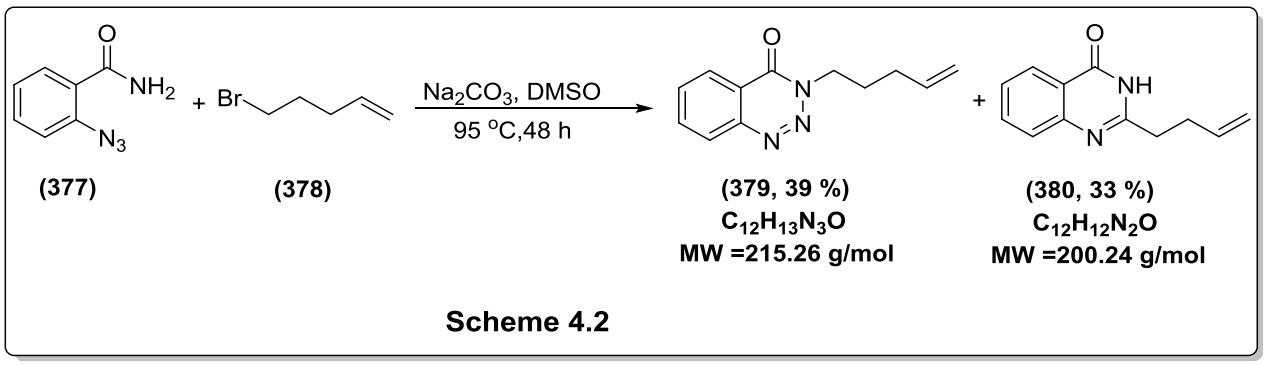
2-Aminobenzamide (**376**) was reacted with sodium nitrite and HCl at 0 ^{o}C to form the diazonium salt as an intermediate. Reaction between the diazonium intermediate and sodium azide by the displacement of nitrogen by the azide anion gave 2-azidobenzamide (**377**). The 2-azidobenzamide (**377**) was treated with alkyl bromides in the presence of sodium carbonate as a base in anhydrous DMSO to give benzotriazinones (**195**) and quinazolinones (**169**) as shown in Scheme 4.1. This investigation came about as a result of a wider investigation of the attempted aminohydroxylation reactions discussed previously in this thesis.



Scheme 4.1

4.1.2. Reactivity of 2-azidobenzamide.

4.1.2.1. Reactivity of 2-azidobenzamide with alkyl bromides.



Scheme 4.2

The aim of this reaction was to alkylate the amide in order to provide a precursor for the aminohydroxylation discussed in an earlier chapter.

Compound (**377**) was treated with 5-bromo-1-pentene (**378**) in the presence of sodium carbonate as a base in anhydrous DMSO and heated at 95 ^{o}C for 48 hours under a nitrogen atmosphere and the reaction mixture was purified by column chromatography in order to investigate two new products.

It was immediately obvious that the expected product was not formed. Spectroscopic analysis confirmed the identity of the first compound as compound (**379**) [see Scheme 4.2]. The ^{1}H NMR spectrum showed four aromatic protons with signals at 7.72 ppm as a doublet of doublets, 7.86 ppm as a doublet of doublets, 8.07 ppm as a doublet and 8.27 ppm as a doublet. The six CH_2 protons appeared as a triplet of doublets at 1.95 ppm, an apparent quintet at 2.12 ppm and a triplet at 4.41 ppm as well as the alkenic CH_2 protons and CH proton which appeared at 4.92 (C**H**H), 5.00 (CH**H**) and 5.71-5.82 (C**H**) ppm, respectively. In the ^{13}C NMR, the 3 alkyl CH_2s appeared at 27.93, 30.74 and 49.40 ppm whilst the sp^2 CH_2 signal appeared at 115.58 ppm. The appearance of five sp^2 CH signals at 125.06, 128.22, 132.26, 134.72 and 137.14 as well as the C=O signal confirmed the assignment.

It was further determined that the compound contained a carbonyl group from a peak at υ_{max} 1679.5 cm^{-1} in the infrared spectrum which also showed no peak for the azide group and also the absence of the amide NH_2 absorption peak. Mass spectrometry further supported the

structure of product with a measured mass of 215.1059 for the ion $[M]^+$ for a required mass of 215.1059.

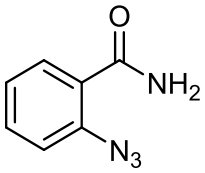
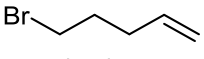
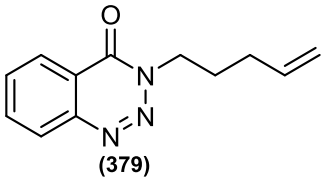
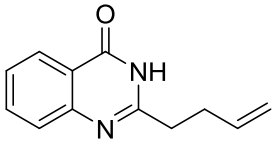
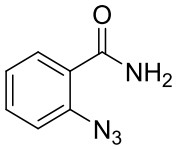
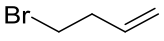
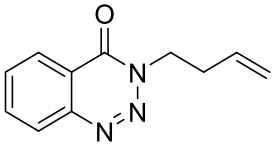
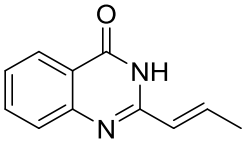
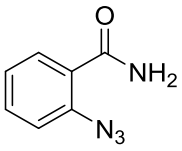
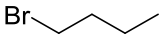
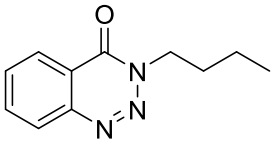
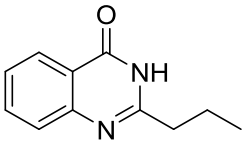
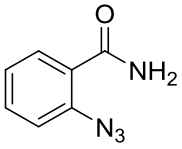
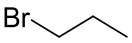
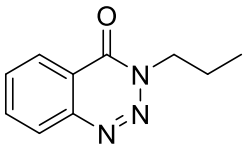
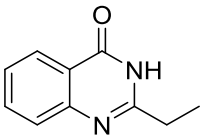
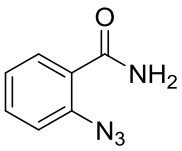
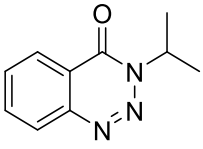
The identity of the second product (**380**) was confirmed by IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

The ^{1}H NMR spectrum showed a signal at 12.11 ppm indicating the NH group. Two signals at 2.59 and 2.84 ppm confirmed the presence of the four protons of the butenyl as well as the three protons of the ethylene which showed at 4.97 ppm (C**H**H) as a doublet, at 5.08 ppm (CH**H**) as a doublet of doublets and 5.82-5.92 ppm (C**H**) as a multiplet. The four aromatic protons at 7.40, 7.63, 7.70, and 8.21 ppm with the multiplicity of dd, d, dd, d indicated the 1,2-disubstitution pattern of the benzene ring. The ^{13}C NMR spectrum showed the four quaternary carbons at 120.53, 149.45, 156.07 and 164.39 ppm. The two upfield CH_2s appeared at 31.31 and 35.19 ppm whilst the presence of the four aromatic proton CH signals was seen at 126.44, 127.26, 134.82 and 136.43 ppm in addition to the characteristic signals of the alkene downfield at 116.29 ppm (CH=C**H$_2$**) and 126.24 ppm (C**H**=CH_2). Furthermore, the IR spectrum displayed a broad NH absorption peak at υ_{max} 3168.3 cm^{-1} while no peak appeared for the azide group. A sharp peak at υ_{max} 1673.1 cm^{-1} showed the carbonyl group.

Mass spectrometry further supported the structure of the product with a measured mass of 201.1023 for the ion $[M+H]^+$ for a required mass of 201.1022.

This process was explored further by investigating the reaction of 4-bromo-1-butene, 1-bromobutane, 1-bromopropane, 2-bromopropane, bromocyclohexane, 3-bromo-2-methylpropene, benzyl bromide, 2-bromo-2-methylpropane, bromodiphenylmethane and triphenylmethyl bromide with 2-azidobenzamide.

Each of 4-bromo-1-butene (**391**), 1-bromobutane (**384**) and 1-bromo propane (**381**) gave two products whilst each of 2-bromopropane (**395**), bromocyclohexane (**389**), 3-bromo-2-methylpropene (**387**), benzyl bromide (**397**) and 2-bromo-2-methylpropane (**405**) gave a single product. In addition bromodiphenylmethane (**399**) and triphenylmethyl bromide (**402**) did not react with 2-azidobenzamide but gave a benzophenone **(401)** and triphenylmethanol (**404**), respectively. The yields and physical properties of the products are shown in the Table 4.1.

No.	Starting material (1)	Starting material (2)	Compound (1)	Compound (2)
1	 **(377)**	 **(378)**	 **(379)** Colour=dark orange oil % = 39 %	 **(380)** Colour= light yellow m.p=167-169 °C % = 33 %
2	 **(377)**	 **(391)**	 **(392)** Colour= yellow oil % = 35 %	 **(393)** Colour= Yellow solid m.p=148-150 °C % = 29 %
3	 **(377)**	 **(384)**	 **(385)** Colour=Light yellow oil % = 37 %	 **(386)** Colour=light yellow oil % = estimated 20 %
4	 **(377)**	 **(381)**	 **(382)** Colour=Light yellow solid m.p = 49-51°C % = 37 %	 **(383)** Colour=light yellow solid m.p=209-211 °C % = 23 %
5	 **(377)**	 **(395)**	 **(396)** Colour=Light yellow solid m.p = 47-49 °C % = 34 %	No

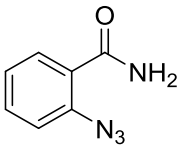
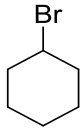
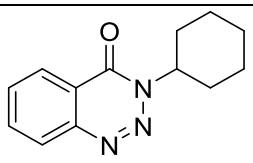
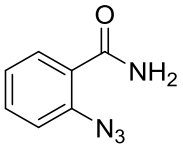
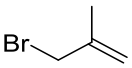
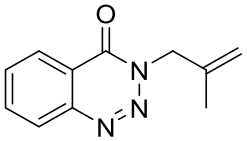
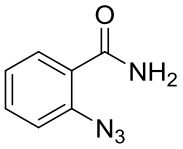
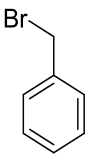
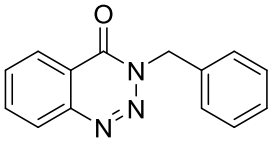
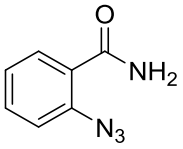
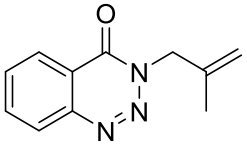
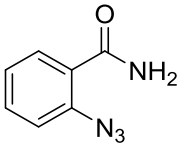
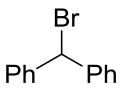
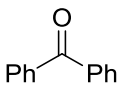
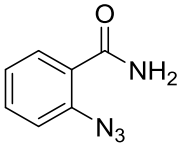
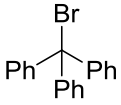
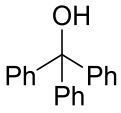
6	 **(377)**	 **(389)**	 **(390)** Colour=light yellow solid m.p = 137-139 °C % = 30 %	No
7	 **(377)**	 **(387)**	 **(388)** Colour=light yellow solid m.p = 69-71 °C % = 36 %	No
8	 **(377)**	 **(397)**	 **(398)** Colour=yellow solid m.p = 110-112 °C % = 33 %	No
9	 **(377)**	 **(405)**	 **(388)** Colour= light yellow oil % = 20 %	No
10	 **(377)**	 **(399)**	 **(401)**	No
11	 **(377)**	 **(402)**	 **(404)**	No

Table 4.1: Synthesis and Appearance of Benzotriazinones and Quinazolinones.

The structures of the triazinone products were confirmed by IR spectroscopy, ^{1}H NMR spectra, ^{13}C NMR spectra, mass spectrometry, and the results are summarised in Table 4.2.

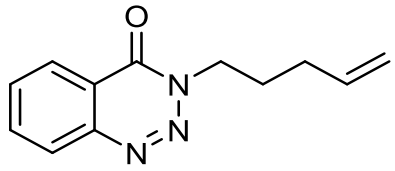
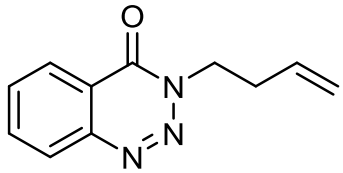
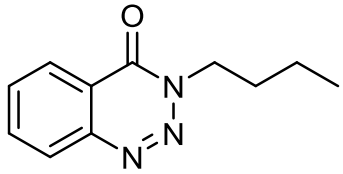
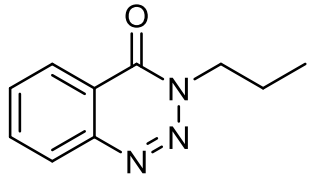
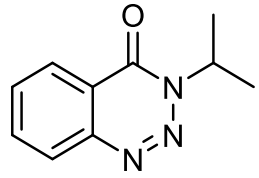
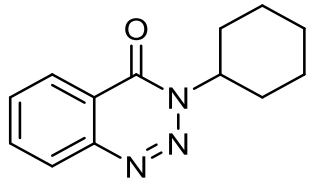
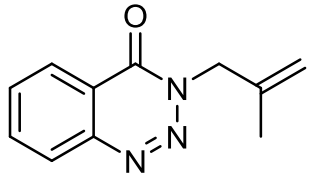
Typically in these compounds, the ^{1}H NMR spectra showed the presence of four aromatic protons downfield at around 7.00-8.00 ppm in a 1,2-disubstituted pattern with the alkyl neighbouring the N-C=O seen at around 4.37 – 5.65 ppm. All samples gave signals consistent with their alkyl sidechain, and also showed the absence of the starting material amide protons.

All the ^{13}C NMR spectra showed the presence of a carbonyl (C=O) upfield at around 155.09-155.52 ppm and the appearance of four aromatic CH signals downfield at around 120.0 -130.0 ppm. All compounds gave other ^{13}C data that was fully consistent with the assigned structures.

Further proof for the structures was given by the infrared spectra, with the presence of the carbonyl (C=O) stretching peak at around υ_{max} 1640.6-1683.8 cm^{-1} and the loss of the azide group and absence of the NH_2 group.

For all the examples, the correct accurate masses were observed by high resolution mass spectrometry.

Two alkyl halides (**387**) and (**405**), gave the same triazinone product (**378**). In the second case, the product might arise as a result of a free-radical mechanism. A suggested mechanism for these reactions is discussed in full later.

No.	Compound (1)	^{13}C NMR (400 MHz, $CDCl_3$, ppm)	IR (cm^{-1})	HRMS
		C=O	**C=O**	
1	 **(379)**	155.52	1679.5	215.1059 $[M]^+$, [Calc.=215.1059]
2	 **(392)**	155.50	1681.0	202.0970 $[M+H]^+$, [Calc.=202.0975]
3	 **(385)**	155.50	1678.4	204.1127 $[M+H]^+$, [Calc.=204.1131]
4	 **(382)**	155.52	1640.6	190.0973 $[M+H]^+$ [Calc.=190.0975]
5	 **(396)**	155.09	1676.5	190.0970 $[M+H]^+$, [Calc.=190.0975]
6	 **(390)**	155.12	1681.1	230.1285 $[M+H]^+$, [Calc.=230.1288]
7	 **(388)**	155.43	1683.8	202.0975 $[M+H]^+$, [Calc.=202.0975]

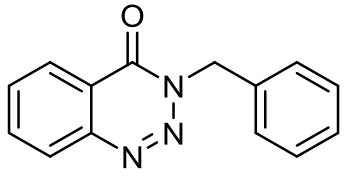
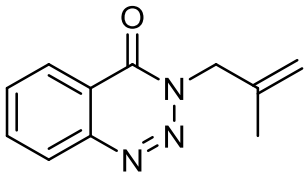
8	 **(398)**	155.39	1681.8	238.0977 $[M+H]^+$, [Calc.=238.0975]
9	 **(388)**	155.43	1683.8	202.0982 $[M+H]^+$, [Calc.=202.0975]

Table 4.2: Characteristic spectroscopic data for the benzotriazinone derivatives.

The structures of the second series of products (**380, 393, 386** and **383**) were confirmed as the quinazolinones by IR spectroscopy, ^{1}H NMR, ^{13}C NMR spectra and mass spectrometry, and the data is summarised in Table 4.3.

The ^{1}H NMR spectra showed the disappearance of the two broad singlets for the amide proton and the appearance of a new NH signal at around 11.12-12.17 ppm confirming the NH group as well as the four aromatic protons at around 7.00 – 8.30 ppm characteristic of the 1,2-disubstitution pattern of the benzene ring. The alkyls neighbouring the N=C were seen at around 2.68-6.40 ppm.

The ^{13}C NMR spectra of these products showed the carbonyl signal at 164.12-164.57 ppm with the appearance of the C=N signal at around 150.89-157.17 ppm as well as the presence of four aromatic proton CH signals at 123.46-136.43 ppm.

The infrared spectra displayed a broad NH absorption peak at around υ_{max} 3163.1- 3182.1 cm^{-1} while no peak was observed for the azide group. A sharp peak at υ_{max} 1650.0-1674.3 cm^{-1} showed the carbonyl group in addition to the disappearance of the NH_2 group at υ_{max} 3362 cm^{-1}. For all the examples, the correct accurate masses were observed by high resolution mass spectrometry giving further proof for the structures, and all showed ^{1}H and ^{13}C spectra consistent with their particular side chain. Compound (**393**) presumably arises from the rearrangement of the initial non-conjugated product into the more conjugated (**393**).

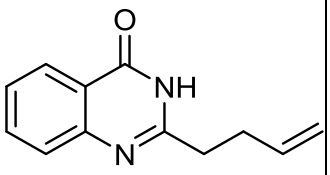
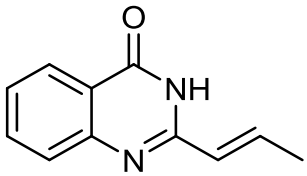
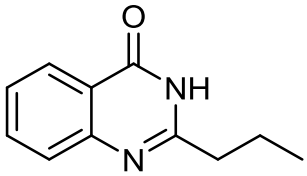
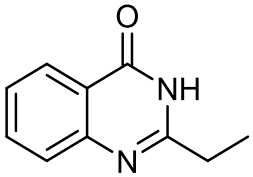
No	Compound (2)	NMR (400 MHz, $CDCl_3$, ppm)			IR (cm^{-1})		HRMS
		^{1}HNMR	^{13}C NMR				
		NH	C=O	C=N	C=O	NH	
	 (380)	12.11	164.39	156.07	1673.1	3168.3	201.1023 $[M+H]^+$ [Calc.=201.1022]
	 (393)	11.98	164.12	150.89	1658.7	3182.1	187.0860 $[M+H]^+$ [Calc.=187.0793]
	 (386)	11.12	164.25	157.17	1650.0	3173.6	189.1023 $[M+H]^+$ [Calc.=189.1022]
	 (383)	12.17	164.57	156.78	1674.3	3163.1	175.0869 $[M+H]^+$ [Calc.=175.0866]

Table 4.3: Characteristic spectroscopic data for the quinazolinone derivatives.

The mechanism for the formation of the benzotriazinone and quinazolinones is not clear but Figure (4.1) shows how the quinazolinones might form and Figure (4.2) attempts to account for triazinones. Path A (Figure 4.1) gives the nitrene of 2-azidobenzamide which then picks up the alkyl halide, loses hydrogen, cyclises and loses more hydrogen to give the quinazolinone. Evidence for the nitrene comes from the presence of 2-aminobenzamide as a product. The alternative (Path B, Figure 4.1) is less likely as the alkylation (first step) is not known and no azide or amine intermediate could be detected. For the benzotriazinone (Figure 4.2) path B (initial alkylation) is unlikely so path C is proposed. Here, the azide reacts with a nucleophile and then eliminates a single nitrogen (picked up by the nucleophile) to give a diazonium which cyclises to the parent unsubstituted benzotriazinone which then alkylates. It

is possible that the nucleophile could be dimethyl sulfide formed by interaction of DMSO with the alkyl halide (see Figure 4.2)

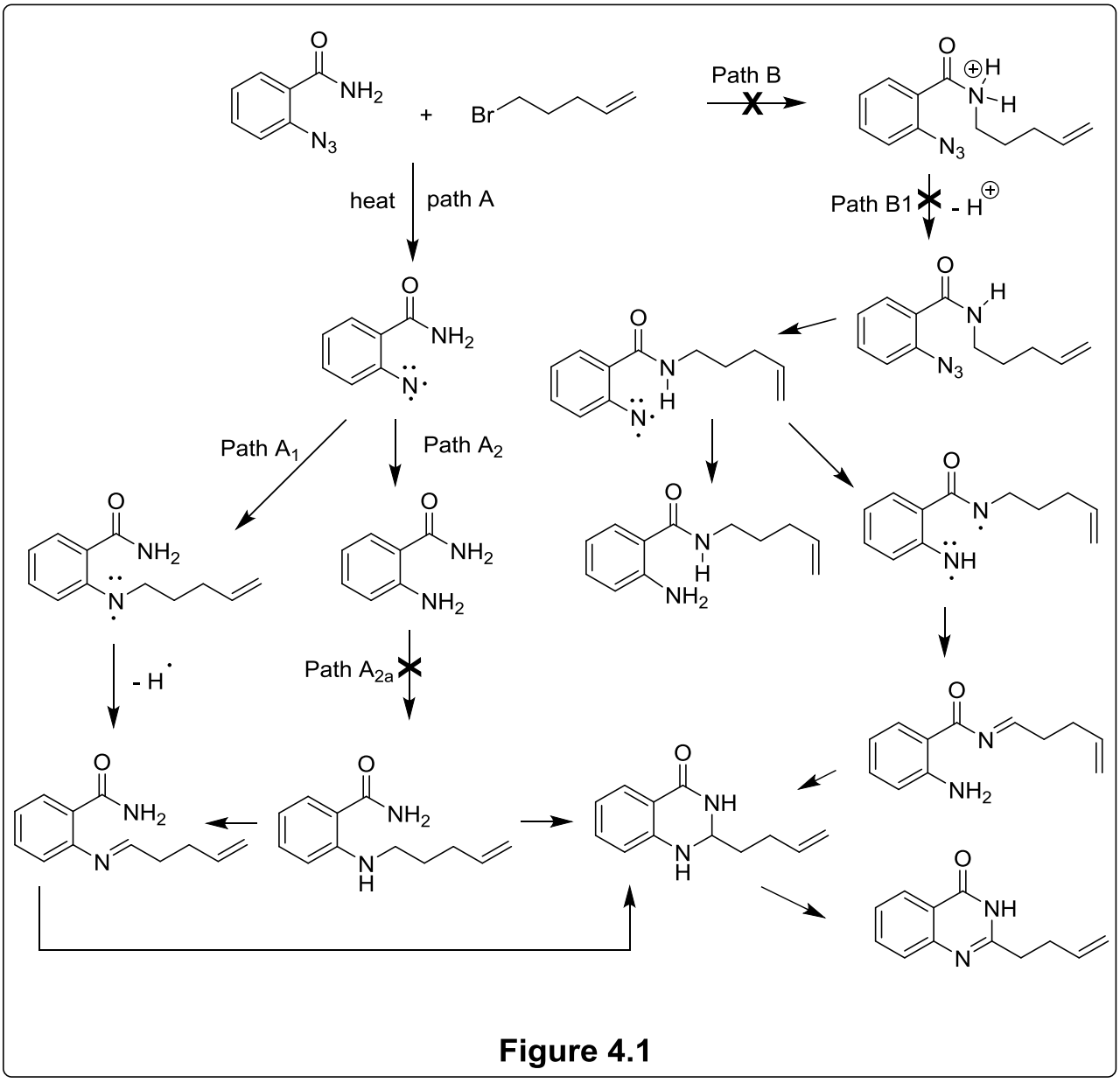


Figure 4.1

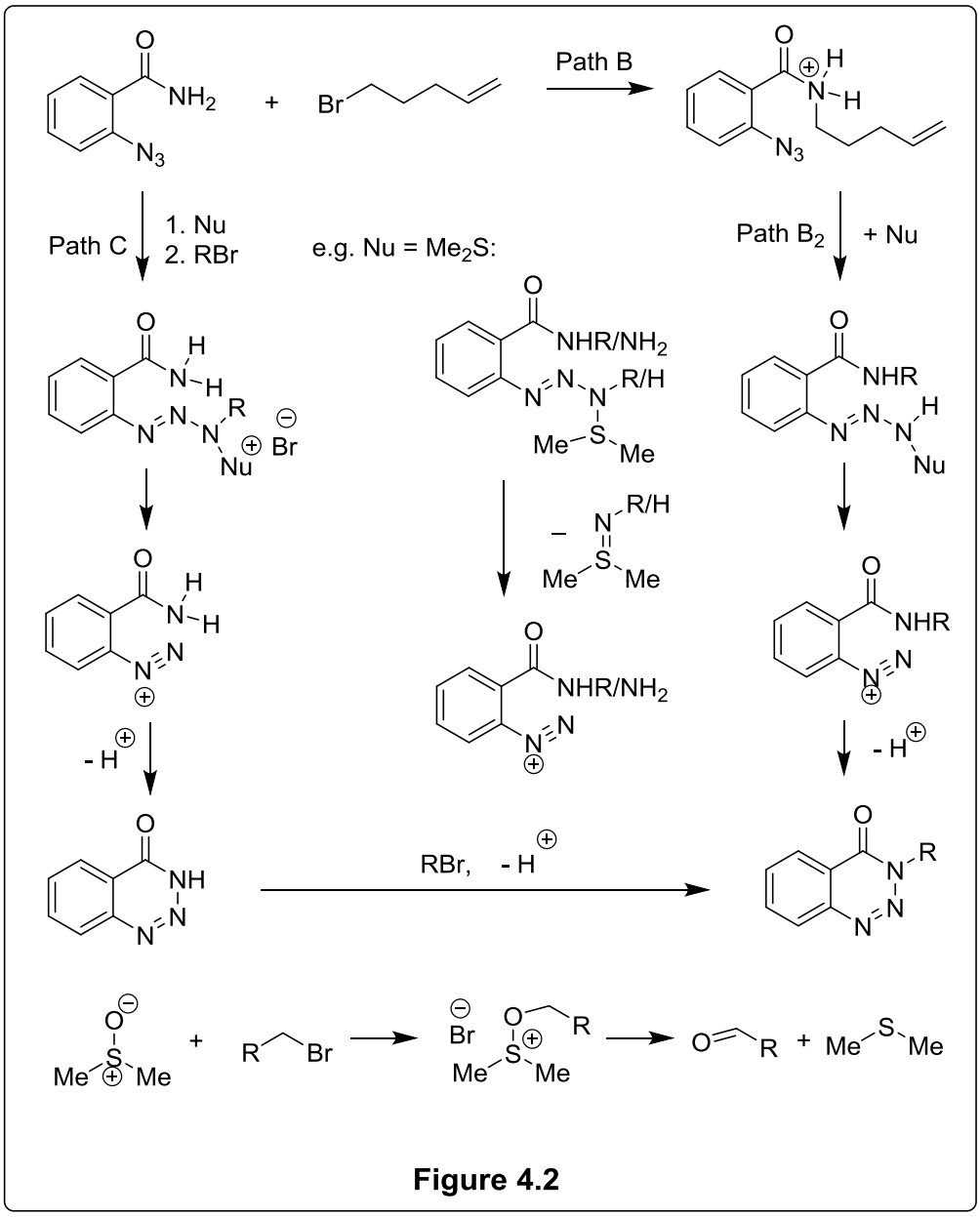
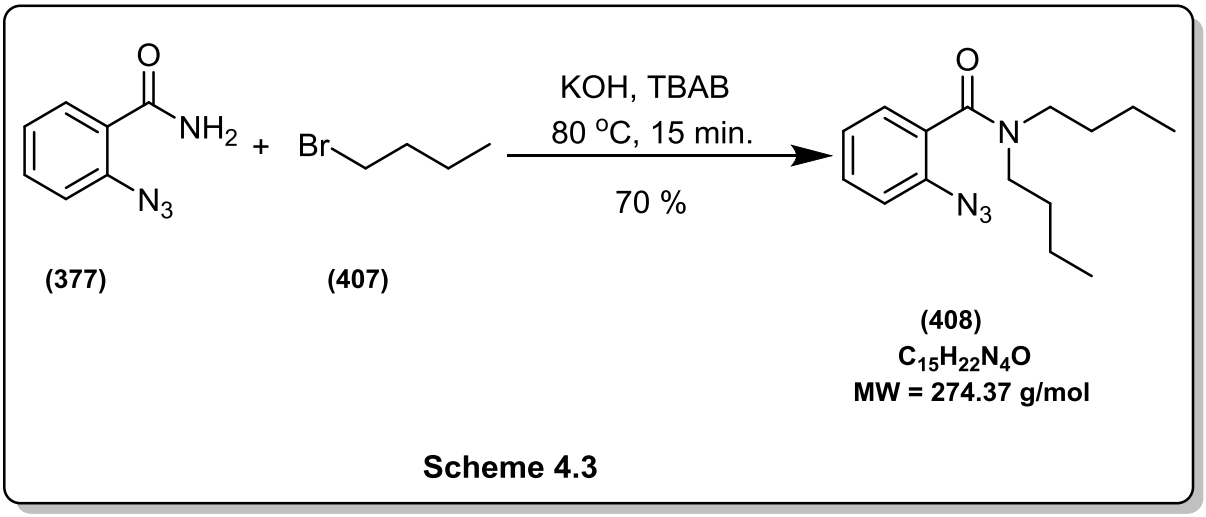


Figure 4.2

4.1.2.2. Reactivity of 2-azidobenzamide with 1-bromobutane.

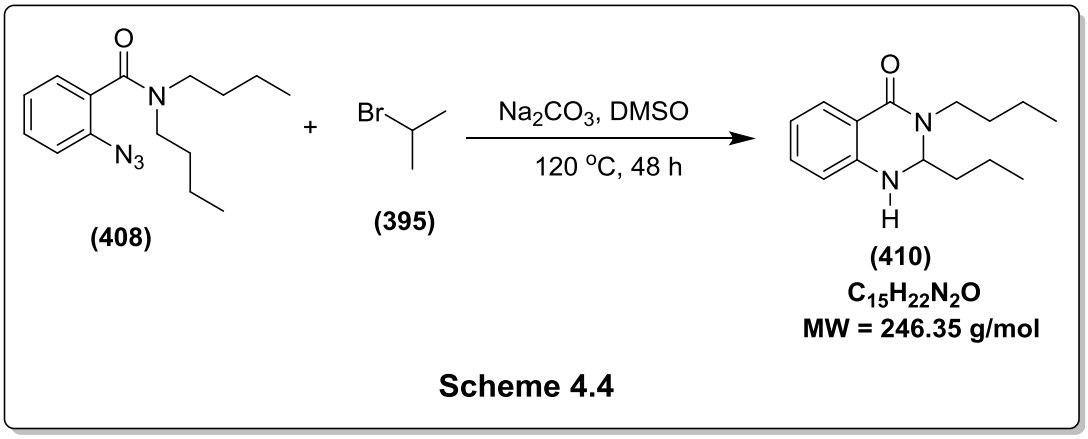
4.1.2.2.1. Synthesis of 2-azido-*N*,*N*-dibutylbenzamide with 2-bromopropane.



Scheme 4.3

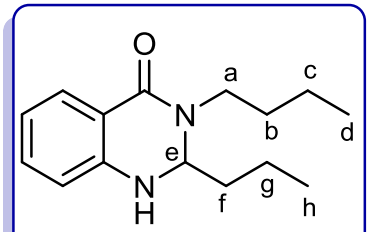
The reaction[209] of 2-azidobenzamide (**377**) with bromobutane (**407**) was used to produce the N,N-dialkyl amide (**408**), with the idea of exploring the reactivity of this material.

2-Azido-N,N-dibutylbenzamide (**408**) was heated with sodium carbonate as a base in anhydrous DMSO in the presence and absence of 2-bromopropane. The mixture was heated to 95 °C for 48 hours (no reaction) and then to 120 °C for 48 hours. After the completion of the reaction, the mixture was purified by column chromatography. Compound (**410**) was isolated in good yield as a yellow oil as shown in Scheme 4.4, below. In this reaction, the unsaturated (C=N) compound was not seen.



Scheme 4.4

The structure of compound (**410**) was confirmed IR spectroscopy, NMR spectra and mass spectrometry. The ^{1}H NMR spectrum showed the signals of the alkyl chain CH_2s and the critical sp^3 CH at 1.15-1.24 (1H), 1.29-1.36 (3H), 1.50-1.59 (3H), 1.84 (1H), 2.72-2.79 (1H) and 4.48-4.50 (2H) ppm. The NH was seen at 4.00-4.07 ppm.



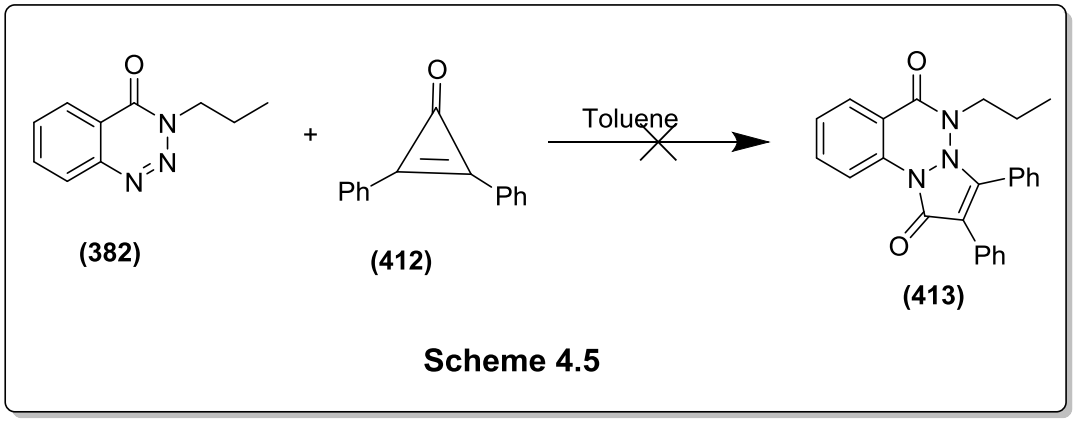
(410)

Figure 4.3

The ^{13}C NMR spectrum showed the presence of the carbonyl signal at 164.34 ppm. The terminal methyl signals (carbons d and h) appeared at 13.68 ppm and 13.89 ppm and the signals of the alkyl chain sp^3 carbons appeared at 18.64 (CH_2), 20.15 (CH_2), 30.48 (CH_2), 35.48 (CH_2), 44.88 (CH_2) and 69.25 (CH) ppm whilst the four aromatic CH signals were at 114.81, 118.41, 128.41 and 133.06 ppm.

Further proof for the structure was given by the infrared spectrum which displayed a broad NH absorption peak at υ_{max} 3284.2 cm^{-1} and showed a sharp peak at υ_{max} 1610.1 cm^{-1} for the carbonyl group. There was no sharp peak at υ_{max} 2097.8 cm^{-1} for the azide group. Mass spectrometry further supported the structure of product with a measured mass of 247.1802 for the ion $[M+H]^+$ for a required mass of 247.1805.

4.1.3. Attempted reaction of 3-propylbenzo[d][1,2,3]triazin-4(3H)-one with cyclopropenones.



Scheme 4.5

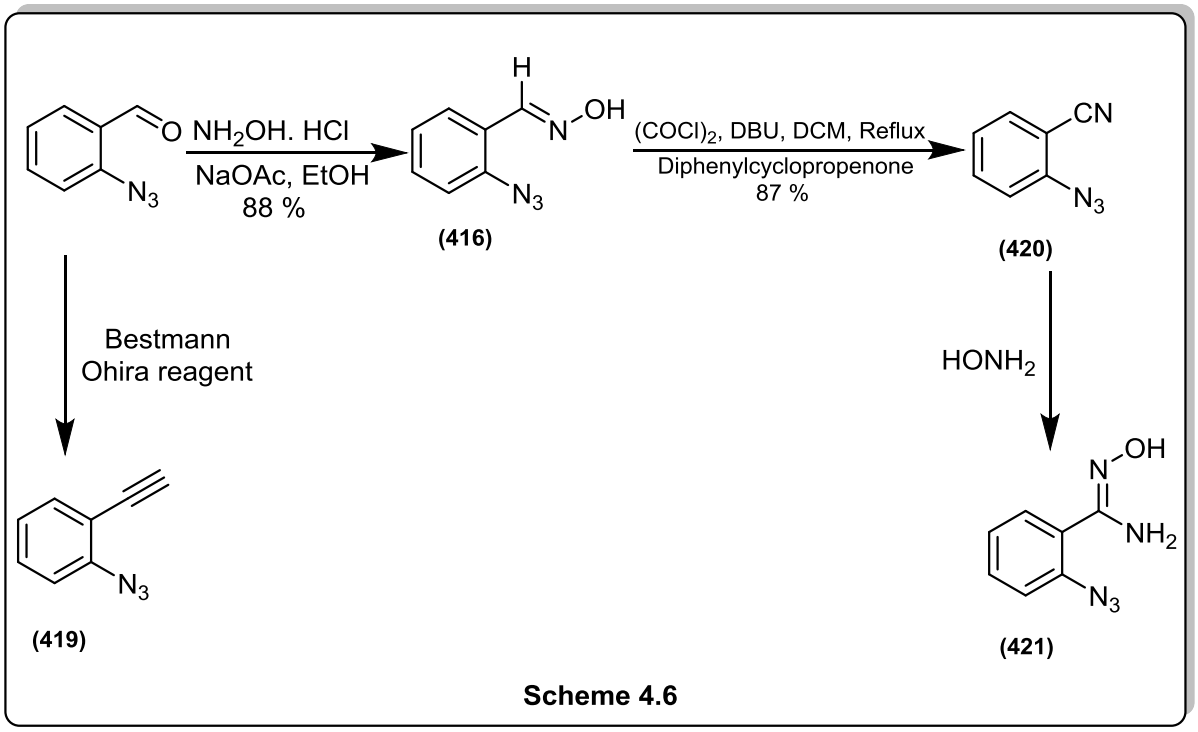
Following a literature report[210] that some triazines react with cyclopropenone, the reactivity of triazines towards cyclopropenone (**412**) was investigated.

The reactivity of compound (**382**) was investigated by mixing with diphenylcyclopropenone. Compound (**382**) was treated with diphenylcyclopropenone in toluene. The reaction mixture was heated at 80 ^{o}C for 48 hours whilst being monitored by TLC which showed no reaction. The reaction mixture also was heated to reflux for 3 days. None of the desired product (**413**) could be identified and only starting material (**382**) could be isolated.

Attempted reaction of benzotriazinone **(398**) with diphenylcyclopropenone was also unsuccessful.

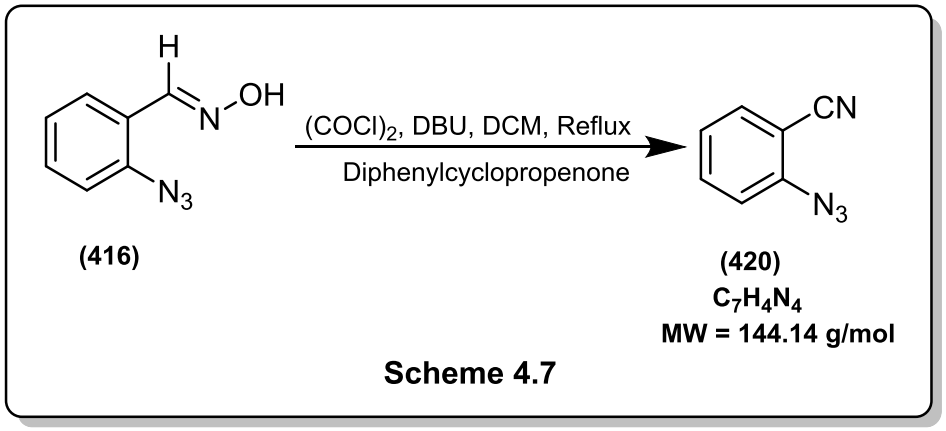
4.2. Reactivity of 2-azidobenzaldoxime and 2-azidobenzaldehyde.

In this section, some reactions of 2-azidobenzaldehyde, oxime **(416)**, its amidoxime derivative (**421**), and the 2-azidobenzonitrile (**420**) and alkyne (**419**) are explored. This work formed part of a group-wide project looking at the synthesis and reactivity of bifunctional arylazides and especially their use in the synthesis of potential ligands in organometallic chemistry, a collaboration with an inorganic group.



Scheme 4.6

4.2.1. Synthesis of 2-azidobenzonitrile.



Scheme 4.7

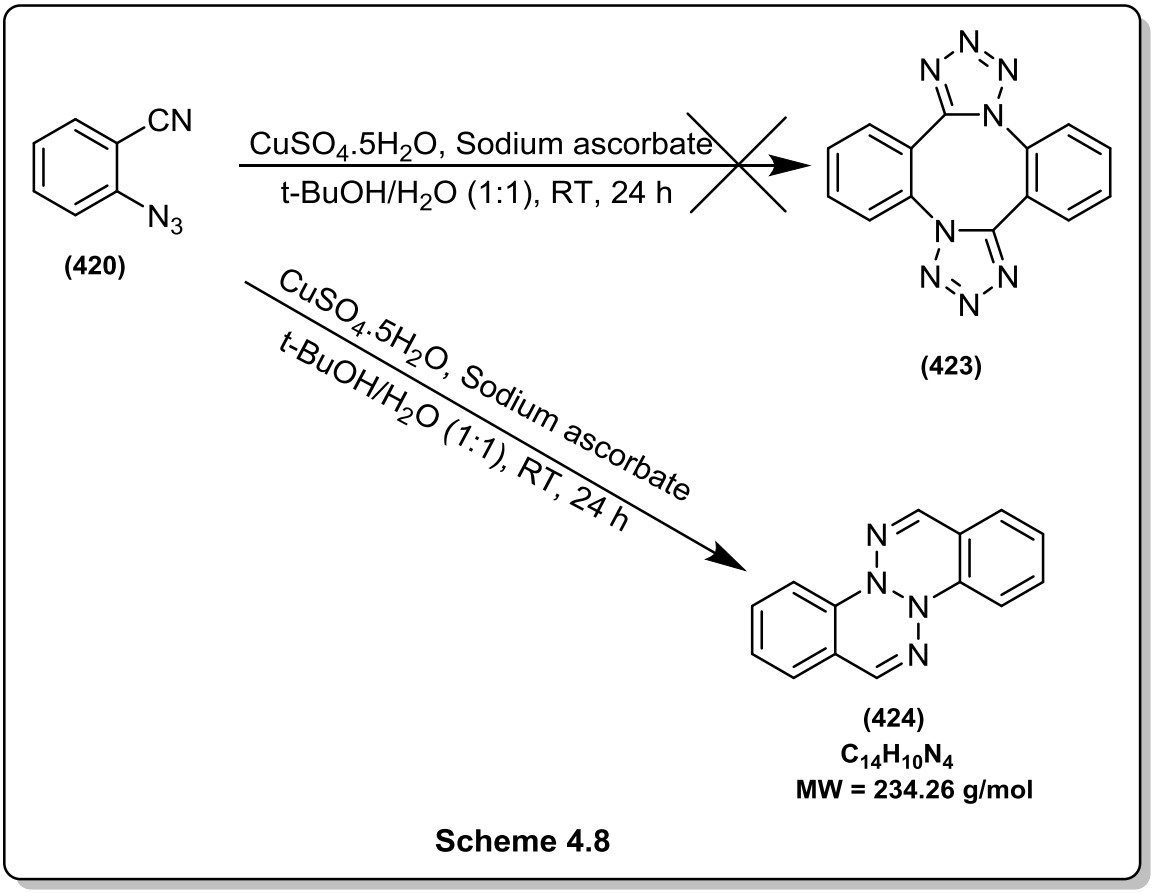
The oxime **(416)** was synthesised in our work by reaction of the aldehyde with hydroxylamine. The reaction[173] proceeded easily and gave the product in 89 % yield and was identical to that reported previously in the group[211].

The oxime (**416**) was dehydrated to form a nitrile in the presence of diphenylcyclopropenone, $(COCl)_2$ and DBU, a reaction developed in our laboratories as part of another project on diphenylcyclopropenone.[201] A product was isolated from the reaction mixture by extraction with DCM and washed with water and purified by using silica column chromatography to give the desired product as a yellow oil in 87% yield. This is a new route to this known azide.[212,213] The structure of the product (**420**) was confirmed by comparison to literature data[213] and by spectroscopic analysis. IR spectroscopy showed the presence of a peak at υ_{max} 2227.9 cm^{-1} for the CN group and a sharp peak for azide group which displayed at υ_{max} 2109.8 cm^{-1}. It was also seen that the peak for OH group was absent. The ^1H NMR spectrum also indicated the absence of the hydroxyl proton.

The ^{13}C NMR spectrum also confirmed the structure with the correct number of carbons with the nitrile signal appearing at 104.22 ppm. The absence of the oxime signal (CH=N), previously seen at 146.15 ppm was also noted. In mass spectrometry, the molecular mass of the nitrile (**420**) was equal to 233.0790 which was as expected for ion $[2M-2N_2+H]^+$.

4.2.2. Reactivity of 2-azidobenzonitrile.

In an attempt to perform cycloaddition of the nitrile and the azide present in compound **(420)**, it was heated in a variety of solvents with no success. Compound **(420)** was also treated with a solution of $CuSO_4.5H_2O$ in the biphasic system t-BuOH/H_2O as a solvent in the presence of sodium ascorbate. Instead of the desired tetrazole dimer product **(423),** a compound assigned as structure **(424)** was isolated in 10 % yield as shown in Scheme 4.8, below.



Scheme 4.8

The proposed structure of the product (**424**) was suggested by IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

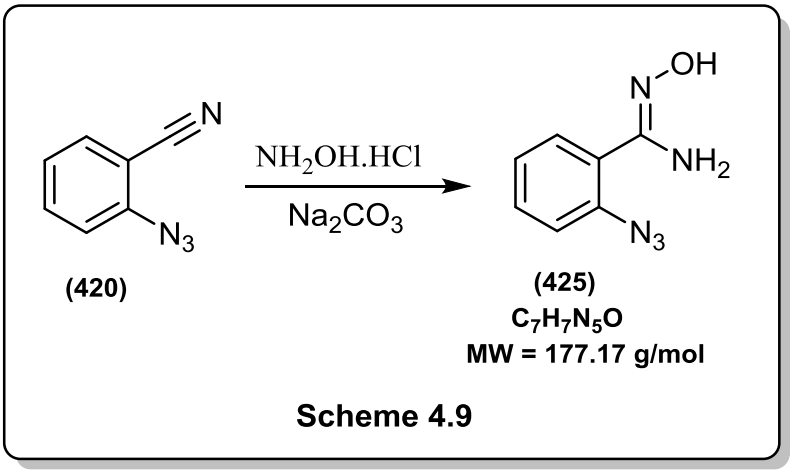
The ^{1}H NMR spectrum showed the presence of ten CH signals at 6.29 (1H), 6.62 (1H), 6.69 (1H), 7.02 (1H), 7.22-7.41 (3H), 7.53-.7.55 (2H), and 7.67 (1H) ppm.

The IR spectrum showed the disappearance of the peaks υ_{max} 2227.9 cm^{-1} and υ_{max} 2109.8 cm^{-1} for nitrile and azide, respectively.

In the ^{13}C NMR spectrum for **(424)**, the ten CH carbons from the aromatic ring appeared at 125.43, 126.71, 128.30, 128.36, 128.98, 129.09, 130.42, 130.52, 143.39 and 143.56 ppm. The absence of the CN group previously seen at 104.22 ppm was also noted.

Further evidence for the structure was given by the HRMS for the measured ion $[M]^+$ which was consistent at 234.0905.

4.2.3. Synthesis of (*Z*)-2-azido-*N*'-hydroxybenzimidamide.



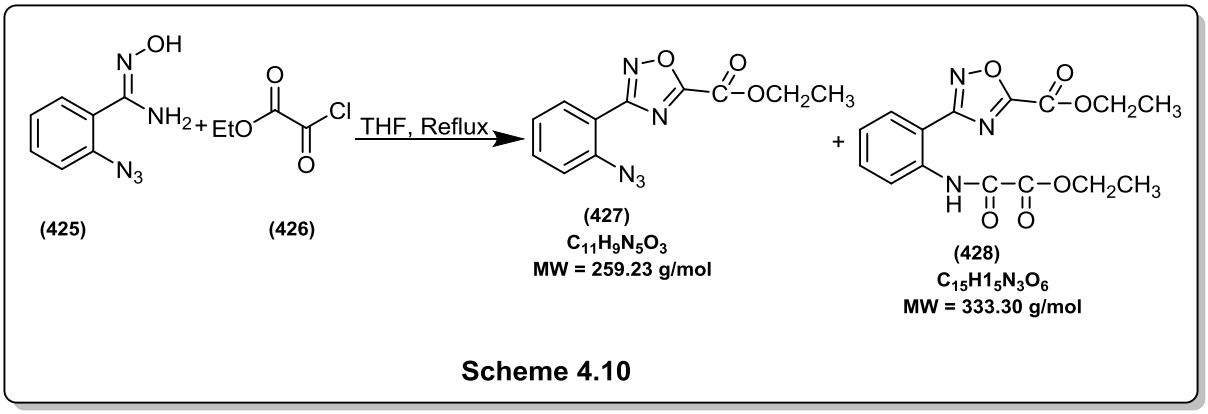
Scheme 4.9

The nitrile (**420**) was converted into the amidoxime (**425**) in 67 % yield by reaction with hydroxylamine hydrochloride in the presence of base.[214] Amidoximes are useful precursors in heterocyclic synthesis[214], as will be shown later.

The structure of compound (**425**) was deduced by its IR spectroscopy, NMR spectroscopy and mass spectrometry.

4.2.3.1. Synthesis of 3-(2´-azidophenyl)-1,2,4-oxadiazole.

We aimed to use the amidoxime in **(425)** to make a 1,2,4-oxadiazole and then use the azide to make a 1,2,3-triazole, hence producing a potentially interesting ligand system.



Scheme 4.10

The synthesis of 1,2,4-oxadiazole (**427**) was achieved in 93 % yield by treating amidoxime (**425**) with 2-chloro-2-oxoacetate in THF. A second product, compound (**428**) was isolated in 5 % yield. A mechanism is shown in Figure 4.4, based upon the known reactivity of amidoximes with acid chlorides.[215] Once compound (**427**) is formed, reduction of the azide to the amine and reaction of the amine with the acid chloride would form compound (**428**). Both compounds gave fully consistent and very distinct spectroscopic data, including HRMS data.

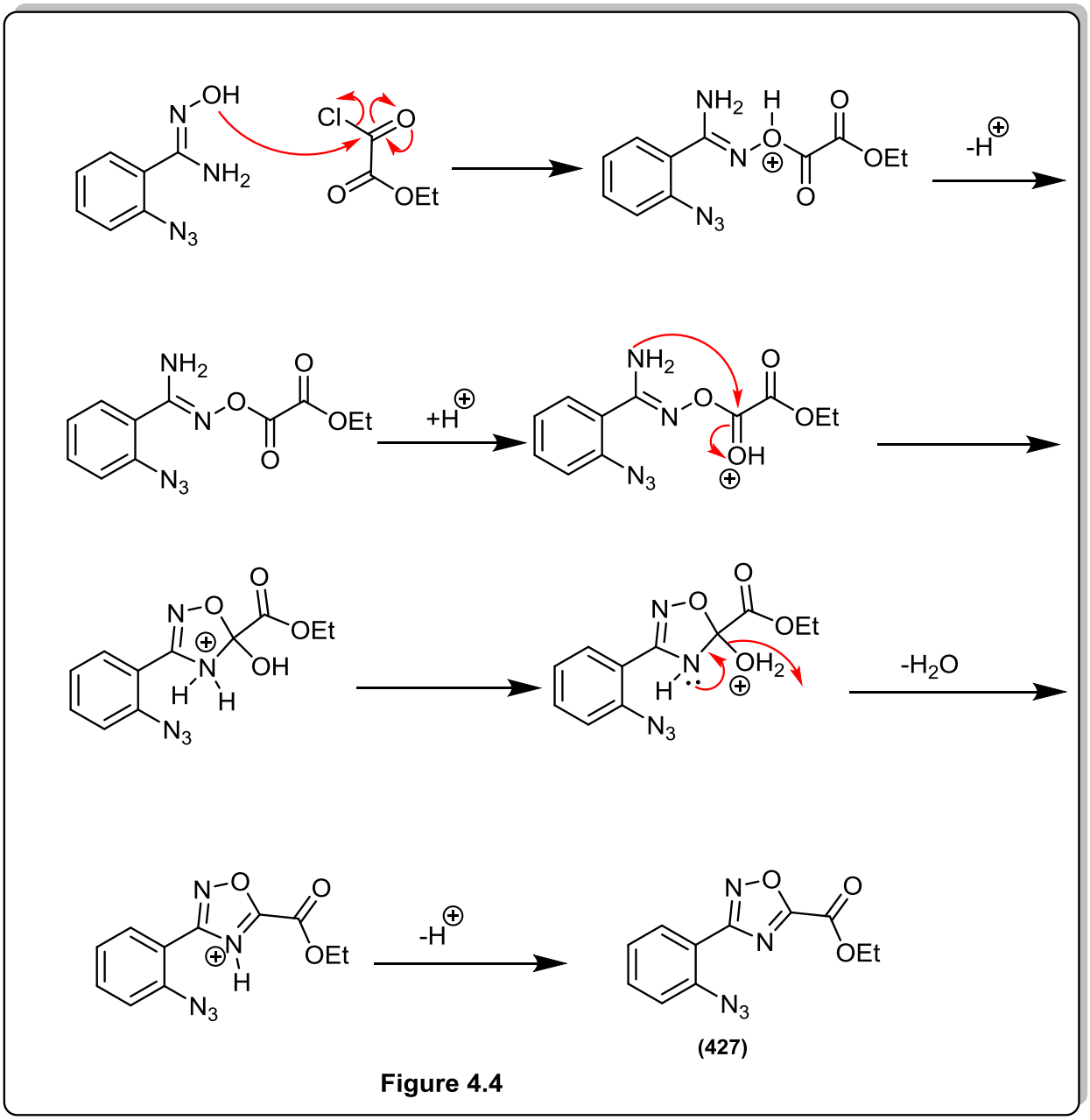
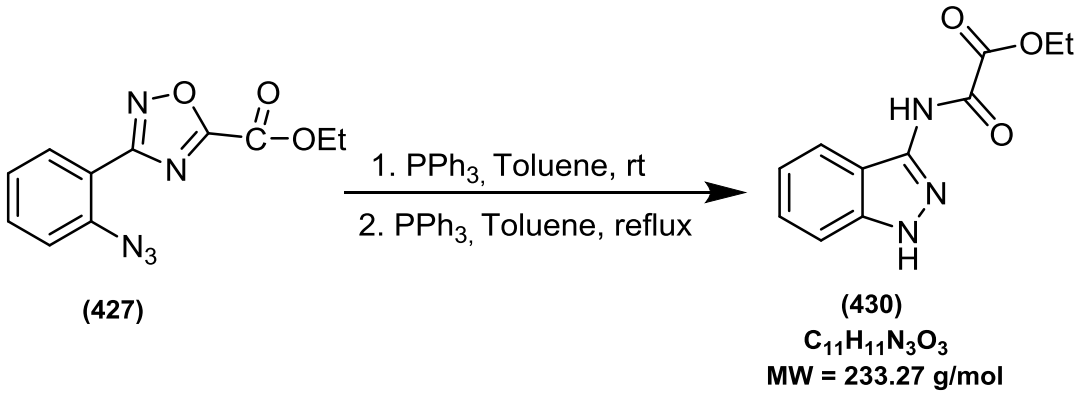

OH
N
NH2
N3
Cl
O
O
OEt
NH2
H
O
N
O
OEt
O
N3
-H
NH2
N
O
O
OEt
N3
+H
NH2
N
O
O
OEt
OH
N3
O
N
O
OEt
H
H
OH
N3
O
N
O
OEt
H
OH2
N3
-H2O
N
O
O
N
H
OEt
N3
-H
N
O
O
N
OEt
N3
(427)

Figure 4.4

4.2.3.2. Synthesis of Ethyl 2-[(1*H*-indazol-3-yl)amino]-2-oxoacetate.

The azide **(427)** was reacted with triphenylphosphine in anhydrous toluene. At room temperature, no reaction occurred. When the mixture was heated at reflux, a new product was isolated and was found to be the unexpected indazole **(430)** in 61 % yield, as shown in Scheme 4.11, below:



Scheme 4.11

Spectroscopic analysis confirmed the structure as compound (**430**). The infrared spectrum confirmed the loss of the azide group from υ_{max} 2097.1 cm^{-1} and the characteristic carbonyl groups were found at υ_{max} 1701.8 cm^{-1} and υ_{max} 1732.1 cm^{-1} . The presence of two NH peaks was seen at υ_{max} 3158.5 and 3376.7 cm^{-1}.

The ^{1}H NMR spectrum showed a triplet at 1.34 ppm and a quartet at 4.33 ppm that correspond to the CH_3 and OCH_2 of the ethoxy unit, respectively. The two NH protons in the product appeared at 11.19 ppm and 12.94 ppm.

The ^{13}C NMR spectrum indicated the terminal methyl of the ethoxy group at 14.30 and the methylene at 62.82 ppm. The two carbonyl signals appeared at 156.89 and 160.97 ppm while the imine peak (C=N) appeared at 141.40 ppm. The four signals for the aromatic (CH) carbons were seen at 110.81, 120.48, 121.72 and 127.01 ppm

The structure of the product (**430**) was further confirmed by HRMS analysis with an accurate measured mass for $[M]^+$ of 233.0799 for a required of 233.0800.

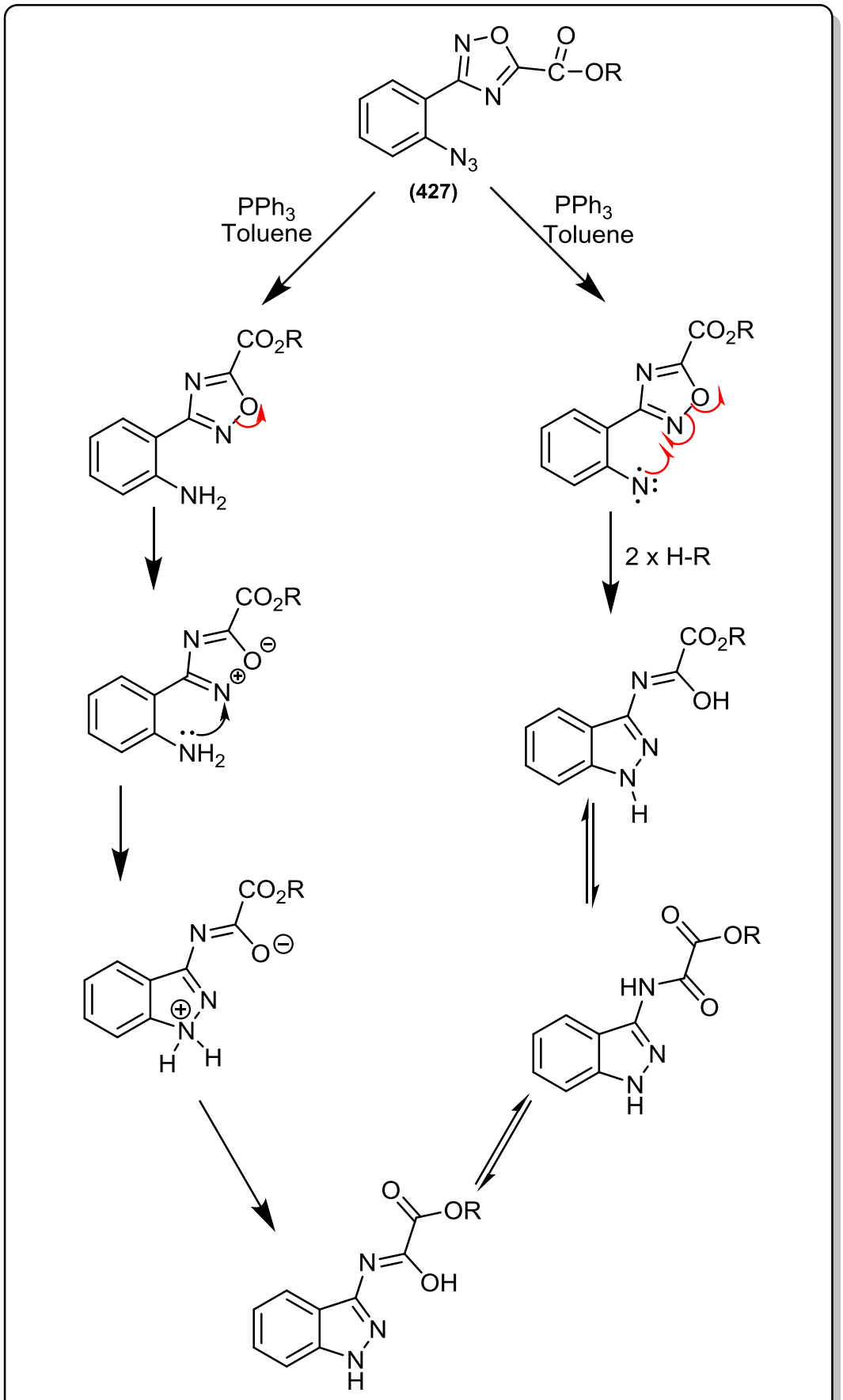


Figure 4.5

Figure 4.5 (above) shows a possible mechanism. The starting material forms either the nitrene or the amine. N-O cleavage is then followed by N-N bond formation to give the indazole. Protonation or $H^{\cdot}$ abstraction and then tautomerisation gives the final product. Indazole formation from a similar compound, 5-methyl-3-(2-aminophenyl)-1,2,4-oxadiazole- is known in the literature[216]. The structure of compound **(430)** was confirmed by X-ray crystallography. The crystal structure shows the methyl ester rather than the ethyl ester due to the solvent of crystallisation being methanol and transesterification, as shown in Figure 4.6.

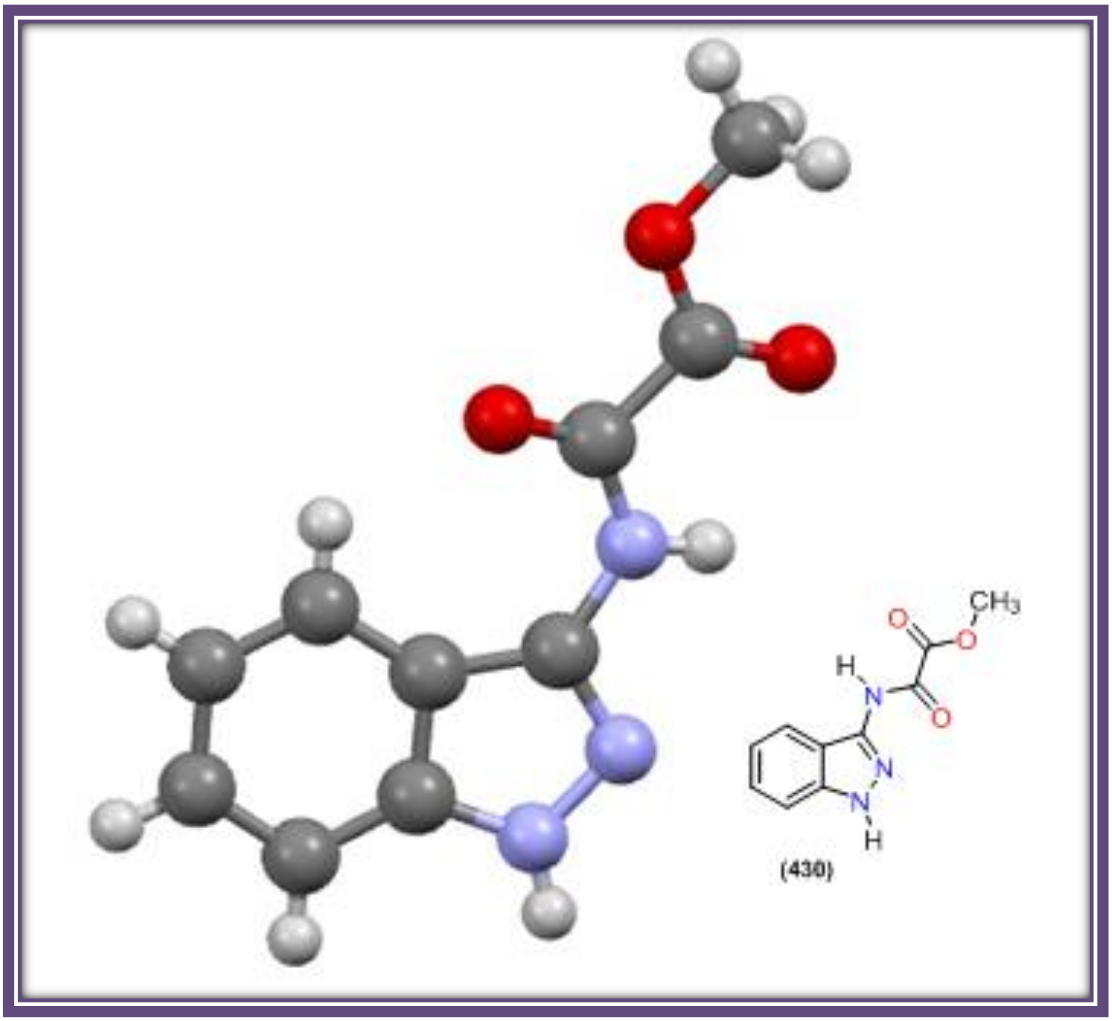
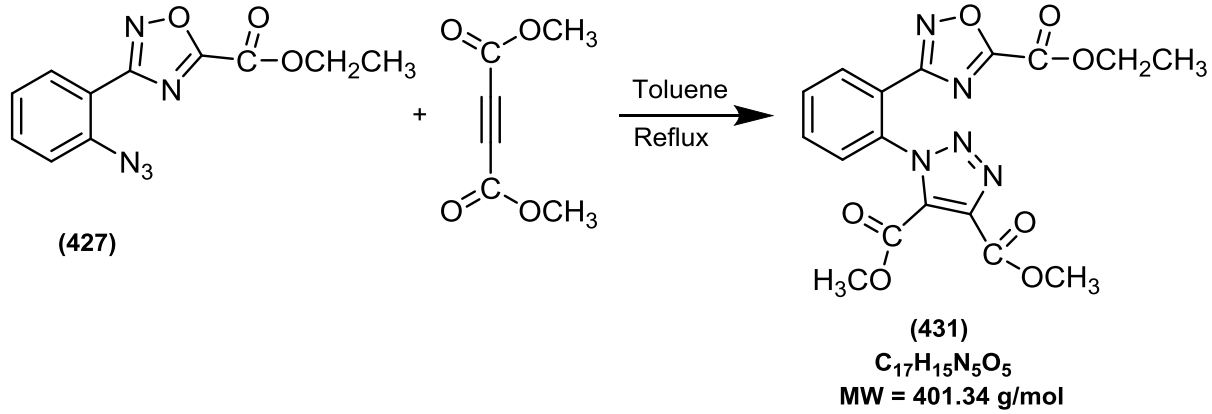


Figure 4.6: Crystal structure of the compound **(430)**

4.2.3.3. Synthesis of dimethyl 1-{2-[5-(ethoxycarbonyl)-1,2,4-oxadiazol-3-yl]phenyl}-1*H*-1,2,3-triazole-4,5-dicarboxylate.



(427)

(431)
$C_{17}H_{15}N_5O_5$
MW = 401.34 g/mol

Scheme 4.12

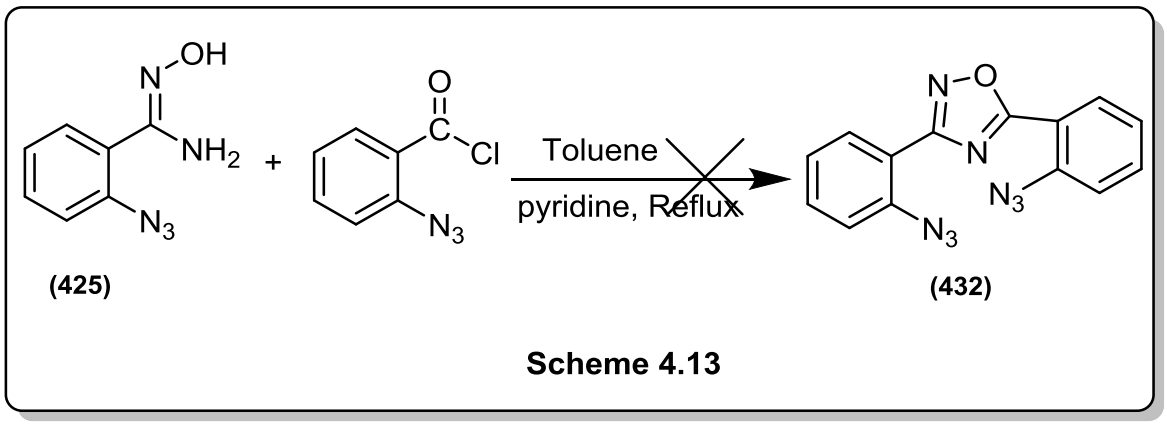
As mentioned above, this type of compound was of interest in a collaborative project that our group has in order to find 1,2,4-oxadiazole ligands. The reaction of compound (**427**) with DMAD was performed in toluene at reflux for 24 hours to give the desired product in 75 % yield. The product (**427**) is substituted with an oxadiazole ring and a triazole ring. The triazole was formed via [3+2] cycloaddition based upon the use of DMAD as an excellent dipolarophile.[217]

The structure of the product (**431**) was confirmed by spectroscopic analysis. The ^{1}H NMR spectrum was consistent with the presence the ethoxy methyl protons as a triplet at 1.43 ppm and the methylene protons as a quartet at 4.50 ppm. The methyls of the two methyl esters appeared as singlets at 3.76 ppm and 4.02 ppm. Three signals integrating to four protons were seen in the aromatic region.

The ^{13}C NMR spectrum showed the presence of two oxadiazole C=N carbons at 153.62 and 158.16 ppm, two quaternary benzene ring carbons at 123.73 and 132.93 ppm, two quaternary carbons at 134.00 and 139.31 ppm for the triazole ring as well as three signals at 160.30, 166.37 and 166.43 ppm for the three carbonyls. The four aromatic CHs appeared at 128.80, 130.72, 131.61 and 132.29 ppm whilst three signals at 13.90, 52.78 and 53.39 ppm appeared for the three methyl carbons with a signal at 64.01 ppm for the methylene carbon.

In the IR spectrum a strong absorption band at υ_{max} 1731. 8 cm^{-1} was seen for the carbonyl groups while the absence of the azide absorption band supported successful cycloaddition. The correct measured mass of 402.0975 for the ion $[M+H]^+$ in the mass spectrum confirmed that the reaction was successful.

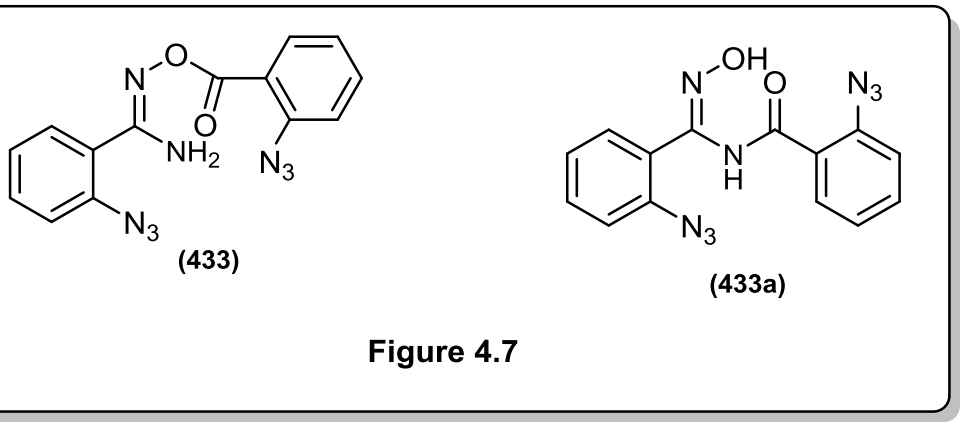
4.2.3.4. Attempted Synthesis of 3,5-bis(2-azidophenyl)-1,2,4-oxadiazole.



(425) (432)

Scheme 4.13

The amidoxime (**425**) was treated with 2-azidobenzoyl chloride in the presence of pyridine as a base in THF at reflux. The mixture was heated for 3 days in toluene whilst monitored by TLC which showed no product. Replacement of the toluene with THF similarly gave no reaction. Product (**432**) could not be formed. However, after 24 hours in THF, it was noted that the O-acyl-amidoxime (**433**) [or its N-acyl-equivalent (**433a**)] could be isolated.



(433) (433a)

Figure 4.7

The intermediate was isolated in 44 % yield.

Spectroscopic analysis confirmed the structure as compound (**433**). The infrared spectrum confirmed the presence of the azide group at υ_{max} 2118.3 cm^{-1} and the characteristic carbonyl group found at υ_{max} 1721.8 cm^{-1}. The presence of the NH_2 peaks were at υ_{max} 3341.7 and 3465.7 cm^{-1}.

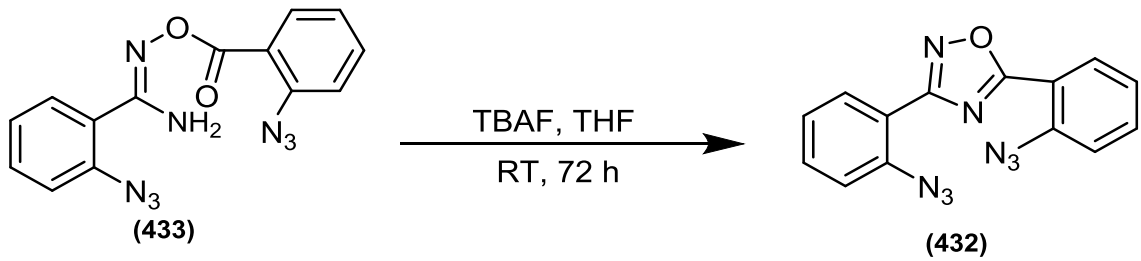
The ^{1}H NMR spectrum showed the eight aromatic (CH) protons downfield at 7.15-7.22 (2H), 7.25 (2H), 7.47 (1H), 7.57 (1H), 7.77 (1H), 8.00 (1H) giving a pattern of m, dd, dd, dd, d and d consistent with two 1,2-disubstituted benzene ring system. The primary amine protons (NH_2) were present at 5.90 (2H, bs), implying **(433)** and not **(433a)** had formed.

The ^{13}C NMR spectrum indicated the presence of the carbonyl signal at 163.26 whilst the imine peak (C=N) was found at 156.49 ppm. The presence of eight signals for the aromatic (CH) carbons at 118.71, 119.25, 124.91, 125.04, 131.21, 131.89, 132.77 and 133.45 ppm in the ^{13}C NMR spectrum, together with four quaternary carbons at 121.85, 122.11, 138.10 and 139.27 ppm confirmed the assignment.

The structure of the product (**433**) was further confirmed by HRMS analysis with an accurate measured mass for $[M+H]^{+}$ of 323.0990 for a required of 323.0999.

It should be noted that O-acyl-amidoximes are well known intermediates in 1,2,4-oxadiazole synthesis.[218]

4.2.3.5. Synthesis of 3,5-bis(2-azidophenyl)-1,2,4-oxadiazole.



Scheme 4.14

In this reaction, the carbonyl group was reacted with the amine and converted to the 1,2,4-oxadiazole by the catalytic[219] use of tetrabutylammonium fluoride as a mild and efficient catalyst in THF. The mixture was heated at reflux for 72 h. The reaction mixture was monitored by TLC, which showed the disappearance of the starting material. A product was isolated from the reaction mixture by purification with silica column chromatography to afford the desired product (**432**) in 90 % yield.

The structure of the compound (**432**) was confirmed by its IR spectroscopy NMR spectroscopy and mass spectrometry.

The mechanism for conversion of acylamidoximes to 1,2,4-oxadiazole and the role of fluoride is shown in Figure 4.8, below.[219]

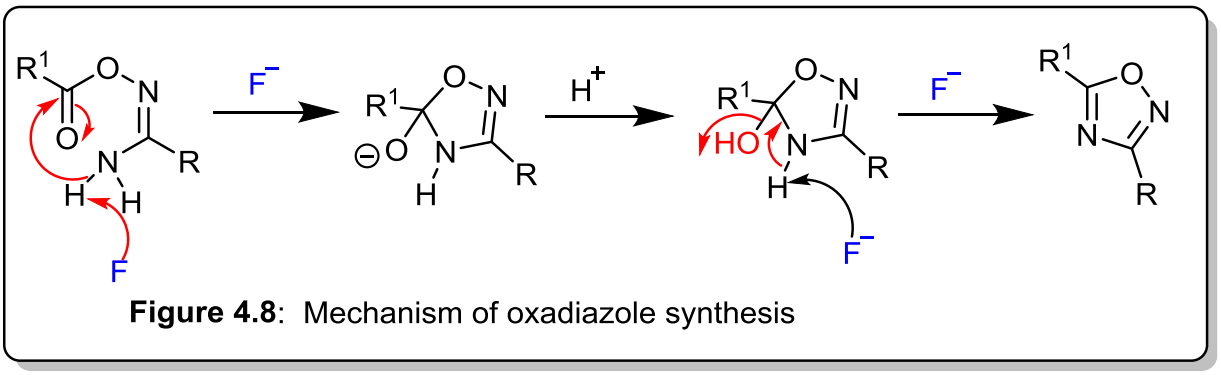
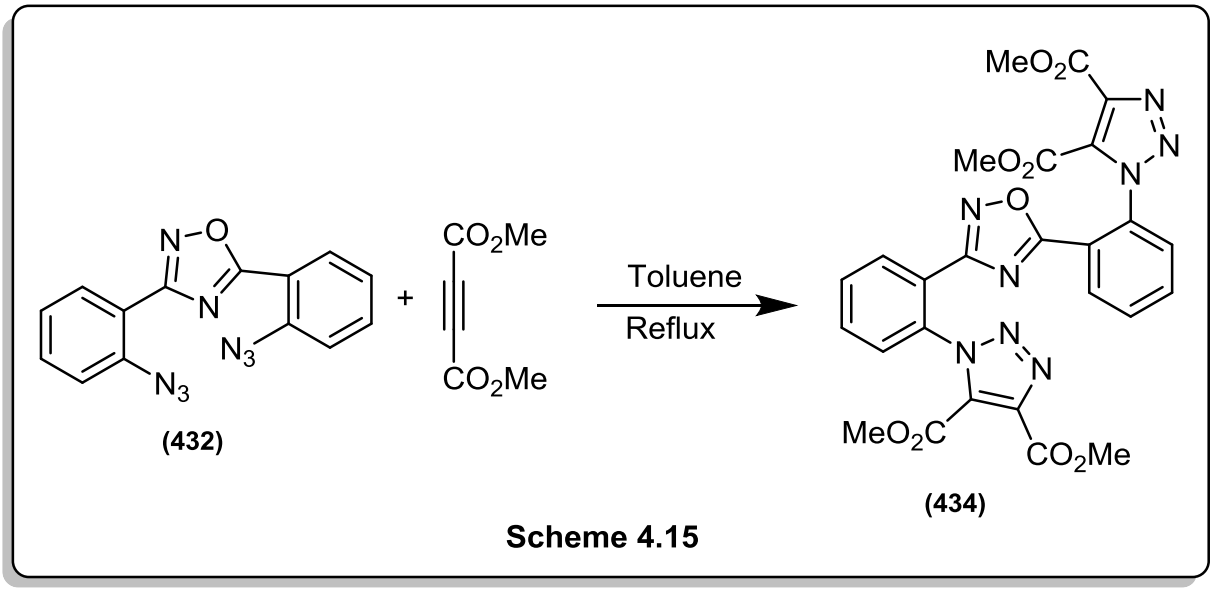


Figure 4.8: Mechanism of oxadiazole synthesis

4.2.3.6. Synthesis of tetramethyl 1,1'-[(1,2,4-oxadiazole-3,5-diyl)bis(2,1-phenylene)]bis(1*H*-1,2,3-triazole-4,5-dicarboxylate).



Scheme 4.15

The reaction of the 1,2,4-oxadiazole (**432**) with DMAD was performed in toluene at reflux for 24 hours. A product was purified from the reaction mixture by silica column chromatography to give the desired product in 95 % yield. The product (**434**) is substituted with an oxadiazole ring and two triazole rings.

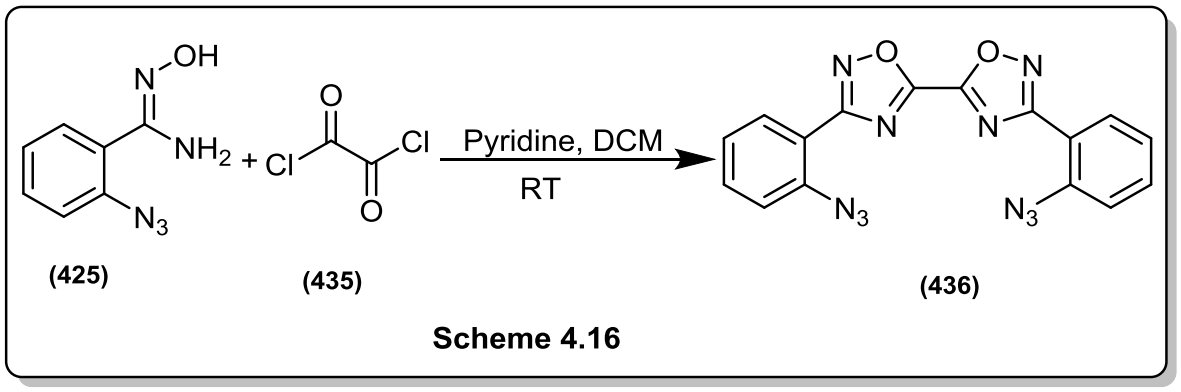
The structure of the product (**434**) was confirmed by spectroscopic analysis. The ^{1}H NMR spectrum was consistent with the methyls of the four methyl esters at 3.64 ppm (6H, bs), 3.94 ppm (3H, s) and 3.98 ppm (3H, s) as well seven signals integrating to eight protons in the aromatic region.

The ^{13}C NMR spectrum showed the presence of two oxadiazole C=N carbons at 165.65 and 171.56 ppm, four quaternary aromatic benzene carbons at 121.14, 123.99, 139.22 and 139.57 ppm, four quaternary carbons at 132.74, 133.04, 133.71 and 134.11 ppm for the two triazole rings as well as four signals at 157.88, 158.06, 160.38 and 160.44 ppm for the four carbonyls. The eight aromatic CHs appeared at 128.60, 129.07, 130.40, 130.64, 131.56, 131.78, 131.85 and 133.58 ppm whilst four signals at 52.79, 52.95, 53.38 and 53.49 ppm appeared for the four methyl carbons.

In the IR spectrum a strong absorption band at υ_{max} 1731.5 cm^{-1} was seen for the carbonyl groups while the absence of the azide absorption band supported successful cycloaddition.

The correct measured mass of 589.1422 for the ion $[M+H]^+$ in the mass spectrum confirmed that the reaction was successful.

4.2.3.7. Attempted synthesis of bis-[3-(2-azidophenyl)-1,2,4-oxadiazole] (436).



Scheme 4.16

The amidoxime (**425**) was treated with oxalyl chloride **(435)** in the presence of pyridine as a base in DCM. The mixture was stirred at room temperature for 24 hours whilst monitored by TLC which showed the disappearance of the starting material. A product was obtained from the reaction mixture by purification with silica column chromatography and identified as the desired product (**436**), in 80 % yield. This same reaction failed when attempted in THF.
The structure of the compound (**436**) was confirmed by its IR spectrum, ^{1}HNMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

The ^{1}H NMR spectrum showed the presence of four signals integrating to eight aromatic protons downfield at 7.14 (2H), 7.17-7.20 (2H), 7.53 (2H) and 7.93 (2H) ppm giving a pattern of dd, m, ddd and dd consistent with the two 1,2-disubstituted benzene ring systems.

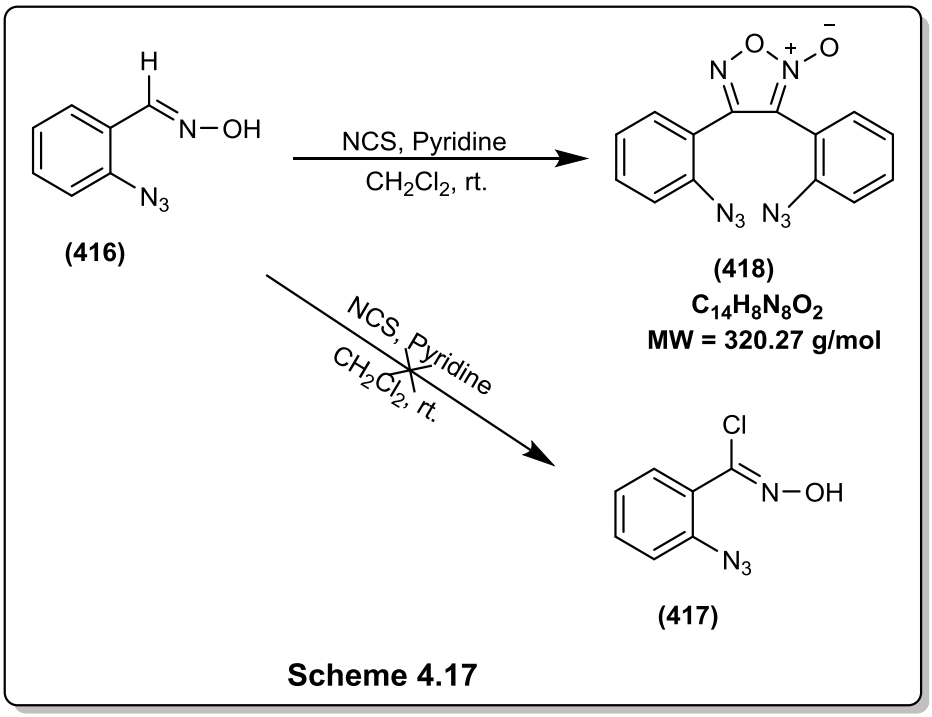
The ^{13}C NMR showed the presence of eight quaternary carbons at 138.93 (2 x qC), 143.37 (2 x qC), 164.28 (2 x qC(C-C)), and 165.76 (2 x qC (C=N)) ppm. The presence of eight signals of the aromatic (CH) carbons appeared at 118.81 (2 x CH), 125.02 (2 x CH), 133.91 (2 x CH) and 134.08 (2 x CH) ppm.

The infrared spectrum confirmed the presence of the azide group at υ_{max} 2111.7 cm^{-1}. The absence of the OH previously seen at υ_{max} 3371.0 cm^{-1} as well as the absence of the NH_2 peaks at υ_{max} 3151.7 and 3483.3 cm^{-1} was also noted.

Mass spectrometry further supported the structure of the product (**436**) with a measured mass of 395.0727 for ion $[M+Na]^+$ for a required mass of 395.0724.

4.2.4. Dimerisation of 2-azidobenzonitrile oxime.

A further diazide made was the dimer (**418**) resulting from the chlorination and dehydrochlorination of the oxime (**416**) as show in Scheme 4.16. This reaction procedure involves the formation of an intermediate nitrile oxide which forms when the o-azidobenzaldoxime (**416**) was treated with N-chlorosuccinimide in anhydrous DCM in the presence pyridine as a base. Compound **(418)** was isolated in 78 % yield and its chemistry along with that of compound **(436)** is being explored by another member of the group.



Scheme 4.17

The proposed mechanism for the formation of the dimer (**418**) is shown in Figure 4.9, and is based upon the known behaviour of nitrile oxides.[220-222]

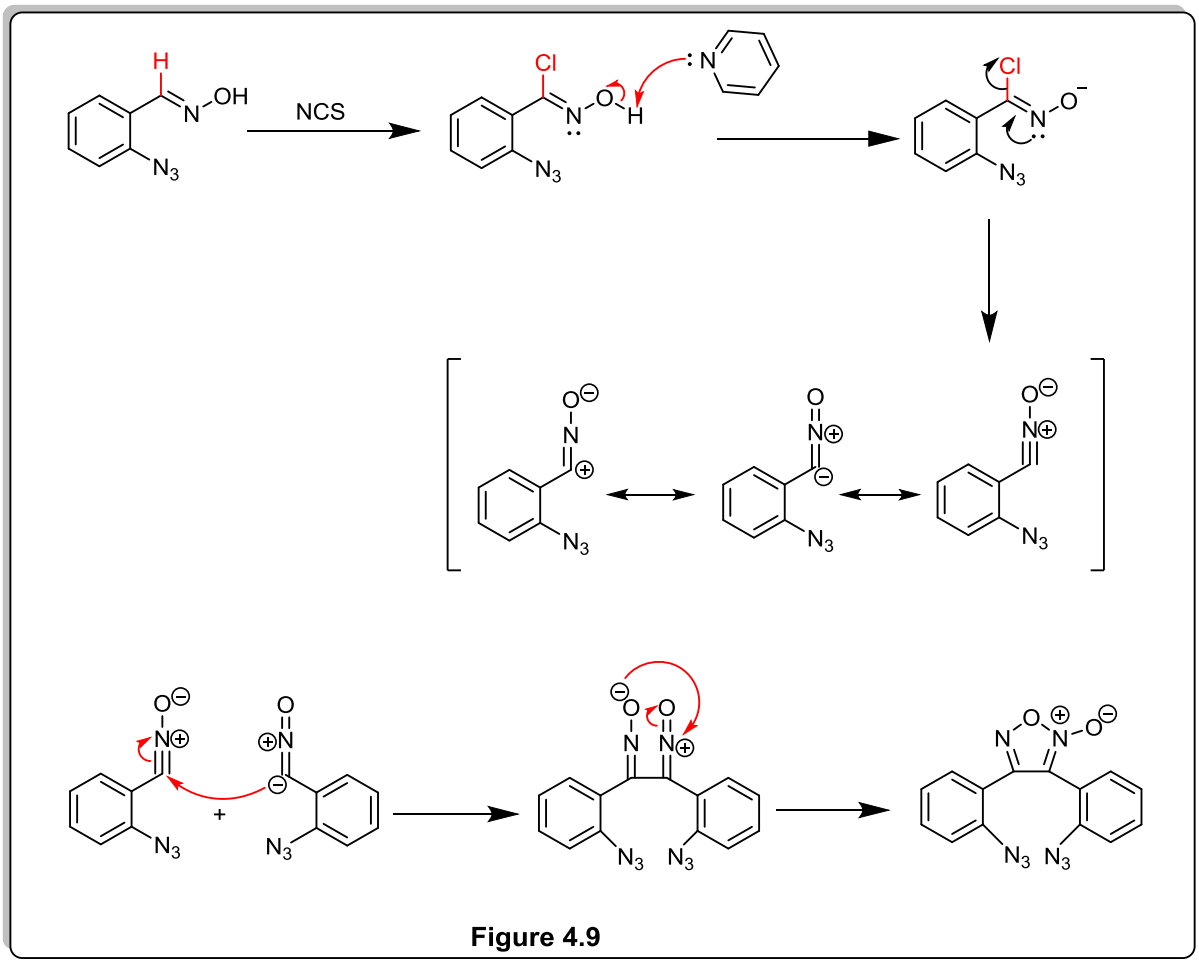


Figure 4.9

The structure of the *o*-azidobenzaldoxime dimer was confirmed by IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

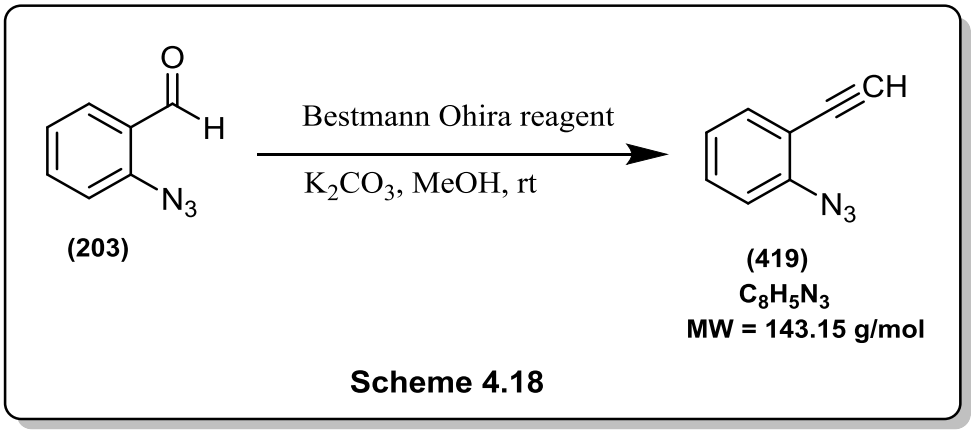
The ^{1}H NMR spectrum showed the presence of eight signals of aromatic protons at 7.06 (1H), 7.09-7.14 (2H), 7.18 (1H), 7.27 (1H), 7.38-7.50 (3H) and the loss of the two (OH and CH) oxime proton signals. The ^{13}C NMR spectrum indicated the presence of six quaternary carbons at 113.61, 115.23, 118.79, 118.83, 138.54 and 139.28 ppm and the presence of eight signals for the aromatic (CH) carbons at 118.90, 118.96, 125.21, 125.27, 130.88, 130.99, 132.12 and 132.30 ppm.

The IR spectrum showed the presence of the azide group at υ_{max} 2091.3 cm^{-1} while showing no peak for the OH group of the oxime that previously appeared at υ_{max} 3162.3 cm^{-1}.

The HRMS spectrum showed the theoretical mass for the $[M\text{-}2N_2+H]^{+}$ ion to be 265.0720, which compared well with the measured accurate mass of 265.0717.

4.2.5. Synthesis of 1-azido-2-ethynylbenzene.

Having looked at some reactions of 2-azidobenzonitrile, we also made the alkyne (**419**). This reaction (Scheme 4.18) was successful but lack of time meant that the chemistry of the alkyne was not explored.



Scheme 4.18

The o-azidobenzaldehyde was treated with freshly prepared Bestmann-Ohira reagent in dry methanol in the presence of potassium carbonate as a base. The mixture was stirred at room temperature for 24 hours. A product was isolated from the reaction mixture by extraction into dichloromethane and purified to give the desired product in 90 % yield as a brown oil.

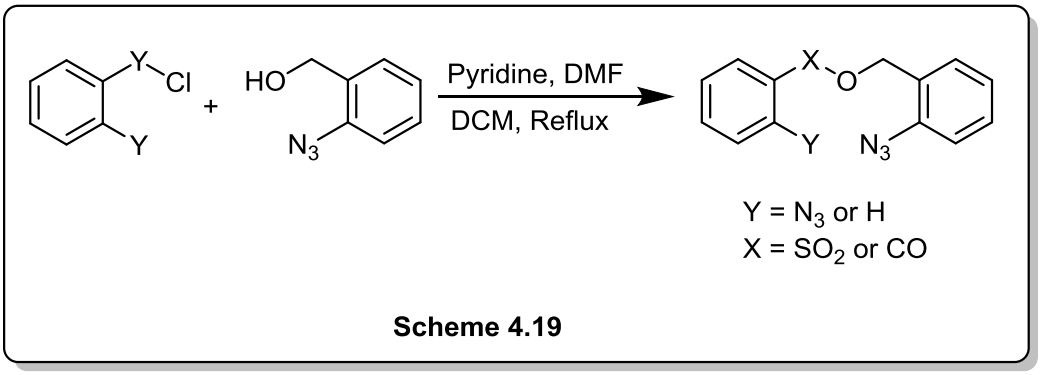
The structure of compound **(419)** was confirmed from its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry, and by comparison to the published data of this known compound,[223] which was previously made by a different route.

In the ^{1}H NMR spectrum, for example the terminal CH of the alkyne proton appeared at 3.30 ppm as a singlet whilst the absence of the aldehyde proton previously at 10.37 ppm was also noted. The terminal CH signal of the alkyne was seen at 79.33 ppm and the presence of four signals for the aromatic (CH) carbons was seen at 114.05, 124.62, 130.13 and 134.28 ppm in the ^{13}C NMR spectrum.

It was confirmed in the infrared spectrum that the compound contained the alkyne group from the peak at υ_{max} 3290.5 cm^{-1} while the presence of the azide group was seen at υ_{max} 2102.8 cm^{-1}. The loss of the broad peak at υ_{max} 1733.3 cm^{-1} for the carbonyl provided further evidence. The correct mass of 286.0958 for the measured ion $[2M]^{+}$ further supported the structural assignment for the compound (**419**).

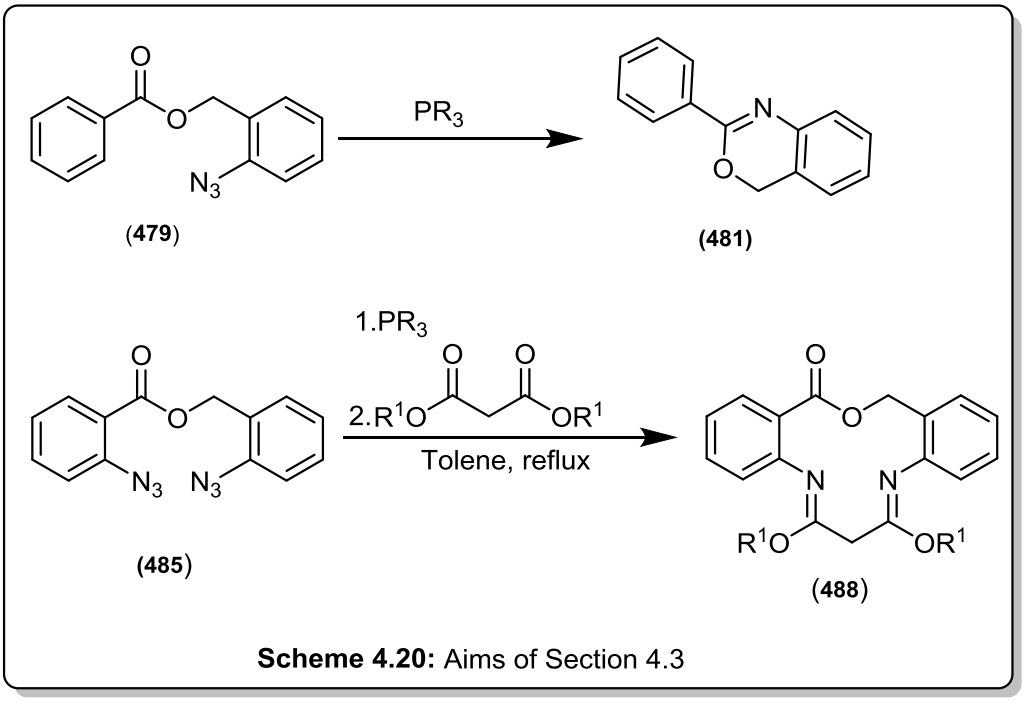
4.3. Further azide reactions.

The final section of this chapter will explore reactions based around the following general process:



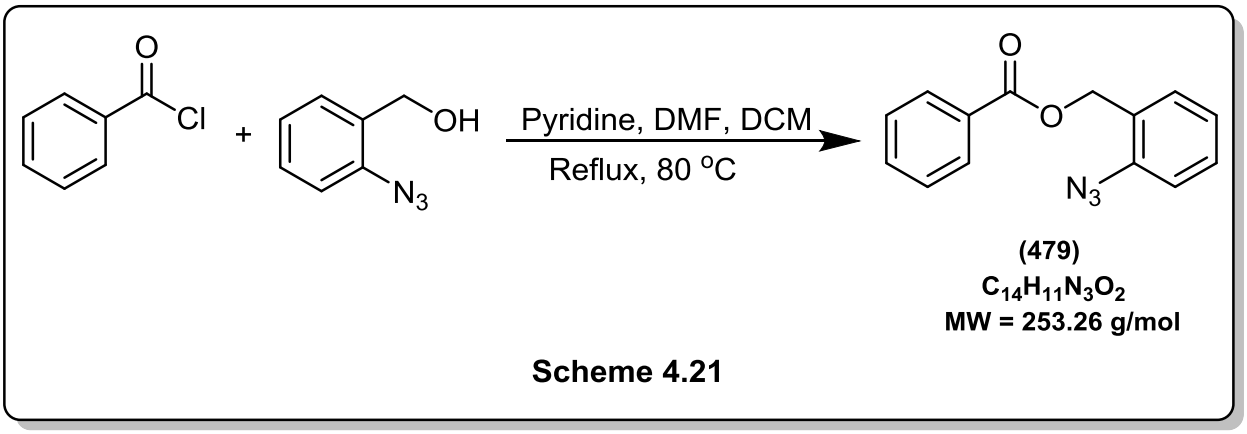
Scheme 4.19

The aim was to then conduct aza-Wittig reactions and Staudinger reactions and make some simple heterocycles and some macrocycles as shown in the examples below. The diazide could also be reacted to form triazoles as seen with other azides in this chapter, above.



Scheme 4.20: Aims of Section 4.3

4.3.1. Synthesis of 2-azidobenzyl benzoate.

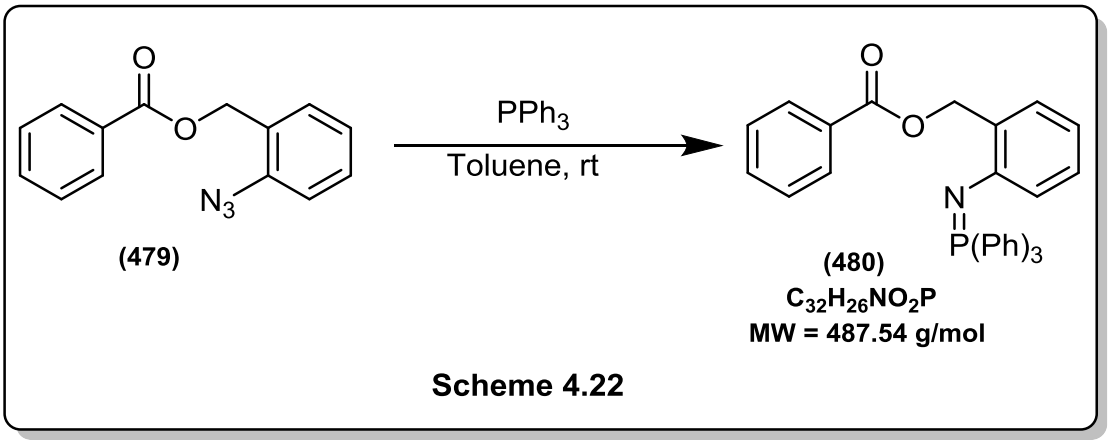


Scheme 4.21

The benzoyl chloride was coupled with o-azidobenzyl alcohol in anhydrous DCM in the presence of pyridine and DMF giving the product (**479**) in good yield (77 %).

The structure of the product (**479**) was confirmed by its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

4.3.2. Synthesis of 2-[(triphenyl-λ^{5}-phosphanylidene)amino]benzyl benzoate.



Scheme 4.22

The azide (**479**) was treated with triphenylphosphine in anhydrous toluene giving the desired product of a successful Staudinger reaction in 75%.

The structure of the product (**480**) was confirmed by its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

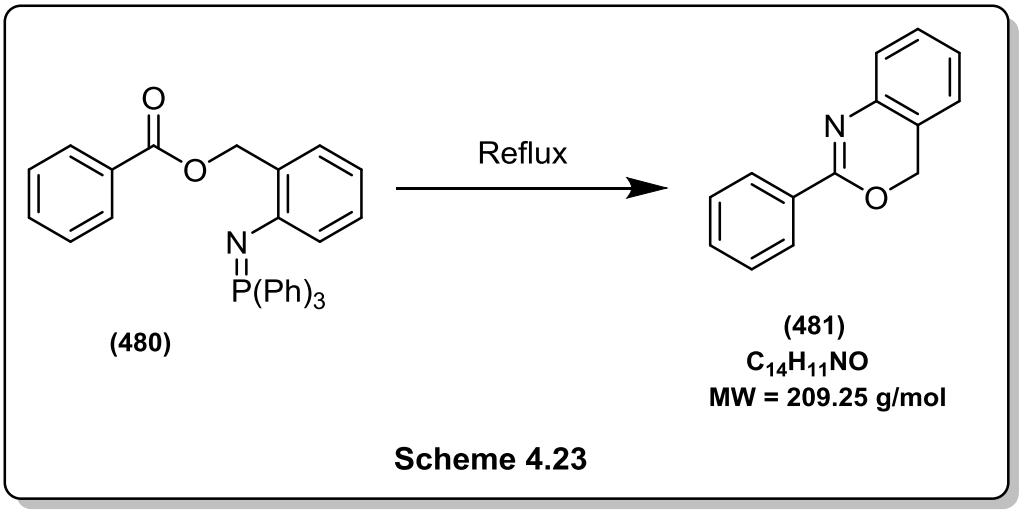
In the ^{1}H NMR spectrum, the presence of the aliphatic CH_2 protons were seen as a singlet at 5.65 ppm. The twenty four aromatic downfield protons showed as a doublet at 6.39 (1H), a triplet at 6.59 (1H), a triplet at 6.79 (1H), a multiplet at 7.24-7.33 (8H), a multiplet at 7.38-7.45 (4H), a doublet at 7.65 (3H), a doublet at 7.67 (3H) and a doublet at 7.96 (3H) ppm.

In the ^{13}C NMR spectrum, the aliphatic CH_2 signal appeared at 65.69 ppm. The twenty four aromatic CHs appeared between 117.11-132.60 ppm and six quaternary carbons were seen at 128.60 (qC), 129.90 (3 x qC), 130.98 (qC) and149.80 (qC) ppm. The carbonyl signal was found at 167.02 ppm.

Infrared spectrum showed the carbonyl absorption group at υ_{max} 1715.9 cm^{-1} and the loss of the azide absorption peak previously seen at υ_{max} 2117.6 cm^{-1}.

Further evidence for the structure was given by the HRMS for the measured ion $[M+Na]^{+}$ was consistent at 488.1777.

4.3.3. Synthesis of 2-phenyl-4H-benzo[d][1,3]oxazine.



(480)

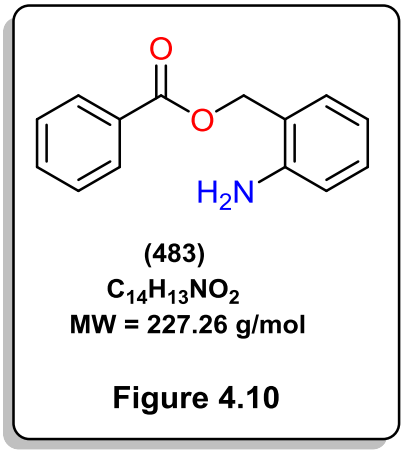
(481)
$C_{14}H_{11}NO$
MW = 209.25 g/mol

Scheme 4.23

The iminophosphorane (**480**) was heated to reflux in dry toluene for 24 hours under a nitrogen atmosphere whilst being monitored by TLC which showed no product formation. The solvent was replaced with anhydrous xylene and the mixture heated to reflux for 24 hours. The mixture was purified by silica column chromatography giving the desired product (**481**) in an excellent yield of 93 %.

The structure of the product (**481**) was confirmed by its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry, and comparison to known data. [224]

The azide (**479**) was also reacted with tributylphosphine in anhydrous toluene in order to compare the reactivity of triphenyl and tributyl phosphine. The mixture was stirred at room temperature for 12 hours. After completion of the reaction, the amine (**483**) was isolated in 60 % yield as a yellow oil.



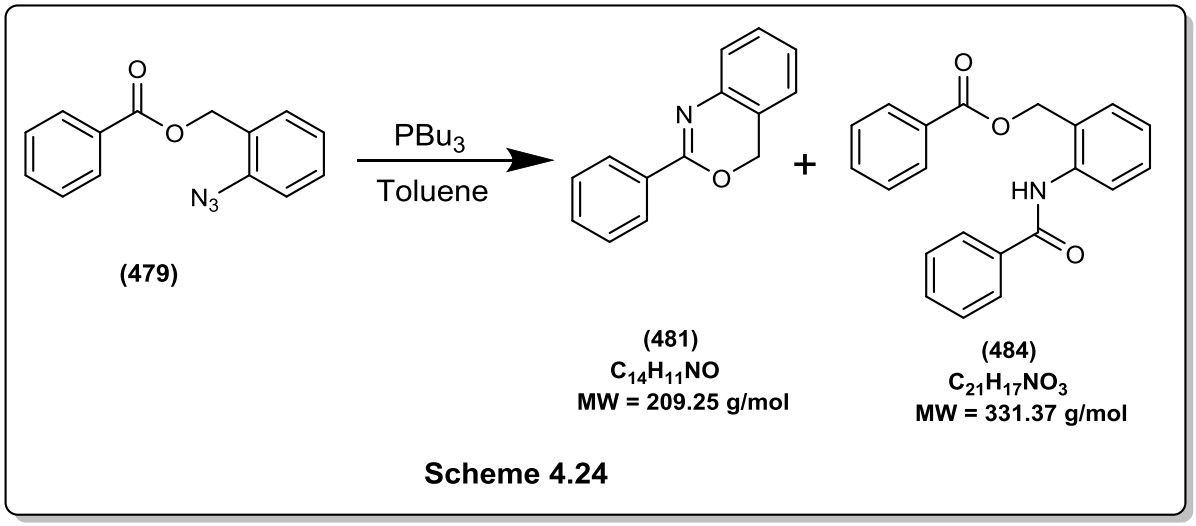
(483)
$C_{14}H_{13}NO_2$
MW = 227.26 g/mol

Figure 4.10

The structure of the compound (**483**) was confirmed using spectroscopic analysis.

In the ^{1}H NMR spectrum, the protons of the NH_2 group appeared at 4.70 ppm as a singlet, and the IR spectrum indicated the appearance of the NH_2 group with a signal at υ_{max} 3376.9 cm^{-1} and also showed the disappearance of the peak at υ_{max} 2117.6 cm^{-1} for azide group, in addition to the presence of the (C=O) peak at υ_{max} 1705.1 cm^{-1}.

The reaction of azide **(479)** with PBu_3 was repeated without attempting to isolate the iminophosphorane. This formed the expected oxazine **(481)** in 69 % yield togther with a second product, compound **(484)**, as shown in Scheme 4.24:



Scheme 4.24

The structure of product (**484**) was deduced from its IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.

The ^{1}H NMR spectrum confirmed the presence of fourteen aromatic protons which indicates the presence of the three aryl groups. The proton of the NH group in the product was seen as a broad singlet at 9.69 ppm. The methylene CH_2 protons were seen as a singlet at 5.31 ppm.

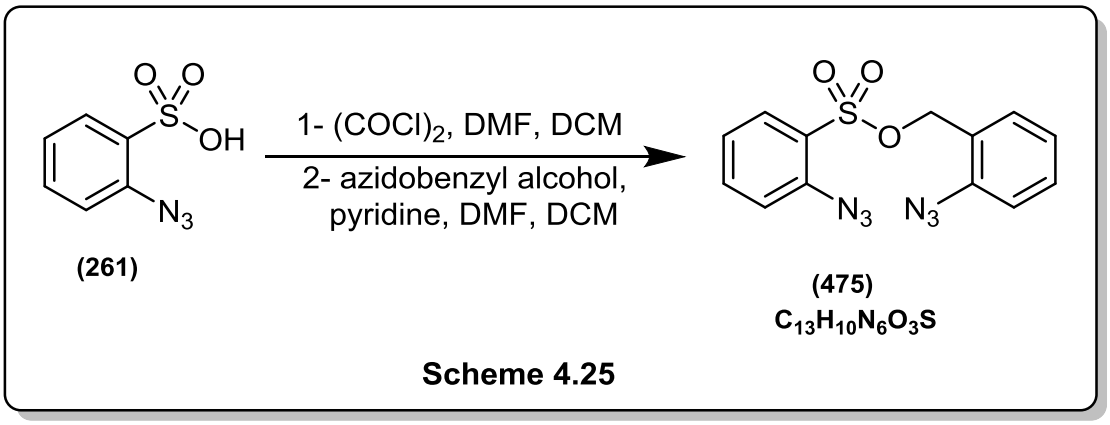
The ^{13}C NMR spectrum indicated the presence of fourteen CH peaks in the three aromatic rings at 124.71 (CH), 125.24 (CH), 127.45 (2 x CH), 128.53 (2 x CH), 128.73 (2 x CH) 129.88 (2 x CH), 130.01 (CH), 131.75 (CH), 131.91 (CH) and 133.60 (CH) ppm whilst the two carbonyl peaks were seen at 165.82 and 167.47 ppm with the methylene CH_2 peak found at 66.12 ppm.

The infrared spectrum showed the disappearance of azide group. The NH peak was found at υ_{max} 3317.1 cm^{-1} and the carbonyl group was seen at υ_{max} 1696.1 cm^{-1}.

Mass spectrometry further supported the structure of product (**484**) with a measured mass of 331.1205 for the ion $[M]^{+}$ for a required mass of 331.1195.

Compound **(484)** could arise from the reaction of the arylamine (**483**) with the ester **(479)**, a process that should eliminate 2-azidobenzyl alcohol, which was not, however, seen in the reaction mixture.

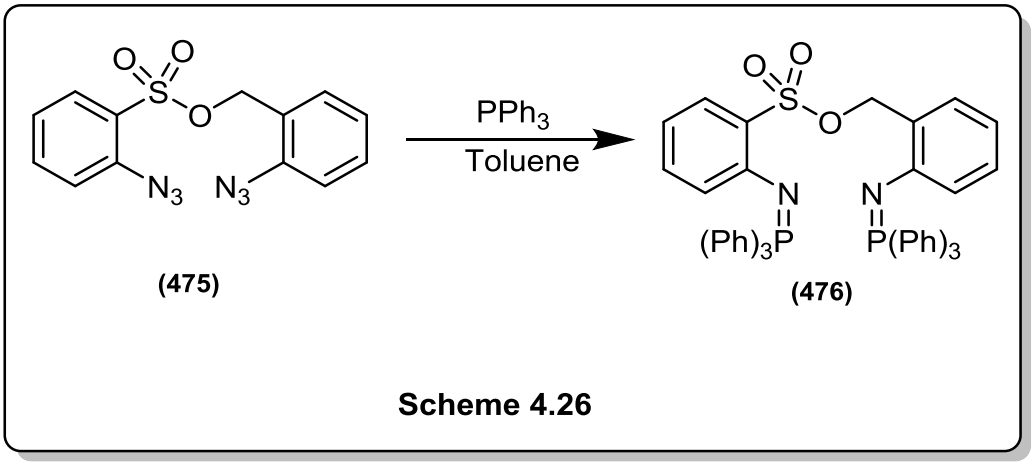
4.3.4. Synthesis and reactivity of 2-azidobenzyl 2-azidobenzenesulfonate.



Scheme 4.25

The sulfonic acid was converted to the sulfonyl chloride by heating at reflux as a suspension in 2M ($COCl_2$) in DCM and DMF. The sulfonyl chloride was treated with o-azidobenzyl alcohol in an aqueous solution of potassium carbonate as the base. The mixture was stirred at room temperature and monitored by TLC which showed no product. The same reaction was repeated using triethylamine and different amounts of DMF. All attempted reactions were unsuccessful at room temperature. The reaction was repeated by heating at 80 ^{o}C for 72 hours. A new product was formed. The mixture was purified to give the desired product **(475)** in good yield (72%).

Compound (**475**) was reacted with triphenylphosphine (PPh_3) in dry toluene. The mixture was stirred at room temperature for 24 hours, after which time the azide had disappeared. The desired product (**476**) was isolated in 71 % yield.



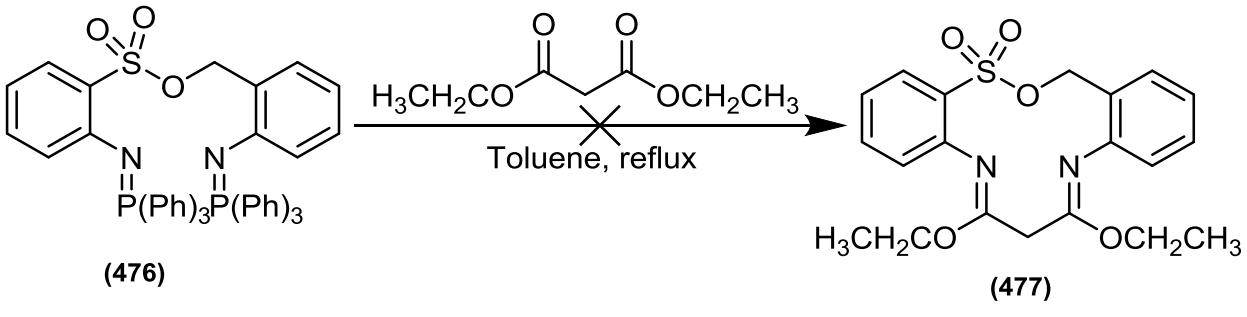
Scheme 4.26

The formation of compound (**476**) was implied from IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy.

The ^{1}H NMR spectrum showed the presence of four signals integrating to thirty eight aromatic protons in the aromatic range between 6.32-8.10 ppm and showed the methylene (CH_2) as a singlet at 5.15 ppm. The ^{13}C NMR spectrum showed the presence of ten quaternary carbons and thirty eight aromatic (CH) carbons and the presence of the methylene (CH_2) at 26.73 ppm. The infrared spectrum showed the disappearance of the azide stretch at υ_{max} 2125.7 cm.$^{-1}$

The iminophosphorane (**476**) was treated with diethyl malonate in anhydrous toluene. The mixture was heated to reflux for 24 hours. The desired product (**477**, Scheme 4.27) could not be identified, and no other identifiable products were found.

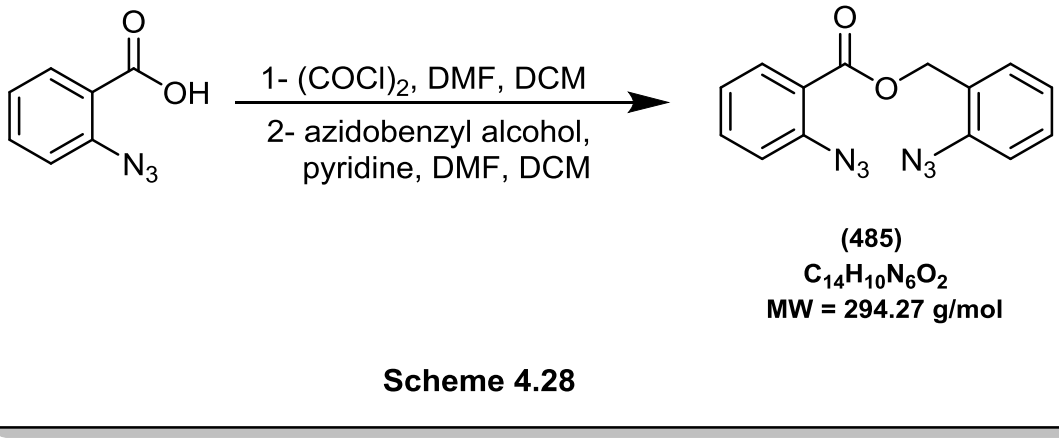
Compound (**476**) also failed to undergo aza-Wittig reaction with benzaldehyde.



(476) **(477)**

Scheme 4.27

4.3.5. Synthesis and reactivity of 2-azidobenzyl 2-azidobenzoate.

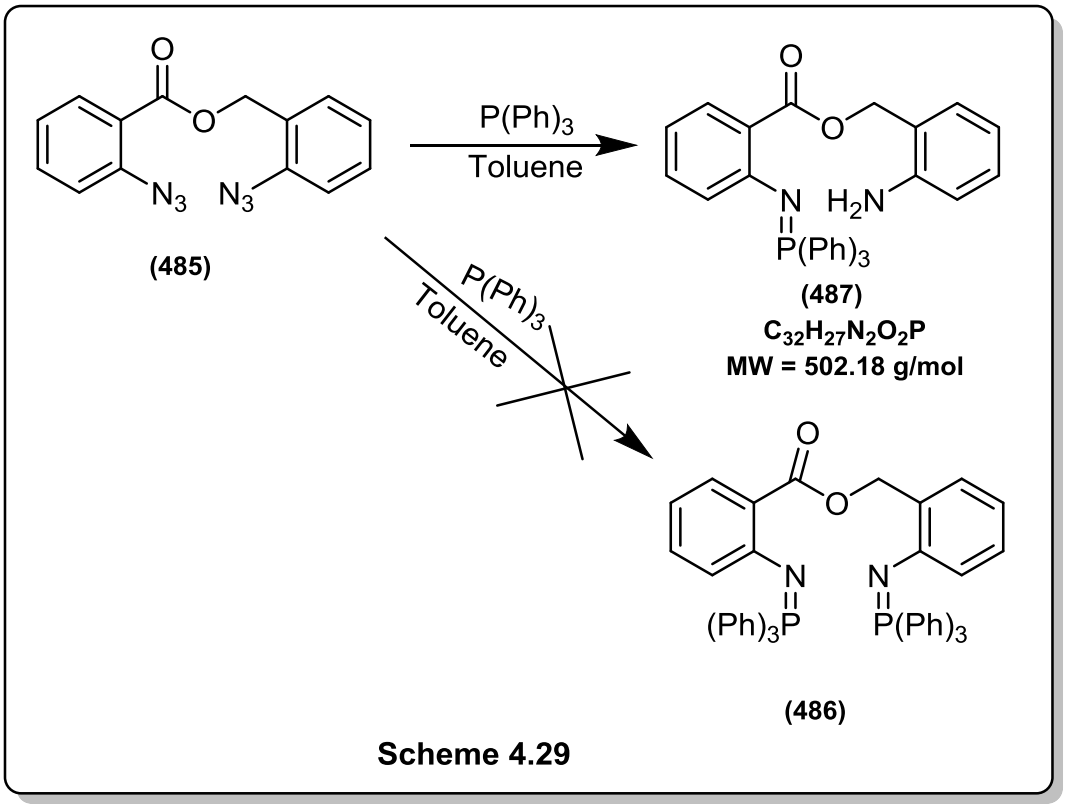


(485)
$C_{14}H_{10}N_6O_2$
MW = 294.27 g/mol

Scheme 4.28

2-Azidobenzoic acid was converted into the 2-azidobenzoyl chloride by heating at reflux with $(COCl)_2$ in dichloromethane and DMF. The o-azidobenzoyl chloride was treated with o-azidobenzoyl alcohol, triethylamine and DMF in DCM. The mixture was stirred at room temperature for 72 hours whilst being monitored by TLC which showed no product. The solvents were removed and replaced with pyridine and the mixture heated for 48 hours whilst being monitored by TLC. A new product was observed and the desired product **(485**) was isolated in good yield (74%), and its structure confirmed by spectroscopic analysis.

The diazido compound was treated with triphenylphosphine in toluene. A single new product was isolated and was identified the arylamino iminophosphorane **(487)** rather that the di-iminophosphorane **(486)**, as shown in Scheme 4.29. Compound **(487)** was formed in 50 % yield.



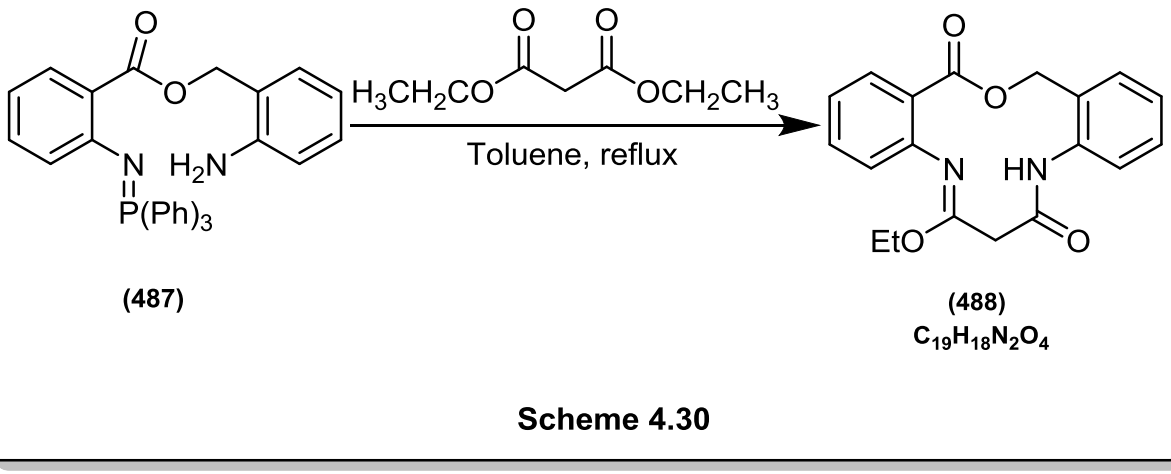
Scheme 4.29

The ^{1}H NMR spectrum of the product showed the presence of the methylene CH_2 protons and the NH_2 group as a broad singlet at 5.72 ppm. The aromatic protons appeared as a doublet at 6.51 (1H), a triplet at 6.56 (1H), a doublet at 6.62 (1H), a triplet at 6.70 (1H), a triplet at 6.90 (1H), a triplet at 7.23 (1H), a doublet at 7.39 (1H), a multiplet at 7.44-7.47 (6H), a multiplet at 7.51-7.55 (3H), a multiplet at 7.76-7.80 (6H) and a doublet at 7.93 (1H) ppm, and confirmed that only one PPh_3 had reacted.

The ^{13}C NMR spectra displayed the quaternary carbons at 111.76, 129.95, 130.17, 130.79, 131.78, 149.92 and 150.21 ppm whilst the expected number of aromatic CH carbons appeared between 116.13 –133.67 ppm. The methylene CH_2 carbon appeared at 65.14 ppm and the carbonyl carbon was seen at 168.52 ppm. The infrared spectrum showed that the azide was absent and also showed the presence of the carbonyl group peak at υ_{max} 1684.0 cm^{-1} in addition to the appearance of the amine absorption group at υ_{max} 3369.8 and 3473.7 cm^{-1}.

Mass spectrometry further supported the structure of product with a measured mass of 503.1883 for ion $[M+H]^+$ for a required mass of 503.1884.

The arylamino iminophosphorane (**487**) was treated at reflux with diethyl malonate in anhydrous toluene giving the product (**488**) in 65 % yield, the structure of which was deduced from its IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry.



(487)

(488)
$C_{19}H_{18}N_2O_4$

Scheme 4.30

The ^{1}H NMR spectrum showed a triplet at 1.20 ppm and a quartet at 4.17 ppm that correspond to the CH_3 and OCH_2 of the ethoxy unit, respectively. The proton of the NH group in the product appeared as a singlet at 13.27 ppm. The eight protons of the two aromatic rings appeared as a doublet at 6.97 (1H), a doublet of doublets at 7.04 (1H), a multiplet at 7.14-7.22 (2H), a doublet of doublets at 7.27 (1H), a doublet of doublets at 7.41 (1H), a doublet at 7.95 (1H) and a doublet at 8.64 (1H) ppm. The methylene CH_2 protons between the ethoxy and amide groups were seen at 3.50 ppm while the protons of the methylene (CH_2) group of the benzyl ester were seen at 5.34 ppm.

The ^{13}C NMR spectrum indicated the terminal methyl of the ethoxy group at 14.15 and the methylene at 61.63 ppm. The two carbonyl signals appeared at 163.94 and 167.46 ppm while the imine peak (C=N) appeared at 158.94 ppm. The eight signals for the aromatic (CH) carbons were seen at 120.40, 122.74, 124.01, 124.12, 127.23, 128.94, 129.23 and 132.71 ppm.

In the infrared spectrum, it was determined that the product contained the NH stretching absorption with a peak at υ_{max} 3161.4 cm^{-1} and a carbonyl group at υ_{max} 1737.5 cm^{-1}.

The HRMS spectrum showed the theoretical mass for the $[M]^+$ ion to be 338.1267, which compared well with the measured accurate mass of 338.1278.

4.4. Conclusion

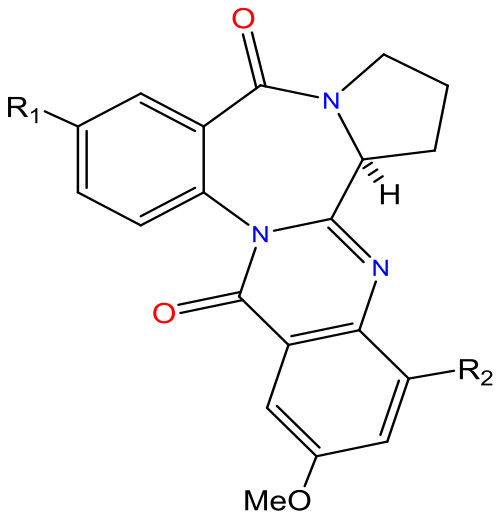
This chapter has shown that a range of simple aryl azides are potentially useful building blocks for the synthesis of benzotriazinones, quinazolines, ligand-like oxadiazolyl substituted 1,2,3-triazolyl benzenes, various diazides and one example of a 12-membered ring macrocyclic oxadiazacyclododecine.

Chapter 5:

5. Results and Discussion: Attempted Synthesis of circumdatin and fuligocandin analogues.

5.1. Introduction and Aims.

Circumdatins D, E, H and J are examples of pyrrolobenzodiazepine alkaloids that were extracted from a terrestrial strain of the fungus Aspergillus as reported by Rahbeak et al. in 1999, and shown in figure 5.1 below.



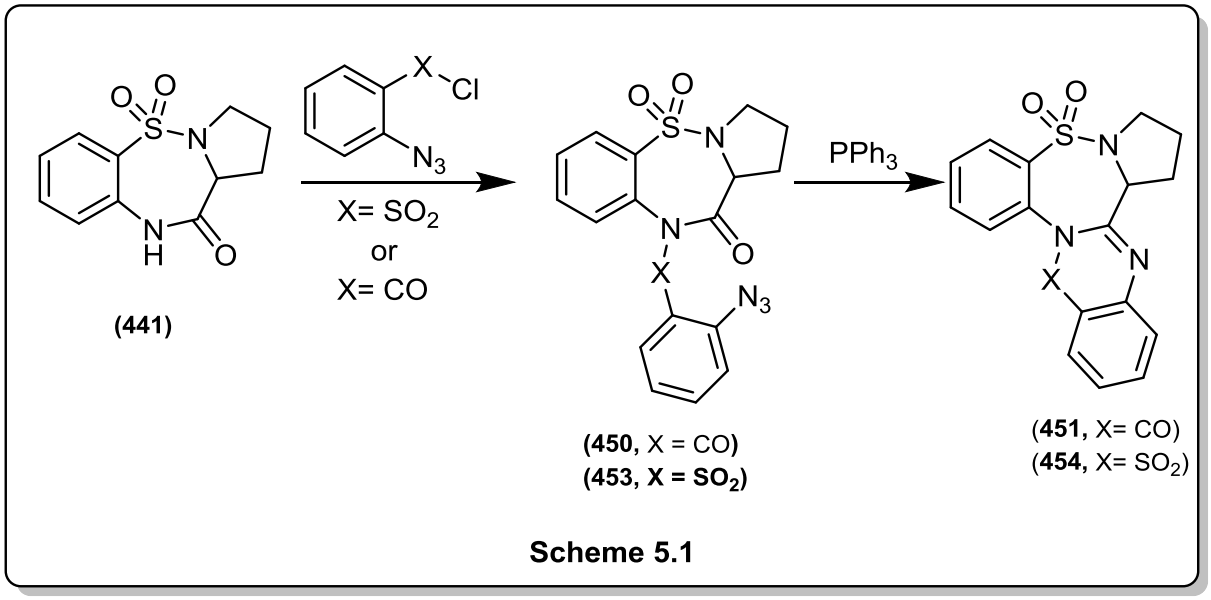
114: R^1= OMe, R^2 = OH (circumdatin D)
115: R^1= H, R^2 =OH (circumdatin E)
116: R^1= H, R^2 = H (circumdatin H)
117: R^1= OMe, R^2 = H (circumdatin J)

Figure 5.1: Structure of known circumdatins.

This chapter will deal with the attempted synthesis of sulfonamide analogues of these circumdatins.

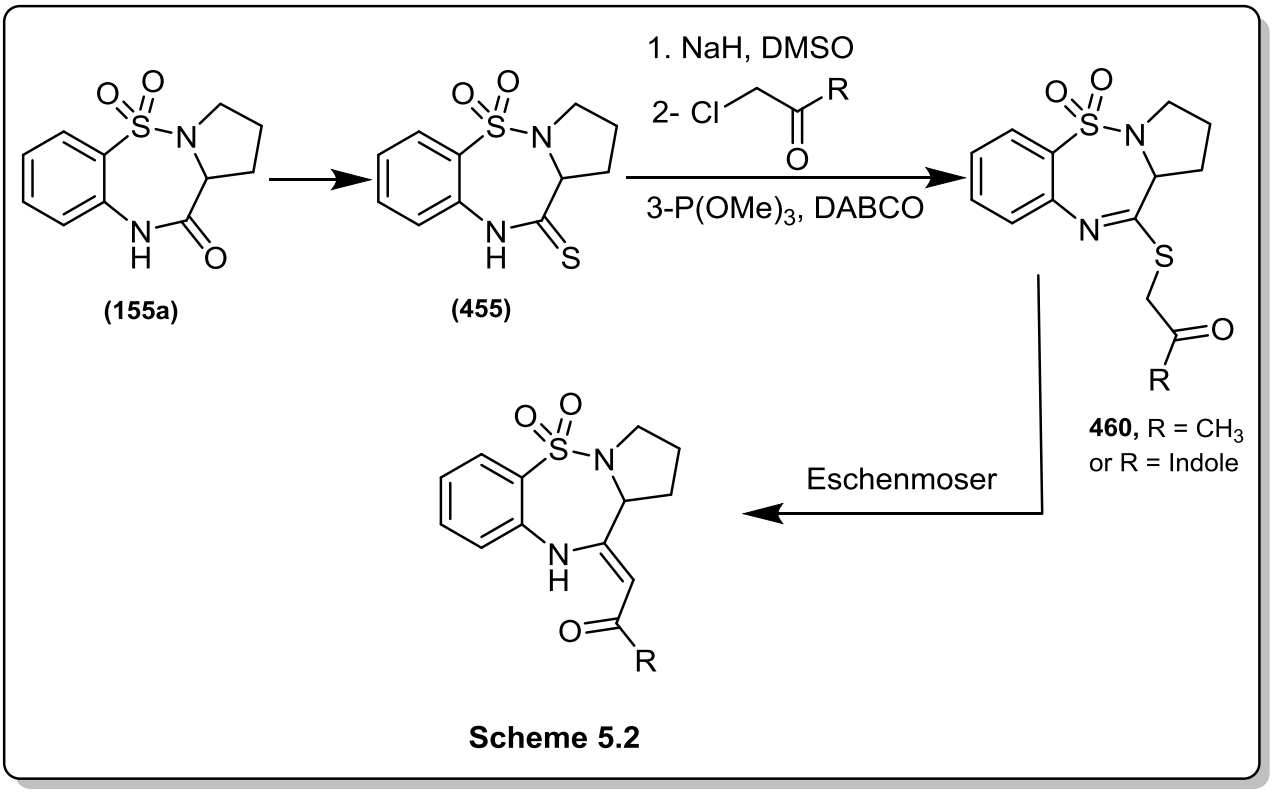
The circumdatins are targets because of the wide range of biological activities they process such as inhibition of mitochondrial NADH oxidase, antifungal, antitumor and antibiotic activity.[135,137,225-227]

This aims of this work are summarised below, and this chapter will look at the synthesis of known[161] compound **(441)** and its reactivity towards 2-azidobenzoyl chloride and 2-azidobenzenesulfonyl chloride to give intermediates **(450)** and **(453)** as shown in Scheme 5.1. Aza-Wittig reaction would then give the circumdatin analogues **(451)** and **(454)**. This is discussed in Section 5.2.



Scheme 5.1

Attempts were also made to convert known[161] compound (**441**) into fuligocandin analogues. The fuligocandins are pyrrolobenzodiazepine natural products that have attracted interest due to anti-leukemia, antitumor activity.[143,228-230] The fuligocandins themselves have been synthesised[143] (see introduction) and again, the aim of this section of the work was to produce sulfonamide analogues based on this route. This is summarised in Scheme 5.2 and is discussed in Section 5.3

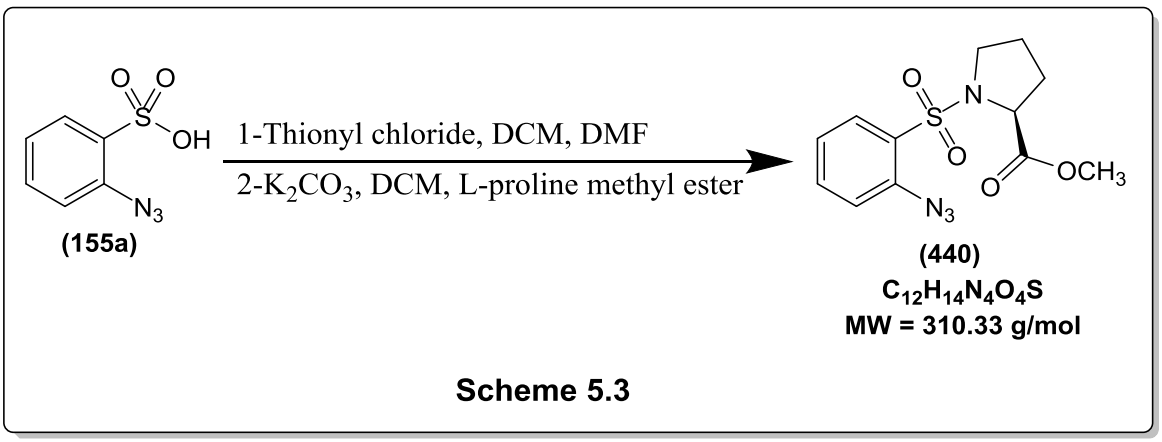


Scheme 5.2

5.2. Attempted synthesis of Circumdatin analogues.

5.2.1. Methoxycarbonyl-1-(2'-azidobenzenesulfonyl)pyrrolidine.

The first step on the way to precursor **(441)** [see aims] was to couple 2-azidobenzenesulfonic acid and L-proline as per Scheme 5.3:

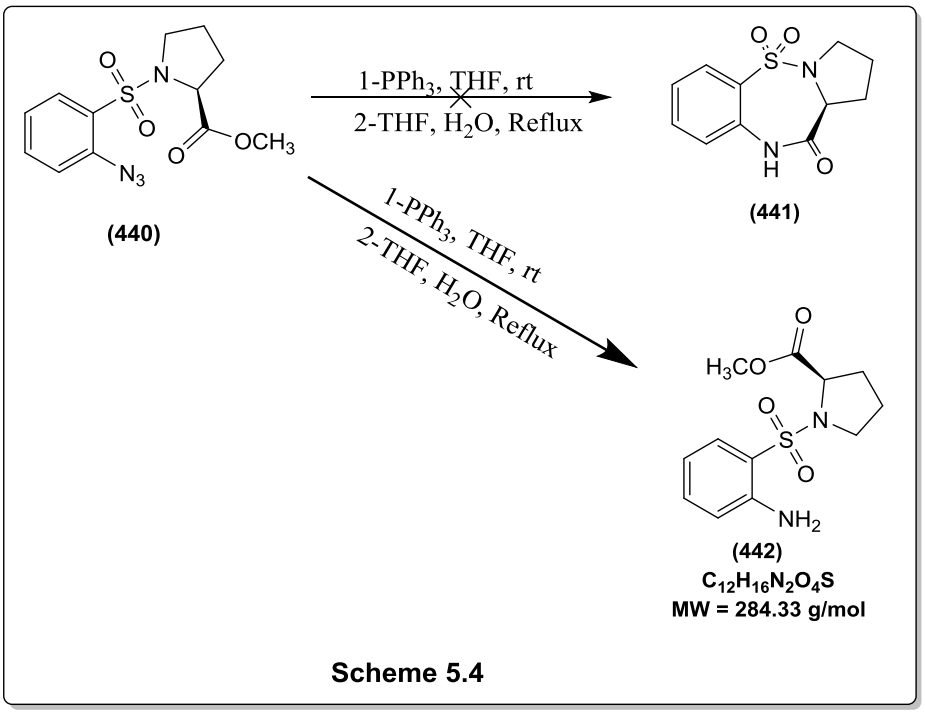


Scheme 5.3

Thus, 2-azidobenzenesulfonic acid[231] was converted into the sulfonyl chloride by heating at reflux in thionyl chloride and DMF. Coupling of the 2-azidobenzenesulfonyl chloride with L-proline methyl ester was performed in a mixed phase process with aqueous potassium carbonate as the base to give the desired product (**440**) in 58 % yield.

Evidence for the successful coupling was given by the ^{1}H NMR spectrum which showed the three protons of the methyl ester at 3.59 ppm. The four aromatic protons were located at 7.16 (1H), 7.22 (1H), 7.51 (1H) and 7.93 ppm (1H) and the pyrrolidine ring CH_2 protons showed at 1.79-1.88 (1H), 1.99-2.04 (2H), 2.08-2.18 (1H), 3.34-3.40 (1H) and 3.56-3.61 (1H) ppm with the CH of the pyrrolidine ring at 4.60-4.63 ppm. The ^{13}CNMR spectrum, infrared and mass spectrum were fully consistent, and the data was identical to that for this compound produced elsewhere in the group for another project[161].

5.2.2. Attempted synthesis of 10,10-dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-4-one.

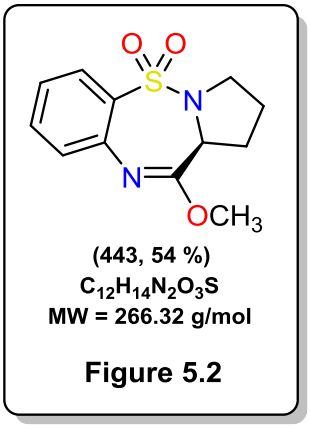


Scheme 5.4

Following a procedure used by Bergman with the corresponding amide[143], reaction of the ester **(440)** and triphenylphosphine in dry THF was attempted at room temperature. After

completion of the reaction by TLC, water was added. The mixture was heated at reflux overnight. The mixture was purified by using column chromatography. Instead of the desired product (**441)**, the amine (**442)** was isolated (39 %), a compound that is known in the literature.[232]

It was possible that triphenylphosphine was the wrong choice of phosphine in this reaction. Thus, the reaction also was attempted with tributylphosphine (PBu_3).[143] After completion of the reaction which was monitored by TLC at regular intervals, a mixture of products (**442)** and **(443)** was isolated. Compound **(442)** was identical to that isolated before. The structure of the compound **(443)** was confirmed by spectroscopic analysis.



(443, 54 %)
$C_{12}H_{14}N_2O_3S$
MW = 266.32 g/mol

Figure 5.2

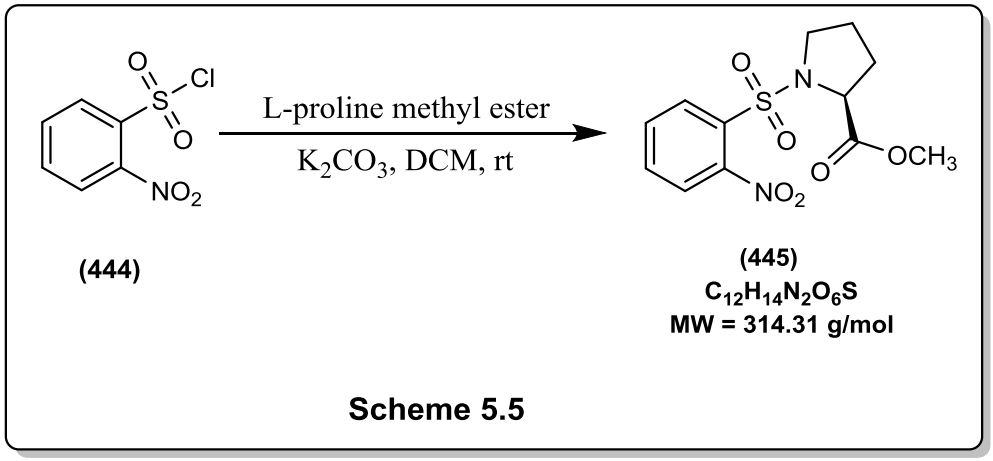
The ^{1}H NMR spectrum indicated the seven pyrrolidine protons at 1.62-1.71 (1H), 1.76-1.95 (2H), 2.21-2.30 (1H), 2.80-2.86 (1H), 3.27-3.32 (1H) and 4.50 (1H) ppm while the methyl protons (CH_3) appeared at 3.71 ppm. The four aromatic protons were observed as a doublet of doublets at 7.02, a doublet at 7.12, a doublet of doublets at 7.39 and a doublet at 7.69 ppm. The ^{13}C NMR spectrum indicated the three quaternary carbons at 131.69, 140.48 and 164.49 ppm while the methyl carbon appeared at 63.75 ppm.

Infrared spectral data confirmed the disappearance of the azide group and confirmed the absence of the carbonyl group peak previously seen at υ_{max} 1736.7 cm^{-1}.

All attempts to convert azide (**440**), amine **(442)** or imine (**443**) into the desired compound (**441**) were unsuccessful. Thus, other routes towards compound **(441)** were explored.

5.2.3. 2-Methoxycarbonyl-1-(2'-nitrobenzenesulfonyl)pyrrolidine.

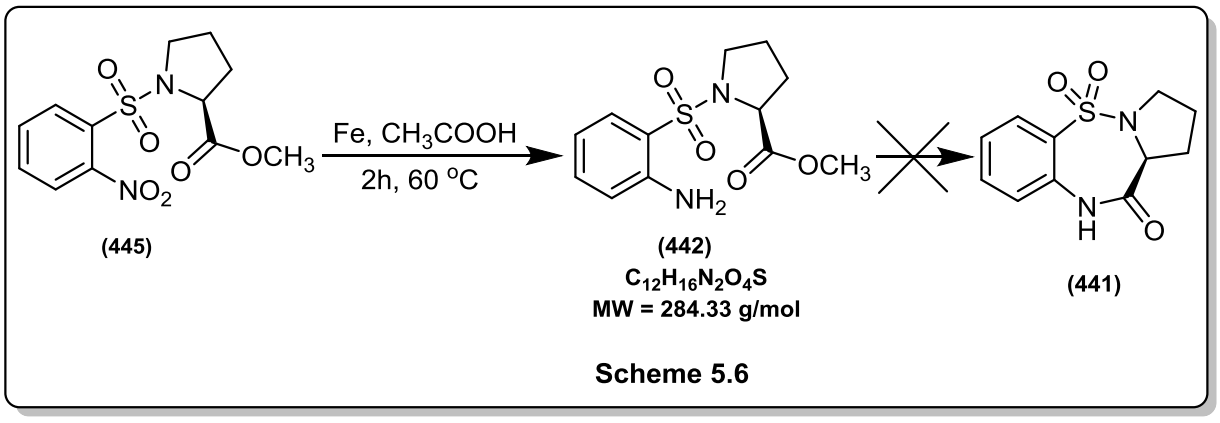
With the azide **(440)** proving to be an unsuccessful precursor, we looked instead at the corresponding nitro compound (Scheme 5.5):



Scheme 5.5

In the first step, the sulfonyl chloride was coupled with L-proline methyl ester in an aqueous solution of potassium carbonate[231] giving the product **(445)** in good 84% yield.

The structure of compound **(445)** was deduced from its IR spectrum, ^{1}H NMR (400 MHz) spectrum, ^{13}C NMR (100 MHz) spectrum and mass spectrometry, and is a known compound.[161]



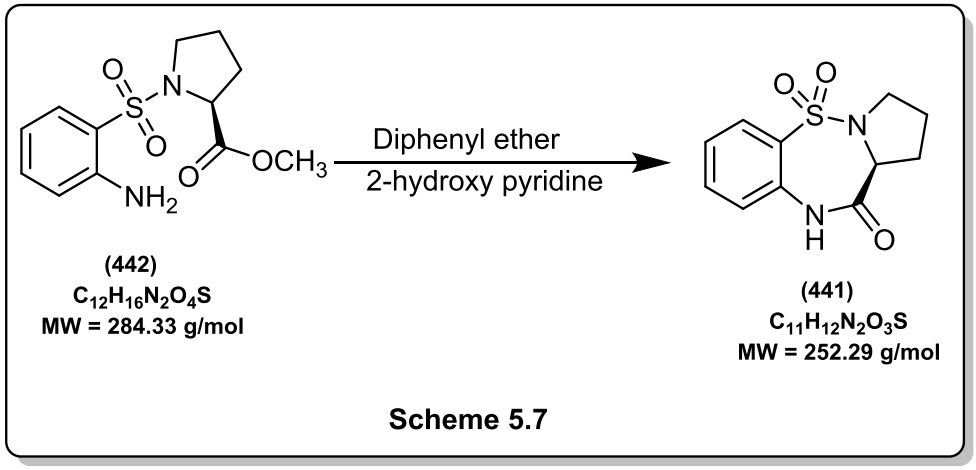
Scheme 5.6

The next step was reduction of the nitro ester to amino ester. The nitro ester was reacted with iron powder in glacial acetic acid[161] and afforded the amino ester **(442)**, identical to that formed above, in 74 % yield.

We had hoped that the amino ester would cyclise under these conditions to give the desired product **(441).** As this did not happen, it became critical to find a method to cyclise compound (**442**). After many efforts, a method was found (next section).

5.2.4. Successful synthesis of 10,10-dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-4-one.

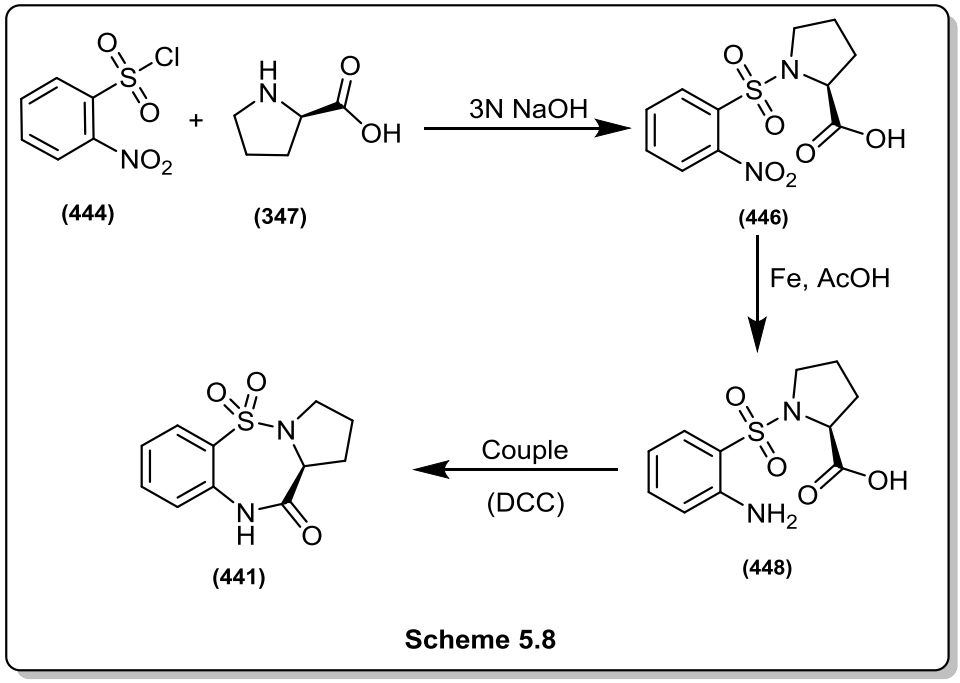
The route chosen was a literature route[233] that had proven very difficult to repeat for a previous worker in the group.[161]



Scheme 5.7

The aminoester **(442)** and 2-hydroxy pyridine were mixed in diphenyl ether and heated under reflux at 205 ^{o}C while monitoring via TLC overnight. A new product was identified. The structure of compound **(441)** was confirmed by its IR spectrum, ^{1}H NMR spectrum, ^{13}C NMR spectrum and mass spectrometry, and was identical to that in the literature[232,233], and to that reported by João from our research group.[161]

Unfortunately, and as reported by João, the reaction was low yielding, often did not work and was not a reliable way of getting the quantity of compound **(441)** needed. Thus, another route to **(441)** was investigated, as summarised in Scheme 5.8:



Scheme 5.8

Thus, 2-nitrobenzenesulfonyl chloride was coupled with L-proline in sodium hydroxide to give the carboxylic acid **(446)** in excellent yield and purity.

Reduction[137] of the nitro carboxylic acid **(446)** to the amino carboxylic acid **(448)** was achieved in 71 % yield with iron powder in glacial acetic acid.

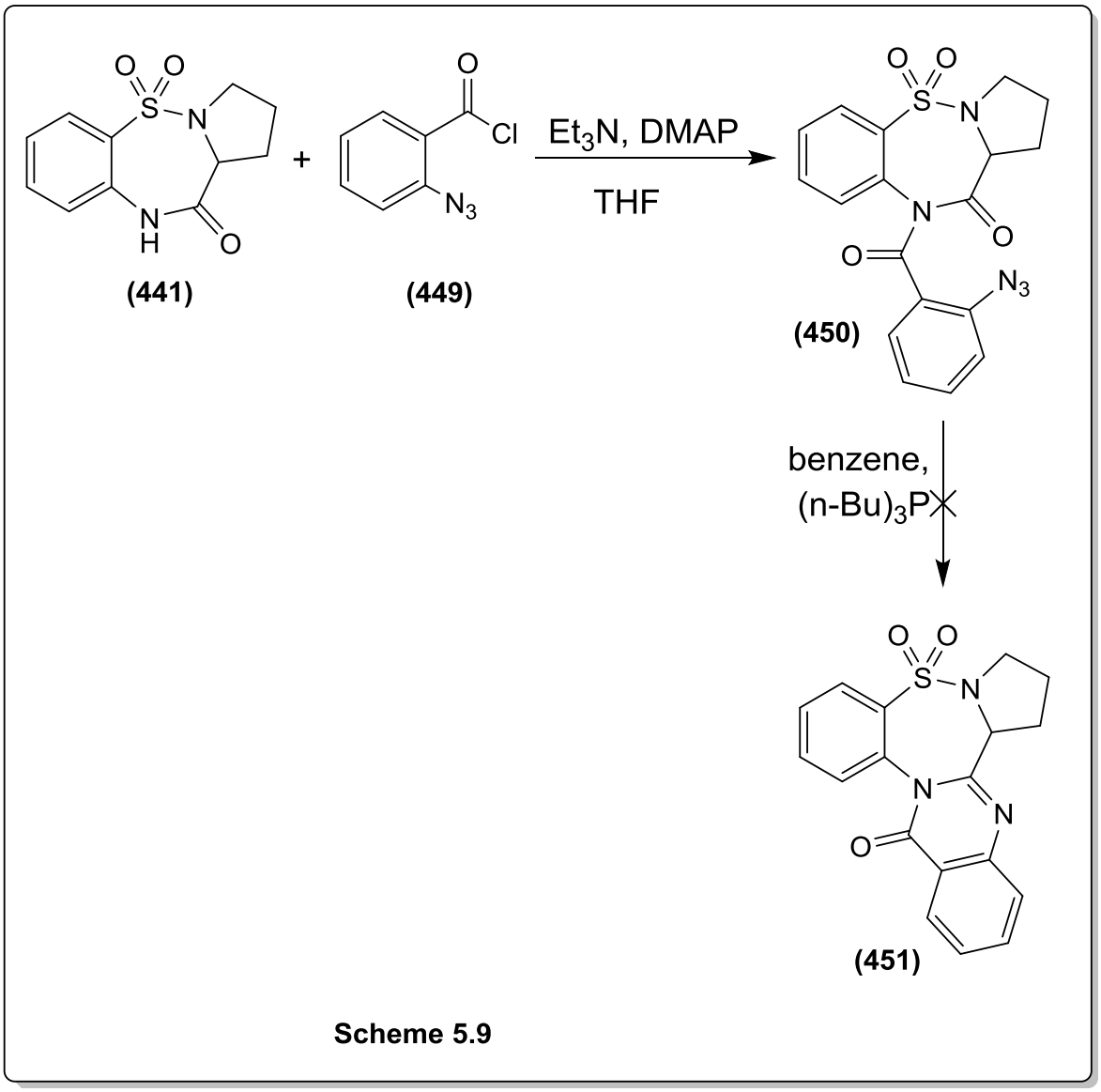
The structure of the amino carboxylic acid (**448**) was confirmed from its IR spectrum and from ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

The amide bond forming reaction was achieved by the addition of N,N'-dicyclohexylcarbodiimide (DCC) in DCM to the amino carboxylic acid **(448)**.[137] The mixture was stirred overnight, and a new product was isolated from the reaction mixture, and found to be (**441**) in 63 % yield.

The structure of the product (**441**) was confirmed by IR spectroscopy, ^{1}H NMR spectrum, ^{13}C NMR spectroscopy and mass spectrometry, and was identical to that formed by the unreliable methods discussed above.

This was found to be the most reliable procedure for the synthesis of known compound (**441**). With a reliable route established, we could at last start to look at routes towards the circumdatin analogues all based on Scheme 5.1 in the aims, above.

5.2.5. Attempted Synthesis of Circumdatin Analogues from Compound (441).



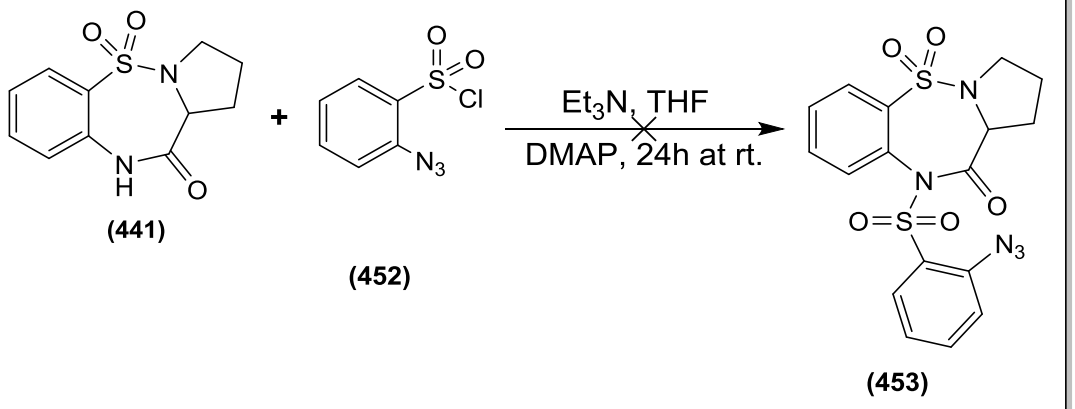
(441) **(449)** **(450)** **(451)**

Scheme 5.9

This followed the method Bergman used for the actual circumdatins. The amide (**441**) was treated with 2-azidobenzoyl chloride in the presence of Et_3N and DMAP and the mixture stirred for 2 hours at room temperature.[137] TLC showed starting material and a new product. This was assumed to be intermediate **(450).** This crude reaction mixture was dissolved in dry benzene and $(n\text{-}Bu)_3P$ was added. The mixture was heated for 1 hour at 60 ^{o}C. None of the desired product **(451)** or intermediate **(450)** could be identified and only starting material **(441)** could be identified, and was recovered in 75 % yield. All attempts to isolate the intermediate **(450)** were unsuccessful under a wide variety of conditions.

This was a very disappointing results as we knew that Bergman had performed this reaction with the amide analogue of **(441)** [ie C=O in place of SO_2].

5.2.6. Attempted synthesis the double sulfonamide.



(441) (452) (453)

Scheme 5.10

This time, amide **(441)** was treated with DMAP, Et_3N and 2-azidobenzenesulfonyl chloride. No product was formed with only starting material being recovered. The conditions followed were those that had previously been successful for Bergman[137] for the synthesis of the circumdatin diamide system. A wide variety of modified conditions also failed to give **(453).**

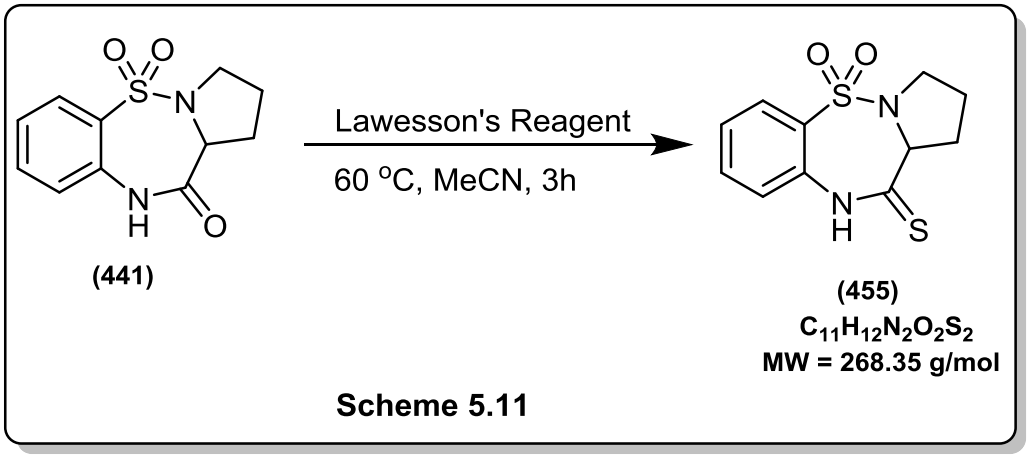
For completion, we also attempted to form compound **(453)** in-situ and react it with tri-n-butyl phosphine. This was also unsuccessful. The difficulty we had in making compound **(441)** and its failure to react was a major problem for the direction of this project, and we had no choice but to stop investigation into the synthesis of sulfonamide analogues of circumdatins.

Previous work in the group[161] had attempted to use the pyrrolobenzothiadiazepine **(441)** to make fuligocandin analogues. This work had revealed several steps that needed to be explored. The rest of this chapter explores the efforts made in this thesis towards completing the group's route to sulfonamide analogues of fuligocandin.

5.3. The Attempted synthesis of Fuligocandin analogues.

Scheme 5.2, above, Summarised the aims of this section of the work.

5.3.1. Synthesis of 1,2,3,11a-tetrahydrobenzo[*f*]pyrrolo[1,2-*b*][1,2,5]thiadiazepine-11(10*H*)-thione 5,5-dioxide.

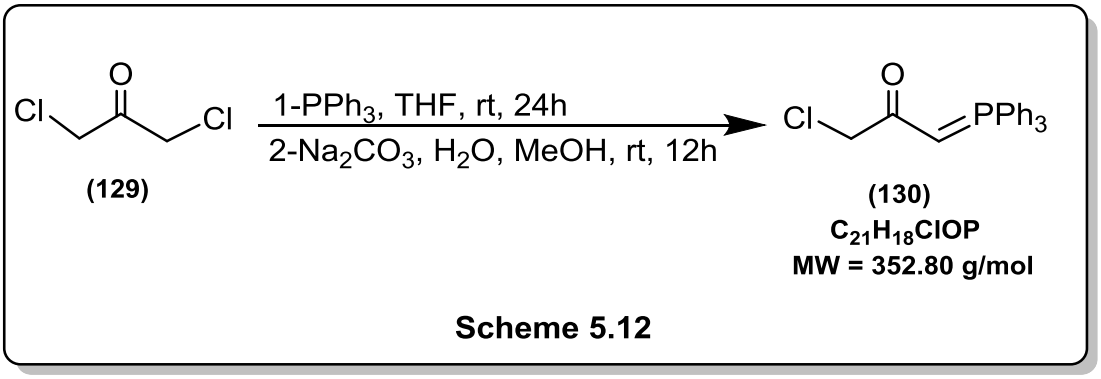


Scheme 5.11

The amide (**441**) was reacted with Lawesson's reagent[143] in MeCN. A product was isolated from the reaction mixture by silica column chromatography and was identified as the desired product in yielded (11 %).

João had previously[161] made compound **(455)** in 37 % yield. However, there were other steps to investigate so we moved on with the fuligocandin analogue synthesis.

5.3.2. Synthesis of phosphorus ylide for the fuligocandin B analogue.

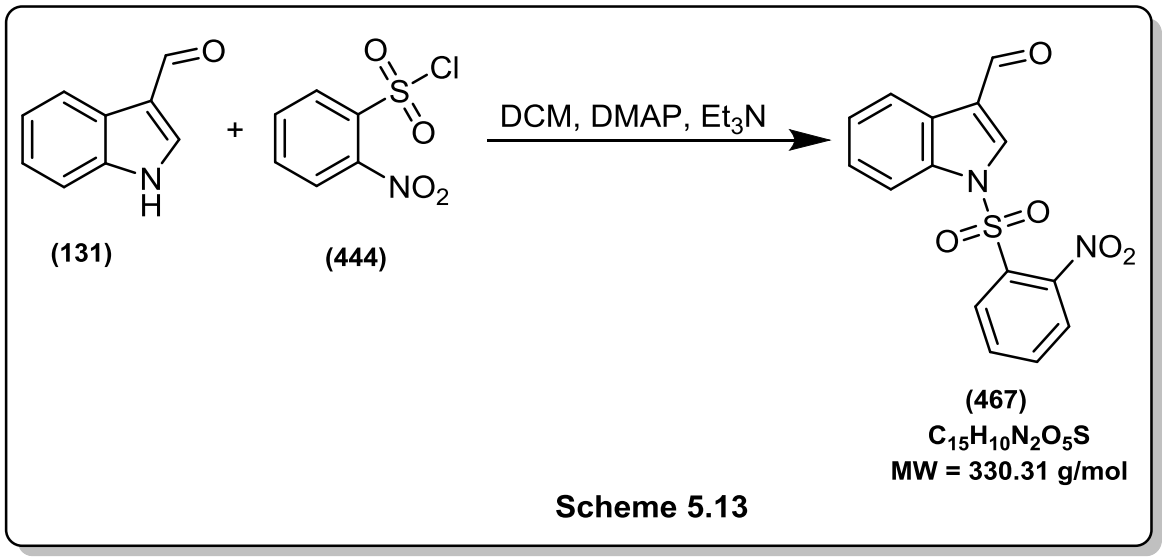


Scheme 5.12

This was prepared from 1,3-dichloroacetone and triphenylphosphine as per Scheme 5.12. The mixture was refluxed for 24 hours, filtered and treated with Na_2CO_3/MeOH-H_2O. The identify of compound **(130)** was deduced from its melting point=179-182 ^oC (Lit. m.p.= 178-180 ^oC)[234], and it was formed in 60 % yield.

5.3.3. Synthesis of the Precursor for Fuligocandin B.

Before attempted to make fuligocandin analogues, the indole needed for fuligocandin needed to be protected. In the literature Bergman[143] used 2-nitrophenylsulfonyl chloride when the actual fuligocandins were made.

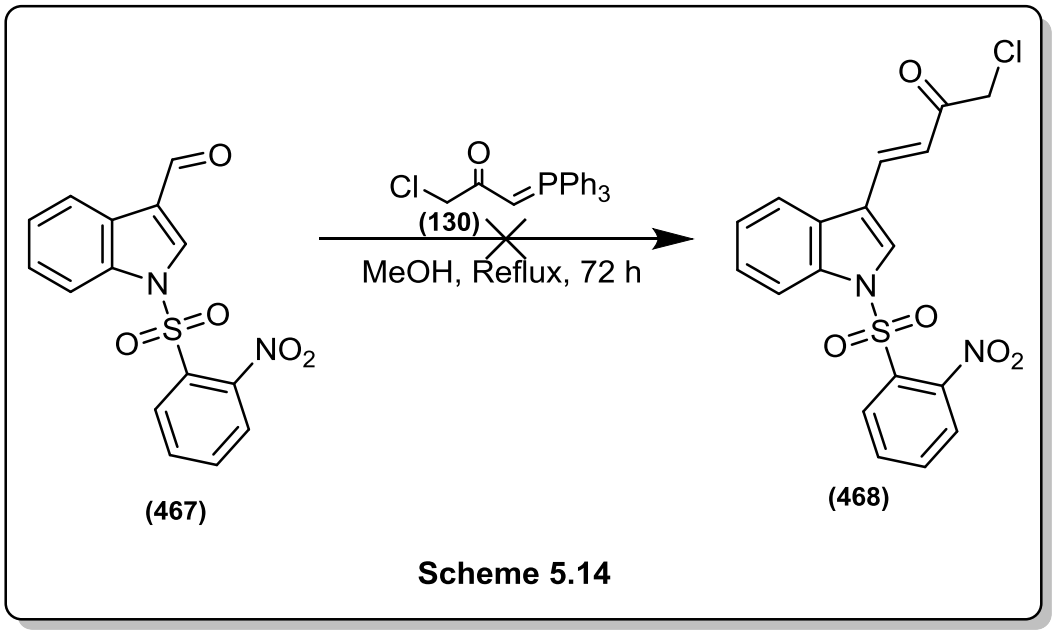


Scheme 5.13

Indole-3-carbaldehyde was successfully reacted with 2-nitrophenylsulfonyl chloride.

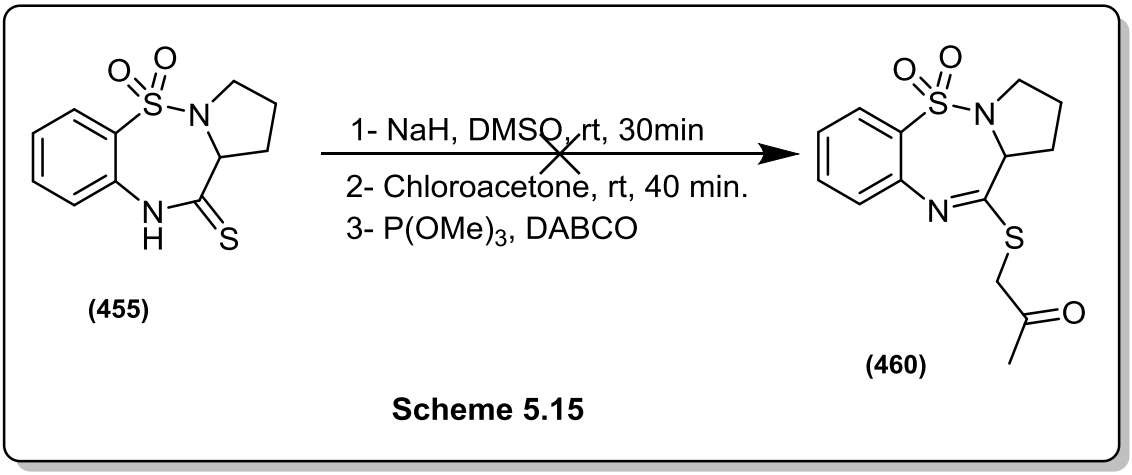
The structure of compound **(467)** was deduced from its IR spectrum, ^1H NMR spectroscopy, ^{13}C NMR spectroscopy and mass spectrometry, and was identical to that synthesised in the previously literature.[143] The 4-nitro analogue was successfully synthesised in the same fashion, again as described previously[161,143]. We also made the previously unreported 2-azidophenylsulfonyl analogue of **(467)**.

All attempts to react the 2-nitro compound[143] or its 4-nitro analogue with phosphorus ylide **(130)** were unsuccessful. This is a well-established literature process and its failure is still being explored in the group. It should be noted that João[161] succeeded with this step but failed to react compound **(468)** with compound **(455)**.



Scheme 5.14

Due to being unable to make the indole needed for the fuligocandin B indole[143] based system we completed this section of the work by attempting the synthesis of the more simple fuligocandin A SO_2 analogue. Reaction of the compound **(455)** with chloroacetone under the Eschenmoser conditions described by Bergman[143] with the corresponding amide was unsuccessful. This confirmed the earlier findings of João, and also implied, in conclusion to this section, that this route to sulfonamide analogues of the fuligocandins was not viable.



Scheme 5.15

The routes explored towards the synthesis of sulfonamide analogues of the circumdatins and fuligocandins were both unsuccessful and this concludes the discussion of this thesis.

Experimental

General Techniques:

For all reactions conducted under anhydrous conditions, the glassware was oven dried and the reaction was carried out under a nitrogen atmosphere, unless otherwise stated.

Solvents and Reagents:

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator.
Reagents and solvents used were obtained from commercial suppliers or purified according to standard procedures. Pet ether refers to distilled light petroleum of fraction (40–60 °C).
THF was distilled over sodium wires (1-2%, w/v) with benzophenone as the indicator.
Dichloromethane and toluene were distilled over calcium hydride (5% w/v) for ~5 h. All other anhydrous solvents and commercially available starting materials were purchased from the following suppliers. Acros, Fisher Scientific and Sigma Aldrich. Deuterated solvents were purchased from Goss Scientific.
All reactions monitored and analysed by thin layer chromatography (TLC) were done so using Macherey-Nagel 0.2 mm pre-coated Alugram® N/UV254 silica gel or alumina gel plates.
Column chromatography was conducted using 60 Å, 70-230 mesh, 63-200 μm silica gel supplied by Sigma-Aldrich. Where necessary, 60 Å, 50-200 μm, basic alumina gel was used and was supplied by Acros.

NMR Spectroscopy:

^{1}H NMR, ^{13}CNMR, DEPT, COSY and HSQC NMR spectra were recorded on Bruker DPX, Bruker AVIII 400 MHz NMR and Bruker AV500 NMR spectrometers. Chemical shifts (δ_H) are quoted in parts per million relative to the residual protiosolvent (δ_H ($CHCl_3$) = 7.24 ppm) against an internal deuterium lock. Coupling constants (*J*) are given in Hertz.
The ^{1}H NMR spectra are reported as follows: δ / ppm (number of protons, multiplicity, coupling constants *J* /Hz, assignment). DEPT and two-dimensional NMR spectroscopy (COSY, HSQC) were used where appropriate to assist the assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra.

Mass Spectrometry:

High resolution mass spectra (accurate mass) were recorded on a 6210-Time-of-Flight LC/LM.

Melting Points:

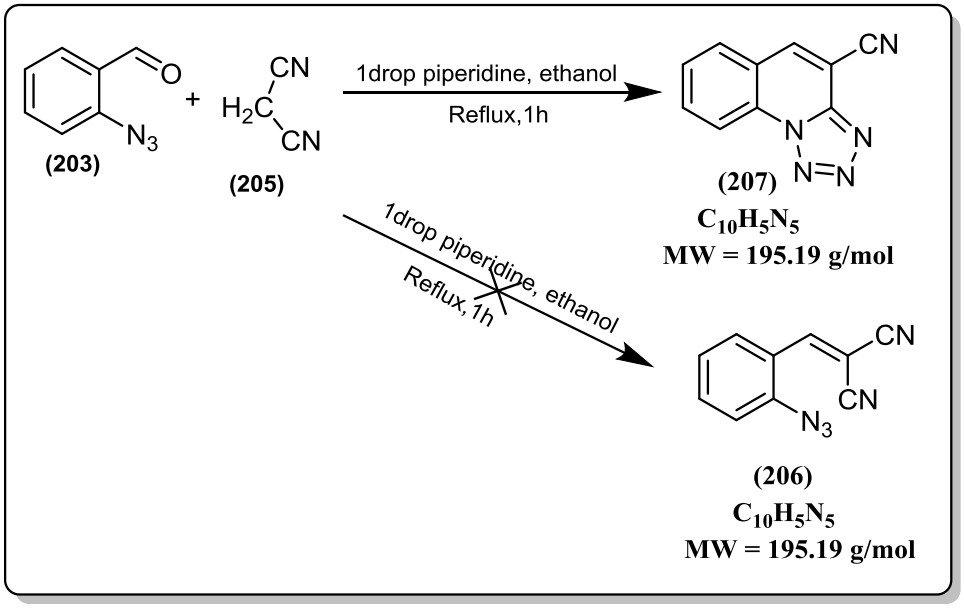
Melting point determinations were recorded on a Stuart SMP 10 digital melting point apparatus.

Infra-Red Spectroscopy:

Infrared spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils and neat for solids.

6. Chapter 6: Experimental for chapter 2: multicomponent reactions (MCRs).

6.1. Synthesis of Tetrazolo[1,5-*a*] quinoline-4-carbonitrile.



o-Azidobenzaldehyde[168] (2.00 g, 13.6 mmol), piperidine (1 drop), malononitrile (1.08 g, 16.31 mmol, 1.2 eq) and ethanol (20 mL) were heated at reflux for 1 hour. The solution was then cooled to room temperature. The solvent was evaporated to yield the product as a brown solid (1.1 g, yield = 68 %, m.p = 274-276 ^{o}C, lit. m.p = 276-278 ^{o}C[173]).

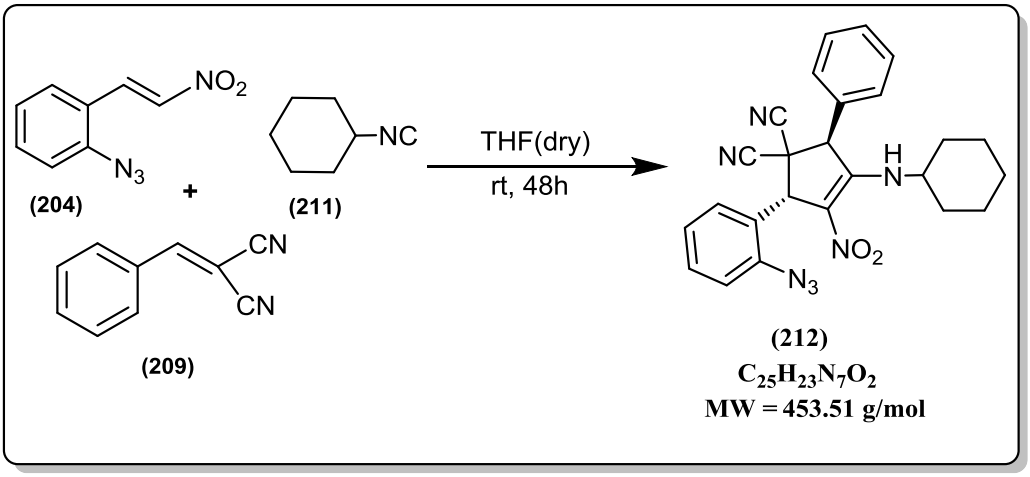
IR: υ_{max} (cm^{-1}): 3061.2, 2980.0, 2236.5, 1614.8, 1600.6, 1579.9, 1533.1, 1235.3, 1221.2, 1153.1, 1041.5, 936.2, 776.6.

^{1}H NMR: δ_H (400 MHz, DMSO): 9.02-9.07 (1H, m, **H**-C=C), 8.80 (1H, d, *J*=7.8 Hz, **H**-Ar), 8.10-8.13 (2H, m, 2 x **H**-Ar), 7.88 (1H, dd, J^1=7.8 Hz, J^2= 1.5 Hz **H**-Ar).

^{13}C NMR δ_c (100 MHz, DMSO): 145.73 (qC), 143.37 (CH), 134.82 (CH), 131.41 (CH), 130.83 (CH), 128.93 (qC), 122.66 (qC), 116.53 (CH), 114.04 (CN), 97.18 (qC).

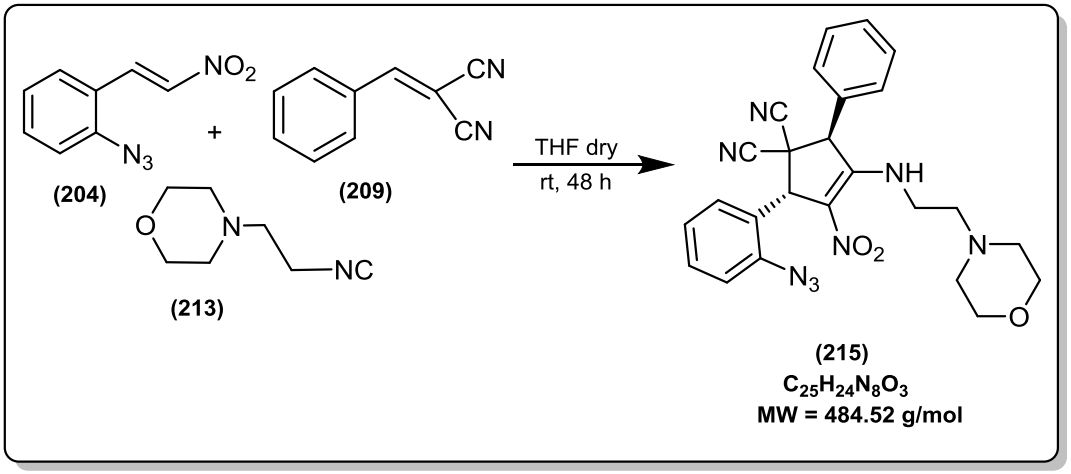
HRMS (m/z): [M + H^+] for $C_{10}H_6N_5$ calculated = 196.0618, measured = 196.0627.

6.2. Attempted synthesis of 2-(2-azidophenyl)-4-(cyclohexylamino)-3-nitro-5-phenylcyclopent-3-ene-1,1-dicarbonitrile.



A mixture of benzylidene malononitrile (77 mg, 0.5 mmol), cyclohexane isocyanide (54.5 mg, 0.5 mmol), and 2-azido nitrostyrene (95 mg, 0.5 mmol) was stirred in dry THF (15 mL) for 24h at ambient temperature. TLC showed no reaction.

6.3. Synthesis of 3-(2-Morpholinoethylamino)-5-(2-azidophenyl)-4-nitro-2-phenylcyclopent-3-ene-1,1-dicarbonitrile.



A mixture of benzylidenemalononitrile[176] (77 mg, 0.5 mmol, 1.0 eq), 2-morpholinoethyl isocyanide (70 mg, 0.5 mmol, 1.0 eq), and 2-azido-β-nitrostyrene[235,162] (95 mg, 0.5 mmol, 1.0 eq) was stirred in dry THF (15 mL) for 48h at ambient temperature. After completion of the reaction, which was monitored by TLC, the solvent was evaporated and the residue was dissolved in diethyl ether (15 mL). After 10 min., the product precipitated directly from the

solution and was filtered and washed with diethyl ether (2 × 15 mL). Purification by silica gel chromatography (petroleum ether/ ethyl acetate:1/2*)* yielded the pure product as a light yellow powder (170 mg, 89 %, m.p.= 187 - 188 ^{o}C).

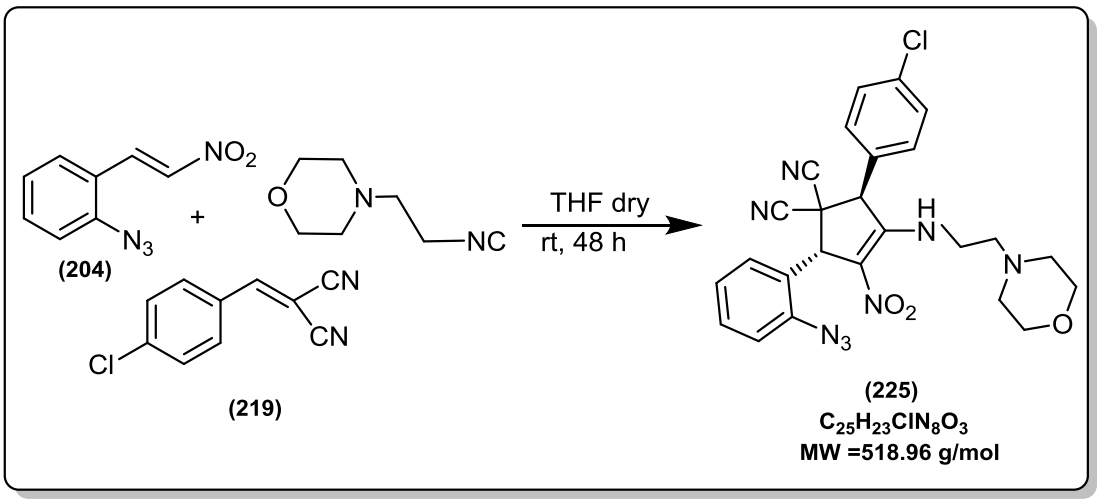
IR: υ_{max} (cm^{-1}): 3196.4 (NH), 3050.0 (C=CH unsat), 2920.5 (CH o.o.p.), 2877.6 (CH sat.) 2190.0 (CN), 2128.5 (N_3), 1638.9 (NO_2), 1600.9 (C=C), 1555.0 (C=Cring), 1231.0 (C-C), 1142.3 (C-N), 737.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 9.80 (1H, s, **H**N), 7.56 (2H, t, *J*=3.2 Hz, Ar**H**), 7.24-7.51 (5H, m, Ar**H**), 7.19 (1H, dd, *J*=7.3 Hz, Ar**H**), 7.12 (1H, dd, *J*=7.3 Hz, Ar**H**), 5.51 (1H, s, C**H**-Ar), 4.76 (1H, s, C**H**-Ar), 3.77 (4H, t, *J*=4.5 Hz, C**H$_2$**-O-C**H$_2$**-), 2.88 (2H, t, *J*=7.6 Hz, C**H$_2$**-CH_2), 2.51 (4H, t, *J*=4.5 Hz, C**H$_2$**-N-C**H$_2$**-), 1.35 (2H, t, *J*=7.6 Hz, CH_2-C**H$_2$**).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 157.79 (qC), 138.79 (qC), 133.35 (qC), 131.18 (CH), 130.50 (CH), 130.18 (2 x CH), 129.36 (2 x CH), 128.20 (CH), 126.59 (qC), 125.74 (CH), 125.52 (CH), 114.47 (qC), 113.99 (CN), 113.02 (CN), 66.61 (2 x CH_2), 56.40 (CH_2), 54.62 (CH), 53.30 (CH), 53.25 (2 x CH_2), 44.63 (qC), 42.12 (CH_2).

MS (m/z): [M + H^{+}] for $C_{25}H_{25}N_8O_3$ calculated = 485.2044, measured = 485.2055.

6.4. Synthesis of 3-(2-Morpholinoethylamino)-5-(2-azidophenyl)-2-(4-chlorophenyl)-4-nitrophenylcyclopent-3-ene-1,1-dicarbonitrile.



A mixture of 4-chloro benzylidenemalononitrile[176] (94.25 mg, 0.5 mmol, 1.0 eq), 2-morpholinoethyl isocyanide (70 mg, 0.5 mmol, 1.0 eq) and 2-azidonitrostyrene (95 mg, 0.5 mmol, 1.0 eq) was stirred in dry THF (15 mL) for 48h at ambient temperature. After completion of the reaction which was monitored by TLC, the solvent was evaporated and the residue was dissolved in diethyl ether (15 mL). After 10 min., the product precipitated directly from the solution and was filtered and washed with diethyl ether (2 × 15 mL). Purification by silica gel chromatography (petroleum ether/ethyl acetate: 1/2, Rf=0.3) yielded the pure product as a pale orange solid (160 mg, 0.218 mmol, 78 %, m.p.=148-150 ^{o}C).

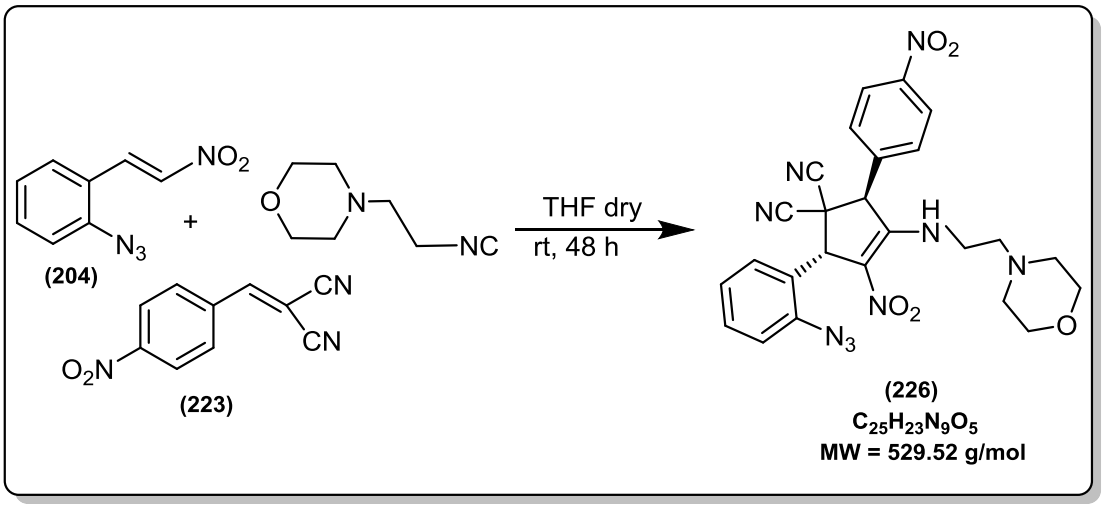
IR: υ_{max} (cm^{-1}): 3232.3 (NH), 3050.0 (C=CHunsat), 2923.2 (o.o.p.), 2819.5 (CH sat), 2195.2 (CN), 2125.4 (N_3), 1626.6 (NO_2), 1583.3 (C=C), 1550.0 (C=Cring), 1231.0 (C-C), 1182.2 (C-N), 752.7 (C-Cl), 730.0 (CH).

^{1}H NMR: δ_H (400 MHz, DMSO): 9.85 (1H, s, **H**N), 7.63 (2H, d, *J*=8.5 Hz, 2 x Ar**H**), 7.47-7.58 (3H, m, 3 x Ar**H**), 7.41 (1H, dd, *J*=7.3 Hz, Ar**H**), 7.27 (1H, dd, *J*=7.3 Hz, Ar**H**), 7.16 (1H, d, *J*=7.3 Hz, Ar**H**), 5.35 (1H, s, C**H**-Ar), 5.25 (1H, s, C**H**-Ar), 3.57 (4H, t, *J*=3.0 Hz, CH_2-O-CH_2-), 3.16 (2H, t, *J*=6.2 Hz, CH_2-CH_2), 3.01 (2H, t, *J*=6.2 Hz, N-CH_2), 1.30-2.44 (4H, t, *J*=3.0 Hz, CH_2-N-CH_2-).

^{13}C NMR δ_c (100 MHz, DMSO): 157.26 (qC), 139.03 (qC), 135.31 (qC), 132.26 (qC), 131.61 (2 x CH), 130.92 (CH), 130.25 (CH), 129.72 (2 x CH), 125.72 (qC), 119.83 (CH), 119.52 (CH), 114.48 (qC), 113.38 (CN), 112.23 (CN), 66.68 (2 x CH_2), 56.40 (CH_2), 54.79 (CH), 53.89 (CH), 53.29 (2 x CH_2), 44.44 (qC), 42.44 (CH_2).

HRMS (m/z): [M+H^{+}] for $C_{25}H_{23}N_8O_3Cl$ calculated = 519.1654, measured = 519.1657.

6.5. Synthesis of 3-(2-Morpholinoethylamino)-5-(2-azidophenyl)-4-nitro-2-(nitrophenyl)cyclopent-3-ene-1,1-dicarbonitrile.



A mixture of of 4-nitrobenzylidenemalononitrile[177] (99.5 mg, 0.5 mmol, 1.0 eq), 2-morpholinoethyl isocyanide (70 mg, 0.5 mmol, 1.0 eq) and 2-azidonitrostyrene (95 mg, 0.5 mmol, 1.0 eq) was stirred in dry THF (15 mL) for 48h at ambient temperature. After completion of the reaction which was monitored by TLC, the solvent was evaporated and the residue was dissolved in diethyl ether (15 mL). After 10 min., the product precipitated directly from the solution and was filtered and washed with diethyl ether (2 × 15 mL). Purification by silica gel chromatography *(*petroleum ether/ethylacetate: 1/2, R_f = 0.3) yielded the pure product as a brown solid (140 mg, 67 %, m.p.=115-117 ^oC).

IR: υ_{max} (cm^{-1}): 3239.8 (NH), 3081.6 (C=CHstr.), 2950.0 (CH (Sat)), 2250.6 (CN), 2125.6 (N_3), 1628.3 (NO_2), 1600.0 (C=C), 1523.6.0 (C=Cring), 1231 (C-C), 1113.7 (C-N), 729.3 (C-H).

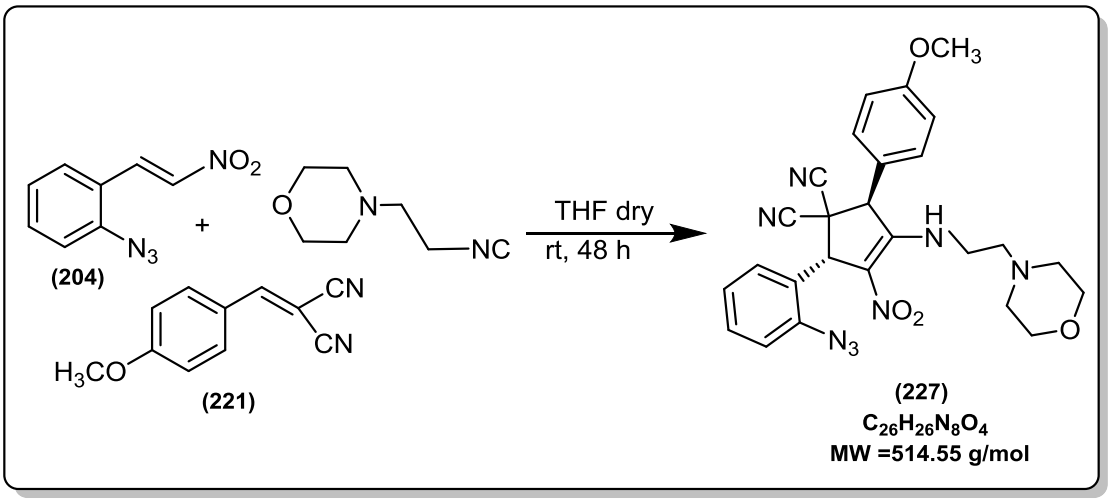
^{1}H NMR: δ_H (400 MHz, DMSO): 9.72 (1H, s, **H**N), 8.11 (1H, d, *J*=8.5 Hz, Ar**H**), 7.73 (2H, d, *J*=8.5 Hz, 2 x Ar**H**), 7.25-7.42 (3H, m, 3 x Ar**H**), 7.14 (1H, dd, *J*=7.3 Hz, Ar**H**), 7.03 (1H, dd, *J*=7.3 Hz, Ar**H**), 5.62 (1H, s, C**H**-ArNO_2), 5.15 (1H, s, C**H**-ArN_3), 3.43 (4H, t, *J*=3.0 Hz, CH_2-O-CH_2-), 3.03 (2H, t, *J*=6.0 Hz, CH_2-CH_2), 2.81 (2H, t, *J*=6.0 Hz, CH_2-CH_2), 2.36 (4H, t, *J*=3.0 Hz, CH_2-N-CH_2-).

^{13}C NMR δ_c (100 MHz, DMSO): 170.81 (qC), 156.58 (qC), 148.87 (qC), 148.49 (qC), 131.64 (2CH), 131.01 (CH), 128.28 (CH), 126.30 (CH), 125.76 (CH), 125.19 (2 x CH),

124.62 (qC), 119.88 (qC), 113.89 (CN), 113.59 (CN), 66.67 (2 x CH_2), 56.28 (CH_2), 54.57 (CH), 53.83 (CH), 53.24 (2 x CH_2)), 44.11 (qC), 42.62 (CH_2).

HRMS (m/z): [M + H^+] for $C_{25}H_{23}N_9O_5$ calculated = 530.1895, measured = 530.1909.

6.6. Synthesis of 3-(2-Morpholinoethylamino)-5-(2-azidophenyl)-2-(4-ethoxy phenyl)-4-nitrocyclopent-3-ene-1,1-dicarbonitrile.



A mixture of of 4-methoxybenzylidenemalononitrile[176] (92 mg, 0.5 mmol, 1.0 eq), 2-morpholinoethyl isocyanide (70 mg, 0.5 mmol, 1.0 eq) and 2-azidonitrostyrene (95 mg, 0.5 mmol, 1.0 eq) was stirred in dry THF (15 mL) for 48h at ambient temperature. After completion of the reaction which was monitored by TLC, the solvent was evaporated and the residue was dissolved in diethyl ether (15 mL). After 10 min., the product precipitated directly from the solution and was filtered and washed with diethyl ether (2 × 15 mL). Purification by silica gel chromatography (petroleum ether/ethyl acetate: 1/2, Rf=0.23) yielded pure product as a light brown powder (50 mg, 20 %, m.p.=152 - 154 ^oC).

IR: υ_{max} (cm^{-1}): 3188.2 (NH), 3050.0 (C=CHstr), 2934.0 (CH (Sat)), 2251.5 (CN), 2123.0 (N_3), 1630.0 (NO_2), 1611.5 (C=C), 1582.7 (C=C) ring, 1253.2(C-C), 1114.1(C-N), 752.3 (C-H).

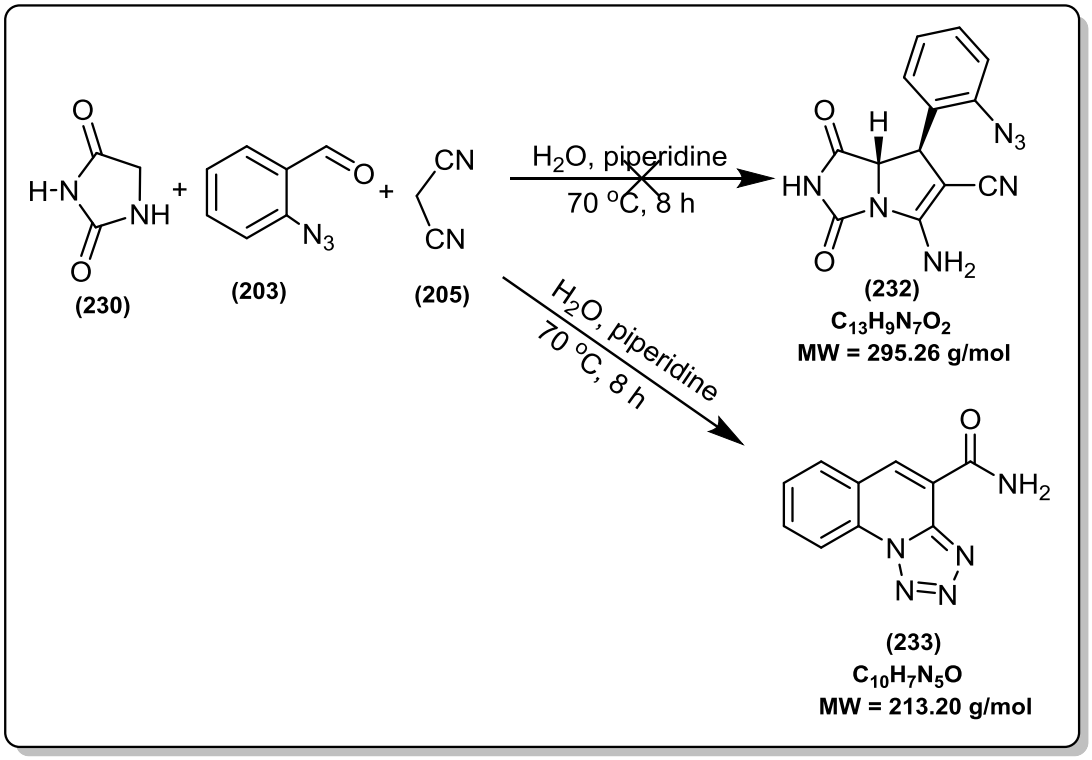
^{1}H NMR: δ_H (400 MHz, DMSO): 9.86 (1H, s, **H**N), 7.39-7.58 (3H, m, 3 x Ar**H**), 7.27 (1H, dd, *J*=7.0 Hz, Ar**H**), 7.16 (1H, t, *J*=7.0 Hz, Ar**H**), 7.09 (2H, d, *J*=8.65 Hz, 2 x Ar**H**), 6.94 (1H, d, *J*=8.5 Hz, Ar**H**), 5.76 (1H, s, C**H**), 5.31 (1H, s, C**H**), 3.56-3.57 (4H, m, CH_2-O-CH_2-),

3.19 (2H, t, *J*=6.8 Hz, CH_2-CH_2), 2.95-3.04 (2H, t, *J*=6.8 Hz, CH_2-CH_2), 2.30 (4H, t, *J*=3.3 Hz, CH_2-N-CH_2-).

^{13}C NMR δ_c (100 MHz, DMSO): 160.70 (qC), 158.13 (qC), 139.01 (qC), 138.79 (qC), 131.20 (2 x CH), 130.82 (CH), 128.18 (CH), 126.66 (CH), 125.74 (CH), 125.54 (2 x CH), 124.21 (qC), 119.81 (qC), 114.97 (CN), 114.08 (CN), 66.69 (2 x CH_2-), 56.49 (CH_2), 55.73 (CH), 55.62 (CH), 54.13 (CH_3), 53.30 (2 x CH_2), 44.90 (qC), 42.21 (CH_2).

HRMS (m/z): [M + H^+] for $C_{26}H_{26}N_8O_4$ calculated = 515.2149, measured = 515.2147.

6.7. Synthesis of tetrazolo[1,5-*a*]quinoline-4-carboxamide



A mixture of of hydantoin (300 mg, 3.0 mmol), 2-azidobenzaldehyde (441 mg, 3 mmol), malononitrile (198 mg, 3.0 mmol), piperidine (10 mmol %) and 25 mL of water were stirred for 8h at 70 ^oC. After completion of the reaction, which was monitored by TLC, the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 1/1, Rf=0.25) which yielded the pure product **(233)** as a light yellow soild (200 mg, 34 %, m.p.= 139 - 141 ^oC).

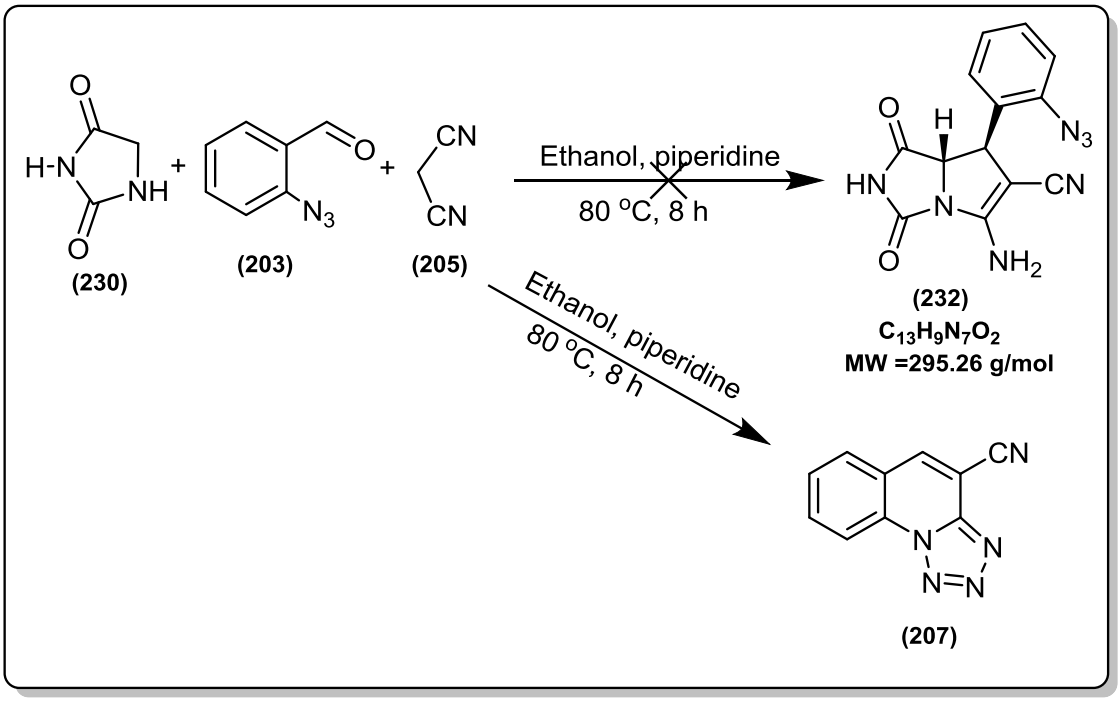
IR: υ_{max} (cm^{-1}): 3385.4, 3300.2, 3153.9, 3048.5, 2923.0, 2852.0, 1703.0, 1619.4, 1599.2, 1596.0, 1213.0, 1148.0, 763.7.

^{1}H NMR: δ_H (400 MHz, DMSO): 8.96 (1H, s, C**H**), 8.68 (1H, d, *J*=8.1 Hz, Ar**H**), 8.33-8.49 (3H, m, (N**H**$_2$ + Ar**H**)), 8.11 (1H, dd, J^1=7.3 Hz, J^2= 7.1 Hz, Ar**H**) 7.89 (1H, dd, J^1=7.2 Hz, J^2= 6.8 Hz, Ar**H**).

^{13}C NMR δ_c (100 MHz, DMSO): 162.44 (C=O), 146.26 (qC), 137.19 (CH), 133.74 (CH), 131.52 (CH), 131.30 (qC), 129.03 (CH), 123.64 (qC), 118.60 (qC), 116.71 (CH).

HRMS (m/z): [M + H^+] for $C_{10}H_7N_5O$ calculated = 236.0543, measured = 236.0552.

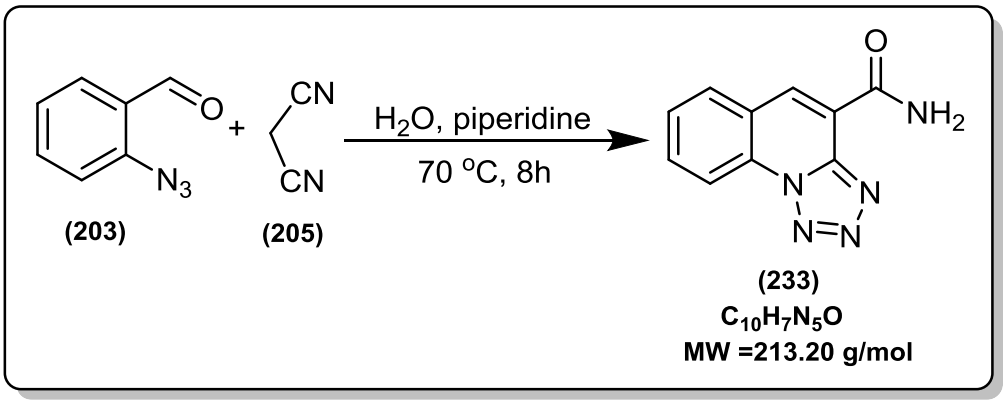
6.8. Synthesis tetrazolo[1,5-*a*]quinoline-4-carbonitrile.



A mixture of hydantoin (300 mg, 3.0 mmol), benzaldehyde (441 mg, 3.0 mmol), malononitrile (198 mg, 3.0 mmol), piperidine (10 mmol %) and 25 mL of ethanol was stirred for 8h at 80 °C. After completion of the reaction which was monitored by TLC, solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 1/1, Rf=0.3) which yielded the pure product **(207)** as a light orange solid (150 mg, 26 %, m.p.= 275 - 277 °C, lit. m.p.= 276 - 278 °C[173]).

Data as reported above.

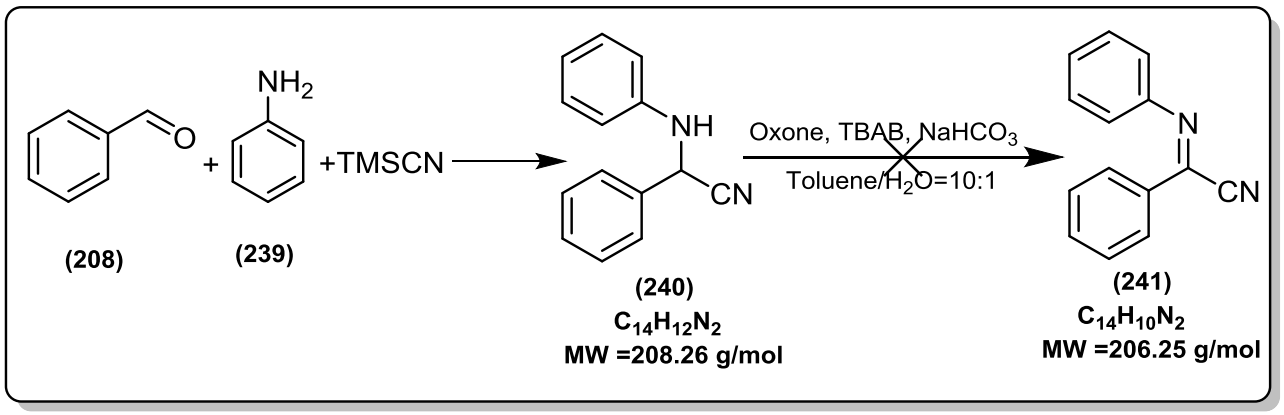
6.9. Synthesis of Tetrazolo[1,5-*a*]quinoline-4-carboxamide.



A mixture of benzaldehyde (441 mg, 3.0 mmol), malononitrile (198 mg, 3.0 mmol), piperidine (10 mmol %) and 25 mL of water were stirred for 8h at 70 ^{o}C. After completion of the reaction which was monitored by TLC, the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 1/1, Rf=0.3) which yielded the pure product as a light yellow solid (200 mg, 39 %, m.p.= 139 - 141 ^{o}C).

Data as reported above.

6.10. Synthesis of 2-Phenyl-2-(phenylamino)acetonitrile.



Aniline (93.13 mg, 1.0 mmol, 1.0 eq.) was added to a stirring solution of benzaldehyde (106.1 mg, 1.0 mmol, 1.0 eq.) in toluene (13 mL) at room temperature, and the mixture stirred until the disappearance of the starting materials. TMSCN (99 mg, 1.0 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min before the portionwise addition of H_2O (10 % by volume),

TBAB (322 mg, 1.0 mmol, 1.0 eq.), Oxone (307 mg, 1.0 mmole, 1.0 eq) and $NaHCO_3$ (126 mg, 1.5 mmol, 1.5 eq) at 0 ^oC. The biphasic mixture was then stirred vigorously at room temperature until the disappearance of the intermediate; the biphasic mixture was then partitioned between EtOAc (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 10/1, Rf=0.24) which yielded the pure product as a brown solid (150 mg, 72 %, m.p.= 73 - 75 ^oC, lit. m.p.= 73 - 74 ^oC)[180].

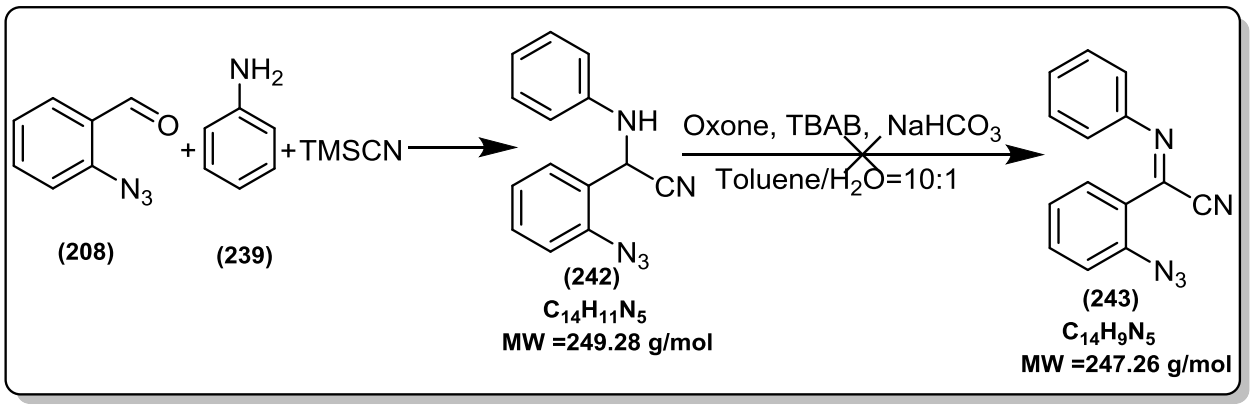
IR: υ_{max} (cm^{-1}): 3335.3, 3034.4, 2960.0, 2880.0, 2180.0, 1680.0, 1598.0, 1514.5, 1279.7, 1242.1, 748.6.

^{1}H NMR: δ_H (100 MHz, DMSO): 8.38 (1H, s, **H**N), 7.52 (2H, d, *J*=6.0 Hz, 2 x Ar**H**), 7.37-7.44 (2H, m, 2 x Ar**H**), 7.06-7.22 (3H, m, 3 x Ar**H**), 6.82 (1H, t, *J*=7.5 Hz, Ar**H**), 6.70 (2H, d, *J*=7.5 Hz, 2 x Ar**H**) 3.97 (1H, s, C**H**).

^{13}C NMR δ_c (100 MHz, DMSO): 144.69 (qC), 134.47 (qC), 129.61 (2 x CH), 129.37 (2 x CH), 127.29 (2 x CH), 120.30 (CH), 116.72 (CN), 115.12 (CH), 114.16 (2 x CH), 50.22 (CH).

HRMS (m/z): [M +H^+] for $C_{14}H_{12}N_2$ calculated = 209.1072, measured = 209.1080.

6.11. Synthesis of 2-(2-Azidophenyl)-2-(phenylamino)acetonitrile .



Aniline (93.13 mg, 1.0 mmol, 1.0 eq.) was added to a stirring solution of 2-azidobenzaldehyde (147.12 mg, 1.0 mmol, 1.0 eq.) in toluene (13 mL) at room temperature,

and the mixture stirred until the disappearance of the starting materials. TMSCN (99 mg, 1.0 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min before the portionwise addition of H_2O (10 % by volume), TBAB (322 mg, 1.0 mmol, 1.0 eq.), Oxone (307 mg, 1.0 mmole, 1.0 eq) and $NaHCO_3$ (126 mg,1.5 mmol, 1.5 eq) at 0 ^oC. The biphasic mixture was then stirred vigorously at room temperature until the disappearance of the intermediate; the biphasic mixture was then partitioned between EtOAc (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 95/5, Rf=0.2) which yielded the pure product as a dark orange solid (140 mg, 56 %, m.p.= 97 - 98 ^oC).

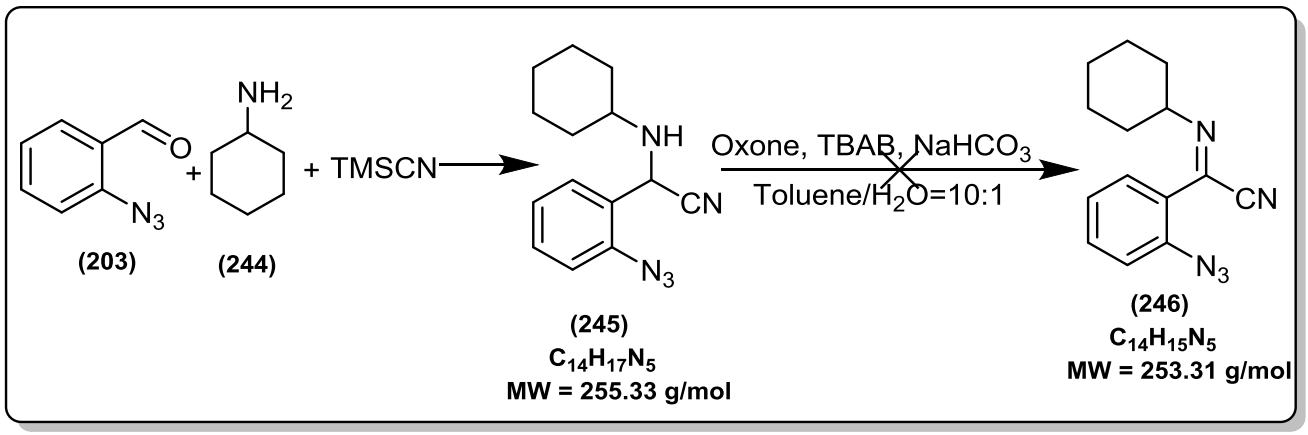
IR: υ_{max} (cm^{-1}): 3350.6, 3026.3, 2970.0, 2880.0, 2190.4, 2121.9, 1599.5, 1587.4, 1240.0, 1159.8, 748.2.

^{1}H NMR: δ_H (400 MHz, DMSO): 8.70 (1H, s, **H**N), 7.52 (1H, d, *J*=7.5 Hz, Ar**H**), 7.39 (1H, dd, *J*=7.5 Hz, Ar**H**), 7.12-7.20 (4H, m, 4 x Ar**H**), 6.81 (2H, t, *J*=7.3 Hz, 2 x Ar**H**), 6.70 (1H, d, *J*=7.5 Hz, Ar**H**), 4.06 (1H, s, C**H**).

^{13}C NMR δ_c (100 MHz, DMSO): 144.62 (qC), 138.16 (qC), 131.10 (CH), 129.59 (2 x CH), 129.18 (CH), 128.09 (qC), 125.52 (CH), 120.40 (CH), 118.88 (CH), 118.08 (CN), 114.39 (2 x CH), 45.99 (CH).

HRMS (m/z): [M +H^+] for $C_{14}H_{11}N_5$ calculated = 250.1087, measured = 250.1092.

6.12. Synthesis of 2-(2-Azidophenyl)-2-(cyclohexylamino)acetonitrile.



Cyclohexylamine (93.13 mg, 1.0 mmol, 1.0 eq.) was added to a stirring solution of 2-azidobenzaldehyde (147.12 mg, 1.0 mmol, 1.0 eq.) in toluene (13 mL) at room temperature, and the mixture stirred until the disappearance of the starting materials. TMSCN (99 mg, 1.0 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min before the portionwise addition of H_2O (10 % by volume), TBAB (322 mg, 1.0 mmol, 1.0 eq.), Oxone (307 mg, 1.0 mmole, 1.0 eq) and $NaHCO_3$ (126 mg, 1.5 mmol, 1.5 eq) at 0 ^oC. The biphasic mixture was then stirred vigorously at room temperature until the disappearance of the intermediate; the biphasic mixture was partitioned between EtOAc (20 mL) and sat. aq.$NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 10/1, Rf=0.24) which yielded the pure product as a yellow solid (170 mg, 67 %, m.p.= 69 - 71 ^oC).

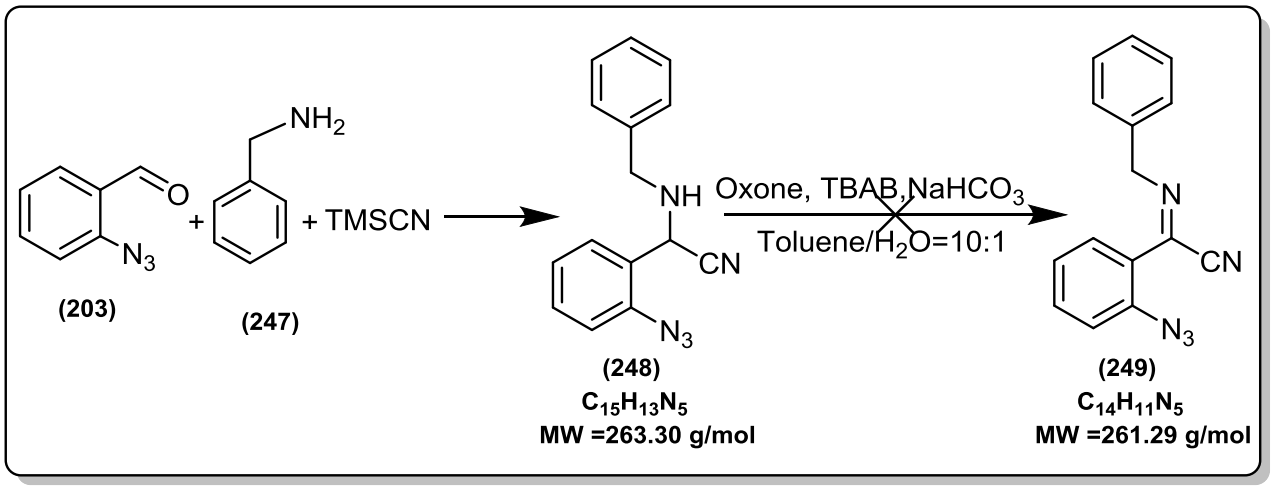
IR: υ_{max} (cm^{-1}): 3306.2, 3062.4, 2923.6, 2854.1, 2187.0, 2130.3, 1600.0, 1570.4, 1286.9, 1114.5, 739.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 8.53 (1H, s, **H**N), 7.43 (1H, d, *J*=7.7 Hz, Ar**H**), 7.35 (2H, dd, *J*=7.7 Hz, 2 x Ar**H**), 7.06-7.22 (2H, m, 2 x Ar**H**), 4.89 (1H, s, C**H**), 1.38-1.01 (11H, m, cyclohexane).

^{13}C NMR δ_c (100 MHz, DMSO): 137.81 (qC), 130.50 (CH), 128.00 (qC), 125.39 (CH), 124.93 (CH), 118.77 (CH), 118.32 (CN), 55.11 (CH), 47.09 (CH), 33.75 (CH_2), 31.97 (CH_2), 25.89 (CH_2), 24.79 (CH_2), 24.39 (CH_2).

HRMS (m/z): [M + H^+] for $C_{14}H_{17}N_5$ calculated = 256.1557, measured = 256.1555.

6.13. Synthesis of 2-(2-Azidophenyl)-2-(benzylamino)acetonitrile.



Benzylamine (107.13 mg, 1.0 mmol, 1.0 eq.) was added to a stirring solution of 2-azidobenzaldehyde (147.12 mg, 1.0 mmol, 1.0 eq.) in toluene (13 mL) at room temperature, and the mixture stirred until the disappearance of the stating materials. TMSCN (99 mg, 1.0 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min before the portionwise addition of H_2O (10 % by volume), TBAB (322 mg, 1.0 mmol, 1.0 eq.), Oxone (307 mg, 1.0 mmole, 1.0 eq) and $NaHCO_3$ (126 mg, 1.5 mmol, 1.5 eq) at 0 ^oC. The biphasic mixture was then stirred vigorously at room temperature until the disappearance of the intermediate; the biphasic mixture was partitioned between EtOAc (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 95/5, Rf=0.28) which yielded the pure product as a brown oil (150 mg, 57 %).

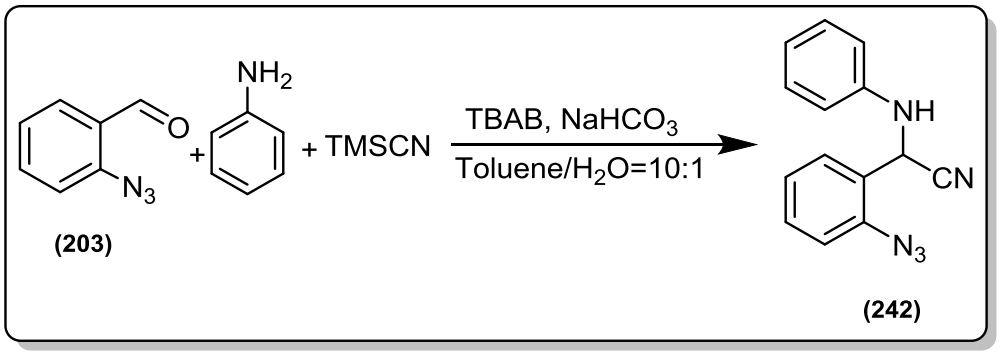
IR: υ_{max} (cm^{-1}): 3327.4, 3029.7, 2979.8, 2840.0, 2199.1, 2126.5, 1680.0, 1600.0, 1560.4, 1287.2, 1140.0, 750.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 8.62 (1H, s, **H**N), 7.10-7.40 (9H, m, 9 x Ar**H**), 4.73 (1H, s, CH), 1.12 (2H, s, C**H$_2$**).

^{13}C NMR δ_c (100 MHz, DMSO): 138.00 (qC), 137.89 (qC), 130.63 (CH), 129.27 (CH), 128.62 (CH), 128.52 (2 x CH), 128.04 (qC), 127.71 (CH), 125.30 (CH), 118.79 (2 x CH), 118.40 (CN), 51.98 (CH_2), 49.43 (CH).

HRMS (m/z): [M+H$^+$] for $C_{15}H_{13}N_5$ calculated = 264.1244, measured = 264.1255.

6.14. Synthesis of 2-(2-Azidophenyl)-2-(phenylamino)acetonitrile.



Aniline (93.13 mg, 1.0 mmol, 1.0 eq.) was added to a stirring solution of 2-azidobenzaldehyde (147.12 mg, 1.0 mmol, 1.0 eq.) in toluene (13 mL) at room temperature, and the mixture stirred until the disappearance of the starting materials. TMSCN (99 mg, 1.0 mmol, 1.0 eq.) was added. The mixture was stirred for 5 min before the portionwise addition of H_2O (10 % by volume), TBAB (322 mg, 1.0 mmol, 1.0 eq.) and $NaHCO_3$ (126 mg, 1.5 mmol, 1.5 eq) at 0 ^oC. The biphasic mixture was then stirred vigorously at room temperature until the disappearance of the intermediate; the biphasic mixture was partitioned between EtOAc (20 mL) and sat. aq. $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 95/5, Rf=0.2) which yielded the pure product as a dark orange solid (150 mg, 60 %, m.p.= 97 - 98 ^oC).

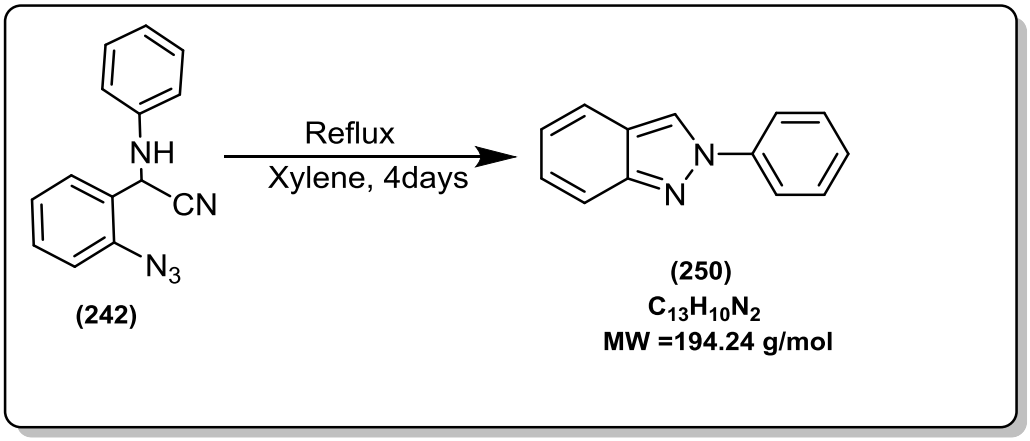
IR: υ_{max} (cm^{-1}): 3350.6, 3026.3, 2970.0, 2880.0, 2190.4, 2121.9, 1599.5, 1587.4, 1240.0, 1159.8, 748.2.

^{1}H NMR: δ_H (400 MHz, DMSO): 8.70 (1H, s, **H**N), 7.52 (1H, d, *J*=7.5 Hz, Ar**H**), 7.39 (1H, dd, *J*=7.5 Hz, Ar**H**), 7.12-7.20 (4H, m, 4 x Ar**H**), 6.81 (2H, t, *J*=7.3 Hz, 2 x Ar**H**), 6.70 (1H, d, *J*=7.5 Hz, Ar**H**), 4.06 (1H, s, C**H**).

^{13}C NMR δ_c (100 MHz, DMSO): 144.62 (qC), 138.16 (qC), 131.10 (CH), 129.59 (2 x CH), 129.18 (CH), 128.09 (qC), 125.52 (CH), 120.40 (CH), 118.88 (CH), 118.08 (CN), 114.39 (2 x CH), 45.99 (CH).

HRMS (m/z): [M +H^+] for $C_{14}H_{11}N_5$ calculated = 250.1087, measured = 250.1092.

6.15. Synthesis of 2-phenyl-2*H*-indazole.



[2-(2-Azidophenyl)-2-(phenylamino)acetonitrile] (50 mg) was heated to reflux temperature in dry xylene (10 mL) under a nitrogen atmosphere for 120 hours. The solvent was removed *in vacuo* and the crude product was purified by silica chromatography (petroleum ether/ethyl acetate: 8/1, Rf = 0.28) to yield the pure product as a white solid (40 mg, 50 %, m.p.= 77 - 79 ^oC, lit. m.p.=84-85 ^oC[181]).

IR: υ_{max} (cm^{-1}): 3057.2, 2979.9, 2890.0, 1630.0, 1610.8, 1519.3, 1199.0, 1150.0, 749.0.

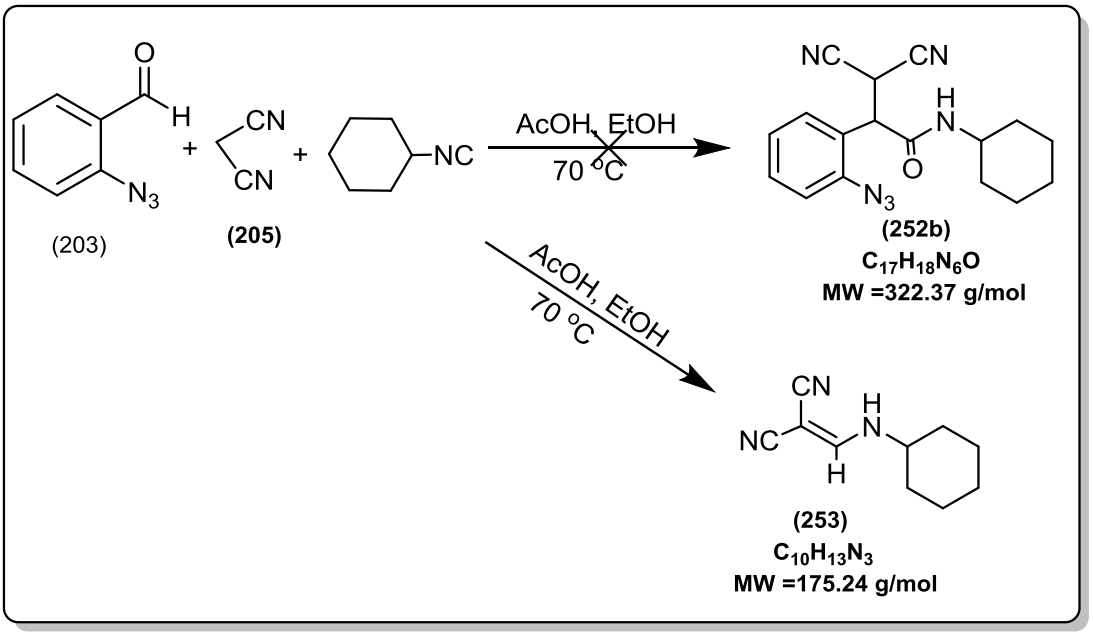
^{1}H NMR: δ_H (400 MHz, DMSO): 8.37 (1H, s, **H**C=N), 7.19-7.85 (9H, m, 9 x Ar**H**).

^{13}C NMR δ_c (100 MHz, DMSO): 129.93 (qC), 129.75 (2CH), 129.21 (qC), 127.91 (CH), 126.83 (CH), 123.87 (CH), 121.02 (2 x CH), 120.43 (CH), 120.37 (CH), 119.24 (qC), 117.94 (CH).

HRMS (m/z): [M + H^+] for $C_{13}H_{10}N_2$ calculated = 195.0917, measured = 195.0922.

The data is identical to the literature.[181]

6.16. Synthesis of 2-[(Cyclohexylamino)methylene]malononitrile.



A solution of 2-azidobenzaldehyde (147 mg, 1.0 mmol, 1.0 eq), acetic acid (60 mg, 1.0 mmol, 1.0 eq) and malononitrile (66 mg, 1.0 mmol, 1.0 eq) in ethanol (10 mL) was stirred at 70 ^{o}C. Cyclohexyl isocyanide (109 mg, 1.0 mmol, 1.0 eq) was added after 30 minutes and the mixture stirred for 12 hours at 70 ^{o}C. After completion of the reaction[182] which was monitored by TLC, the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 1/5, Rf=0.23) to yield the pure product as a light yellow solid (100 mg, 57 %, m.p.= 133 - 135 ^{o}C).

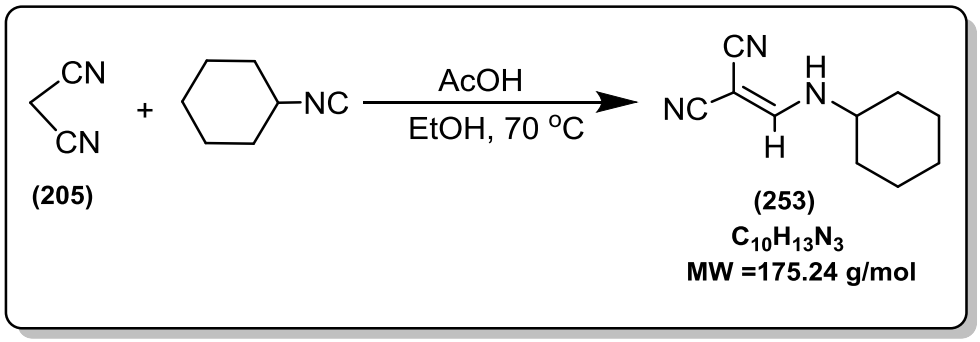
IR: υ_{max} (cm^{-1}): 3228.4 (NH), 3035.7 (CHunsat.), 2935.2 (CHsat.), 2854.6, 2204.4 (CN), 1644.0 (C=C), 1530.0, 1293.3 (C-C), 1183.8 (C-N), 755.4 (C-H).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.41 (1H, s, C=C-**H**), 6.99-7.06 (1H, m, **H**N), 3.17-3.25 (1H, m, CH-NH of cyclohexyl), 1.13- 1.95 (10H, m, 5 x C**H$_2$**).

^{13}C NMR δ_c (100 MHz, DMSO): 158.88 (CH), 115.96 (CN), 114.17 (CN), 59.96 (CH), 49.61 (qC), 33.39 (2CH_2), 24.72 (CH_2), 24.64 (2 x CH_2).

HRMS (m/z): [M + Na^{+}] for $C_{10}H_{13}N_3$ calculated = 198.1002, measured = 198.1008.

6.17. Synthesis of 2-[(Cyclohexylamino)methylene]malononitrile.



A solution of malononitrile (66 mg, 1.0 mmol, 1.0 eq) and acetic acid (60 mg, 1.0 mmol, 1.0 eq) in ethanol (10 mL) was stirred at 70 ^{o}C. Cyclohexyl isocyanide (109 mg, 1.0 mmol, 1.0 eq) was added after 30 minutes and the mixture stirred for 12 hours at 70 ^{o}C. After completion of the reaction which was monitored by TLC, the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate: 1/5, Rf=0.2) to yield the pure product as a light yellow solid (110 mg, 63 %, m.p.= 133 - 135 ^{o}C).

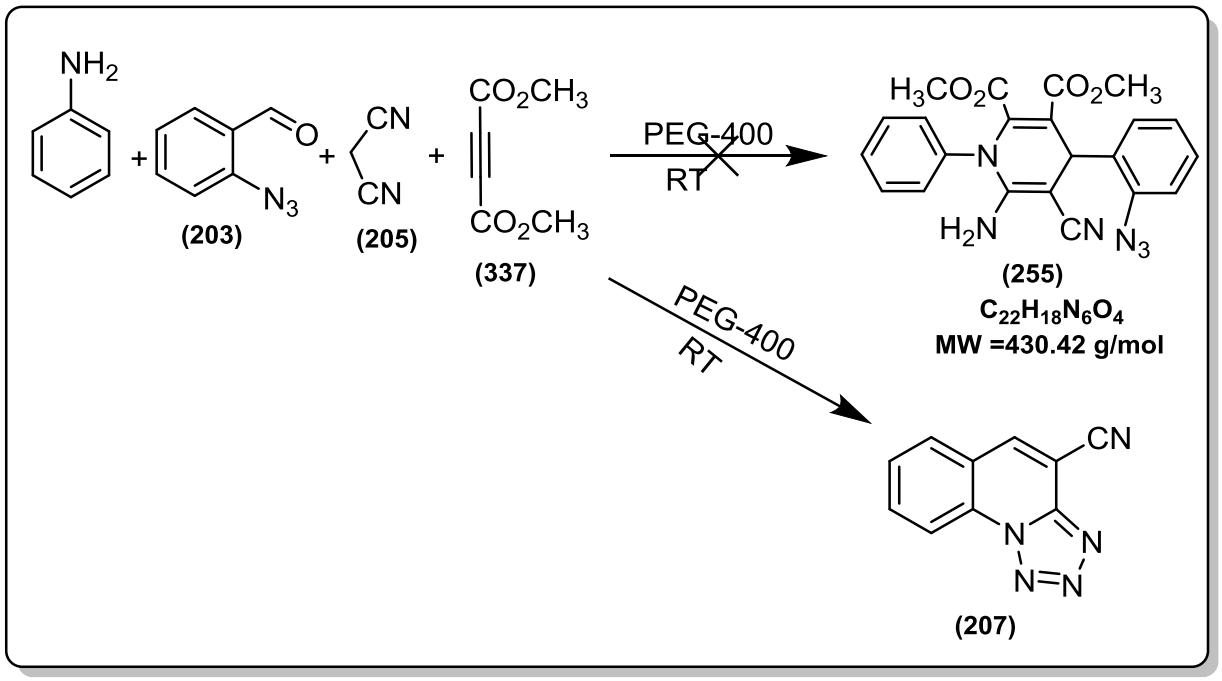
IR: υ_{max} (cm^{-1}): 3224.2 (NH), 3035.4 (CH unsat.), 2934.8 (CH sat.), 2854.8, 2205.5 (CN), 1634.0 (C=C), 1297.3 (C-C), 1183.9 (C-N), 757.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.33 (1H, s, C=C-**H**), 6.79-6.81 (1H, m, **H**N), 3.13-3.18 (1H, m, CH-NH of cyclohexyl), 1.07- 1.88 (10H, m, 5 x C**H$_2$**).

^{13}C NMR δ_c (100 MHz, DMSO): 158.83 (CH), 115.91 (CN), 114.12 (CN), 59.18 (CH), 49.78 (qC), 33.42 (2 x CH_2), 24.72 (CH_2), 24.62 (2 x CH_2).

HRMS (m/z): [M + Na^{+}] for $C_{10}H_{13}N_3$ calculated = 198.1002, measured = 198.1010.

6.18. Synthesis of Tetrazolo[1,5-*a*]quinoline-4-carbonitrile.



A mixture of 2-azidobenzaldehyde (147 mg, 1.0 mmol, 1.0 eq), malononitrile (66 mg, 1.0 mmol, 1.0 eq) in 2.0 mL PEG-400 at room temperature was stirred for 30 minutes. A solution of dimethyl acetylendicarboxylate (142 mg, 1.0 mmol, 1.0 eq) and aniline (93 mg, 1.0 mmol, 1.0 eq) in 2.0 mL PEG was then added to the mixture. The whole solution was stirred at room temperature for 10 hours. After completion of the reaction which was monitored by TLC, the reaction mixture was extracted with diethyl ether and PEG was separated from the products. The combined organic layers were evaporated. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate: 1/1, Rf=0.3) to yield the pure product **(207)** as a yellow solid (100 mg, 51 %, m.p.= 2273 - 275 ^{o}C, lit. m.p.= 276 - 278 ^{o}C[173]).

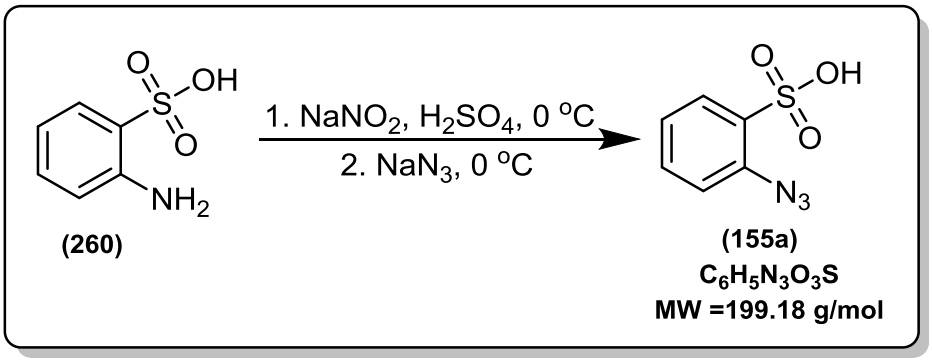
Data as reported above.

Chapter 7:

7. Chapter 7: Experimental for chapter 3: Triazolo and Tetrazolo-benzothiadiazepines and benzodiazepines.

7.1. The synthesis of Triazolobenzothiadiazepines.

7.1.1. Synthesis of 2-azidobenzenesulfonic acid.



(260)

(155a)
$C_6H_5N_3O_3S$
MW =199.18 g/mol

To a suspension of aniline-2-sulfonic acid (5.79 g, 33.4 mmol, 1 eq) in water (22 mL) at 0 °C, was added cooled conc. H_2SO_4 (7.5 mL) dropwise. A solution of $NaNO_2$ (3.0 g, 43.4 mmol, 1.3 eq) in water (15 mL) cooled to 0 °C was added to the suspension dropwise and the whole stirred for 30 mins before a cooled solution of NaN_3 (4.34 g, 66.8 mmol, 2.0 eq) in water (15 mL) was added dropwise and the reaction was allowed to warm to room temperature. The resulting solution was crash cooled in an ice bath to afford the 2-azidobenzenesulfonic acid as a precipitate which was collected by vacuum filtration and dried in the oven at 80-100 °C to give the product as a pale grey solid (4.0 g, 60 %, m.p.=154-156 °C, lit. m.p.=153-155 °C[185]).

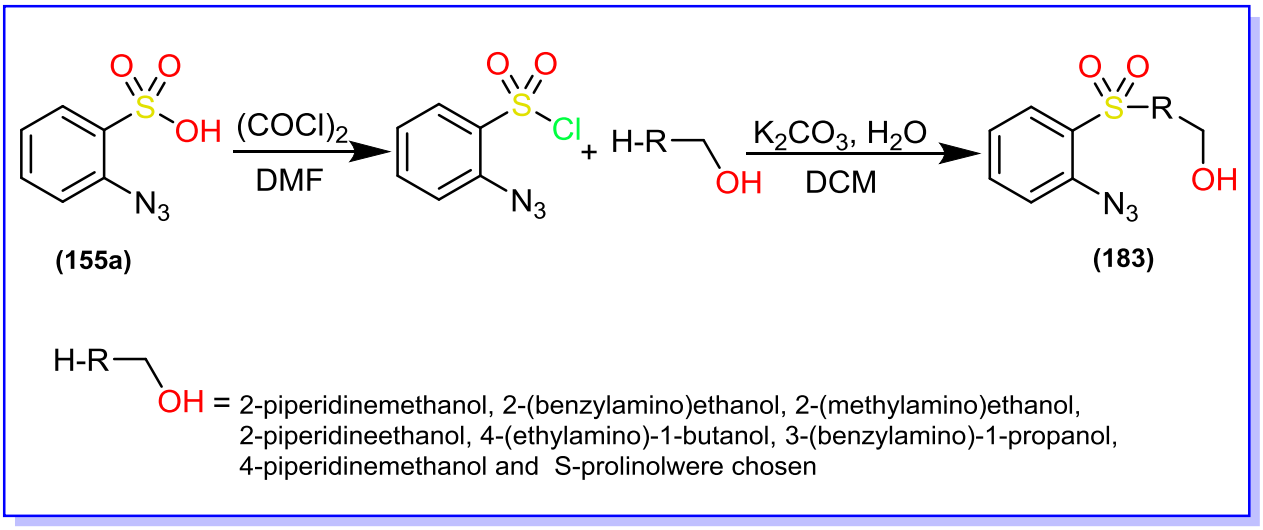
IR: υ_{max} (cm^{-1}): 749.8, 1024.4, 1085.8, 1133.6, 1147.5, 1200.00, 1261.9, 1292.4, 1444.1, 1471.6, 1574.2, 1584.9, 2122.7, 3477.1.

^{1}H NMR: δ_H (400 MHz, DMSO): 7.13 (1H, td, J^1=7.6 Hz, J^2=0.9 Hz Ar**H**), 7.21 (1H, d, J=7.3 Hz, Ar**H**), 7.38 (1H, td, J^1=7.6 Hz, J^2=1.3 Ar**H**), 7.76 (1H, dd, J^1=7.5 Hz, J^2=1.4 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 120.82 (CH), 124.64 (CH), 129.01 (CH), 130.72 (CH), 136.44 (2 qC) ppm.

7.1.2. Coupling of the sulfonic acid with secondary amine alcohols.

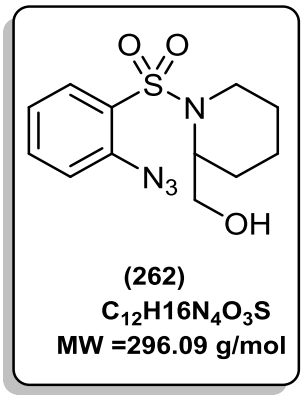
General experimental :



2-Azidobenzenesulfonic acid (437 mg, 2.2 mmol, 2.2 eq) was heated to reflux in a 2M solution of $(COCl)_2$ in dichloromethane (2.5 mL, 5.0 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (4.0 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of the secondary amine alcohol (1.0 mmol, 1.0 eq) in dichloromethane (10 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction[186] was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography.

7.1.2.1. Synthesis of {1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}methanol.



(262)
$C_{12}H16N_4O_3S$
MW =296.09 g/mol

[Eluent*:* petroleum ether/ethyl acetate: 2/1, R_f = 0.22] to yield the product as a yellow oil (85 %).

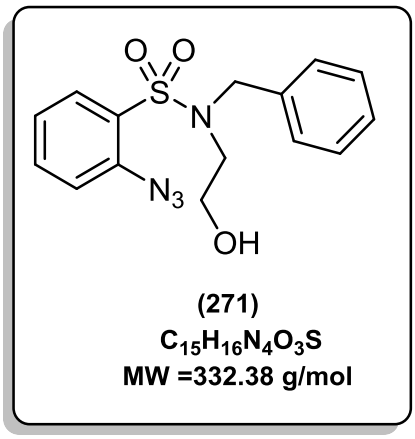
IR: υ_{max} (cm^{-1}): 744.5, 928.5, 1043.7, 1154.5, 1288.3, 1320.4, 1470.9, 1574.3, 2097.7, 2898.5, 2940.7, 3521.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.22-1.59 (5H, m, C**H_2**), 1.69 (1H, d, *J*=12.5 Hz, C***H***H), 2.41 (1H, br.s, O***H***), 3.10 (1H, td, J^1=12.7 Hz, J^2=1.9 Hz, C***H***), 3.55-3.61 (1H, m, NCH***H***), 3.77-3.88 (2H, m, HOC**H_2**), 4.08-4.09 (1H, m, NC***H***H), 7.22 (1H, dd, J^1=7.9 Hz, J^2=7.6 Hz, Ar**H**), 7.29 (1H, d, *J*= 8.0 Hz, Ar**H**), 7.57 (1H, dd, J^1=7.9 Hz, J^2=7.6 Hz, Ar**H**), 7.99 (1H, d, *J*=8.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.95 (CH_2), 24.91 (CH_2), 25.29 (CH_2), 41.30 (CH_2), 54.38 (CH), 60.53 (CH_2), 119.95 (CH), 124.63 (CH), 130.90 (qC), 131.48 (CH), 133.87 (CH), 137.83 (qC) ppm.

HRMS (ESI^+): found 297.1024 $[M+H]^+$, $C_{12}H_{17}N_2O_3S$ requires 297.1016.

7.1.2.2. Synthesis of 2-azido-*N*-benzyl-*N*-(2-hydroxyethyl)benzenesulfonamide.



(271)
$C_{15}H_{16}N_4O_3S$
MW =332.38 g/mol

[Eluent*:* petroleum ether/ethyl acetate: 2/1, R_f = 0.21] to yield the product as a brown solid (88 %, m.p.= 93 - 95 ^oC).

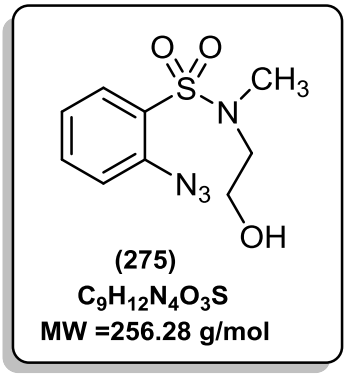
IR: υ_{max} (cm^{-1}): 762.0, 934.6, 993.0, 1052.4, 1155.4, 1336.4, 1468.8, 1571.9, 2101.1, 2939.6, 3359.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 12.22 (1H, br.s, O***H***), 3.41 (2H, br.s, NC**H_2**), 3.49 (2H, br.s, HO-C**H_2**), 4.58 (2H, br.s, Ph-C***H_2***), 7.22-7.36 (7H, m, 7 x Ar***H***), 7.62 (1H, dd, J^1= 7.9 Hz, J^2=7.4 Hz, Ar**H**), 8.05 (1H, d, *J*=7.8 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 50.35 (CH_2), 53.26 (CH_2), 60.74 (CH_2), 119.88 (CH), 124.77 (CH), 127.98 (CH), 128.21 (2 x CH), 128.76 (2 x CH), 130.43 (qC), 131.87 (CH), 134.09 (CH), 136.54 (qC), 138.18 (qC) ppm.

HRMS (ESI^+): found 333.1016 $[M+H]^+$, $C_{15}H_{17}N_4O_3S$ requires 333.1016.

7.1.2.3. Synthesis of 2-azido-*N*-(2-hydroxyethyl)-*N*-methylbenzenesulfonamide.



(275)
$C_9H_{12}N_4O_3S$
MW =256.28 g/mol

[Eluent*:* petroleum ether/ethyl acetate: 2/1, R_f = 0.2] to yield the product as a yellow oil (90 %).

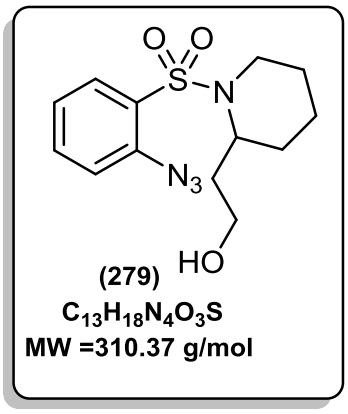
IR: υ_{max} (cm^{-1}): 759.7, 908.0, 975.4, 1059.1, 1143.6, 1265.0, 1287.5, 1323.9, 1442.0, 1470.9, 1574.2, 2099.4, 2929.2, 3516.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.19 (1H, br.s, O**H**), 2.89 (1H, s, C***H*$_3$**), 3.34 (2H, t, *J*=5.2 Hz, N-C***H*$_2$$CH_2$-OH), 3.71 (2H, t, *J*=5.2 Hz, N-CH_2C***H*$_2$**OH), 7.18 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar**H**), 7.24 (1H, d, *J*= 8.0 Hz, Ar**H**), 7.53 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar**H**), 7.92 (1H, d, *J*=8.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 35.80 (CH_3), 52.41 (CH_2), 60.43 (CH_2), 119.88 (CH), 124.71 (CH), 129.36 (qC), 132.04 (CH), 134.07 (CH), 138.18 (qC) ppm.

HRMS (ESI^+): found 257.0703 $[M+H]^+$, $C_9H_{13}N_4O_3S$ requires 257.0703.

7.1.2.4. Synthesis of 2-{1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}ethan-1-ol.



[Eluent*:* petroleum ether/ethyl acetate: 2/1, R_f = 0.25] to yield the product as an orange oil (82 %).

IR: υ_{max} (cm^{-1}): 759.9, 863.8, 949.6, 1073.4, 1154.7, 1288.7, 1320.5, 1442.9, 1470.9, 1574.4, 2097.4, 2867.0, 2941.0, 3537.1.

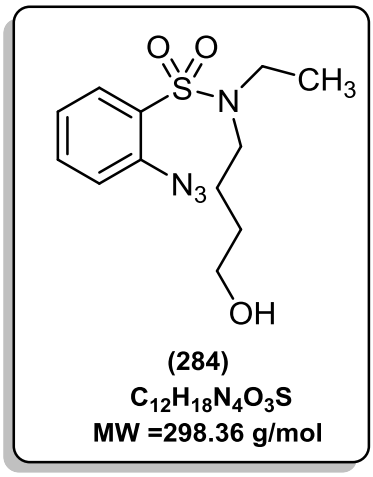
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.11-1.22 (1H, m, C***H***H), 1.45 (5H, br.s, CH***H*** + 2 x C***H*$_2$**), 1.49-1.56 (1H, m, HO-CH_2CH***H***), 1.90-1.97 (1H, m, HO-CH_2C***H***H), 2.84 (1H, bs, O***H***), 2.96 (1H, m, C***H***), 3.55-3.58 (1H, m, NCH***H***), 3.63-3.73 (2H, m, HOC***H*$_2$**), 4.25 (1H, m, NC***H***H),

7.16 (1H, app. td, J^1=8.3 Hz, J^2=1.3 Hz, Ar***H***), 7.24 (1H, app. td, J^1= 8.3 Hz, J^2=1.3 Hz, Ar***H***), 7.51 (1H, app. td, J^1=8.3 Hz, J^2=1.3 Hz, Ar***H***), 7.92 (1H, dd, J^1=8.0 Hz, J^2=1.6 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.40 (CH_2), 24.86 (CH_2), 28.63 (CH_2), 32.52 (CH_2), 40.75 (CH_2), 49.55 (CH), 58.58 (CH_2), 120.00 (CH), 124.68 (CH), 131.24 (CH), 131.35 (qC), 133.79 (CH), 137.63 (qC) ppm.

HRMS (ESI$^+$): found 311.1167 $[M+H]^+$, $C_{13}H_{19}N_4O_3S$ requires 311.1172.

7.1.2.5. Synthesis of 2-azido-*N*-ethyl-*N*-(4-hydroxybutyl)benzenesulfonamide.



(284)
$C_{12}H_{18}N_4O_3S$
MW =298.36 g/mol

[Eluent*:* petroleum ether/ethyl acetate: 2/1, R_f = 0.24] to yield the product as a brown oil (75 %).

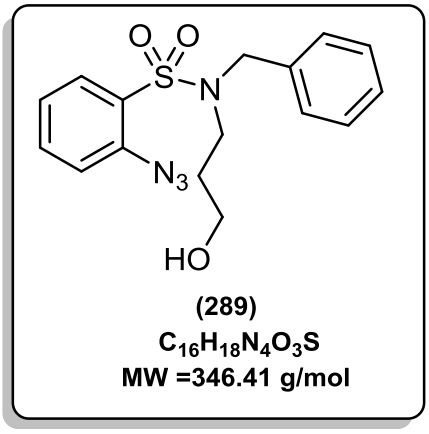
IR: υ_{max} (cm^{-1}): 645.9, 818.5, 906.3, 1031.3, 1058.7, 1155.0, 1288.8, 1324.1, 1443.1, 1471.6, 1575.4, 2098.4, 2980.2, 3527.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.03-1.08 (3H, m, C***H*****$_3$**), 1.51-1.62 (4H, m, NCH$_2$C**H$_2$**C***H*****$_2$**CH2OH), 2.23-2.33 (1H, m, O***H***), 3.30-3.34 (4H, m, C***H*****$_2$**NC***H*****$_2$**), 3.56-3.58 (2H, m, OC***H*****$_2$**), 7.19 (1H, app. td, J^1=8.0 Hz, J^2=1.5 Hz, Ar***H***), 7.25 (1H, d, *J*= 8.0 Hz, Ar***H***), 7.53 (1H, app. td, J^1=8.0 Hz, J^2=1.5 Hz, Ar***H***), 7.91-7.93 (1H, m, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.98 (CH_3), 25.11 (CH_2), 29.51 (CH_2), 42.25 (CH_2), 47.17 (CH_2), 60.07 (CH_2), 119.85 (CH), 124.60 (CH), 131.22 (qC), 131.37 (CH), 133.70 (CH), 137.90 (qC) ppm.

HRMS (ESI$^+$): found 299.1166 [M+H]+, $C_{12}H_{19}N_4O_3S$ requires 299.1172.

7.1.2.6. Synthesis of 2-azido-*N*-benzyl-*N*-(3-hydroxy propyl)benzenesulfonamide.



(289)
$C_{16}H_{18}N_4O_3S$
MW =346.41 g/mol

[Eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.24] to yield the product as a dark brown oil (86 %).

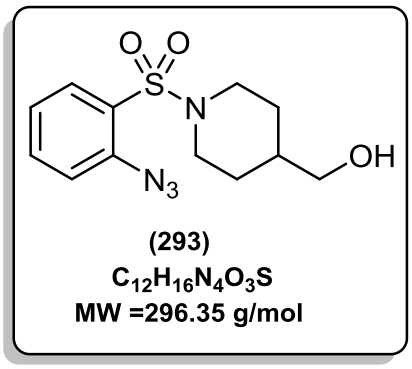
IR: υ_{max} (cm^{-1}): 757.9, 819.4, 938.8, 1059.5, 1123.9, 1156.7, 1265.8, 1289.0, 1328.2, 1442.7, 1471.8, 1495.5, 1574.9, 2101.2, 2877.0, 2947.2, 3542.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.52 (2H, p, *J*=6.0 Hz, $NCH_2C\boldsymbol{H_2}$), 2.18 (1H, br.s, O***H***), 3.45 (2H, t, *J*=6.6 Hz, $NC\boldsymbol{H_2}CH_2$), 3.66 (2H, m, HO-C***H*****$_2$**), 4.51 (2H, br.s, Ph-C***H*****$_2$**), 7.23-7.32 (7H, m, 7 x Ar***H***), 7.61 (1H, td, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 8.03 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 30.73 (CH_2), 44.96 (CH_2), 52.50 (CH_2), 58.75 (CH_2), 119.82 (CH), 124.75 (CH), 127.92 (CH), 128.34 (2 x CH), 128.61 (2 x CH), 130.75 (qC), 131.73 (CH), 133.98 (CH), 136.64 (qC), 138.11 (qC) ppm.

HRMS (ESI$^+$): found 347.1166 $[M+H]^+$, $C_{16}H_{19}N_4O_3S$ requires 347.1172.

7.1.2.7. Synthesis of {1-[(2-azidophenyl)sulfonyl]piperidin-4-yl}methanol.



(293)
$C_{12}H_{16}N_4O_3S$
MW =296.35 g/mol

[Eluent*:* petroleum ether/ethyl acetate: 1/1, R_f = 0.22] to yield the product as a brown oil (70 %).

IR: υ_{max} (cm^{-1}): 654.9, 818.1, 934.5, 1035.3, 1087.6, 1157.8, 1266.4, 1307.9, 1328.2, 1443.1, 1471.6, 1574.1, 2127.6, 2854.5, 2922.0, 3517.0.

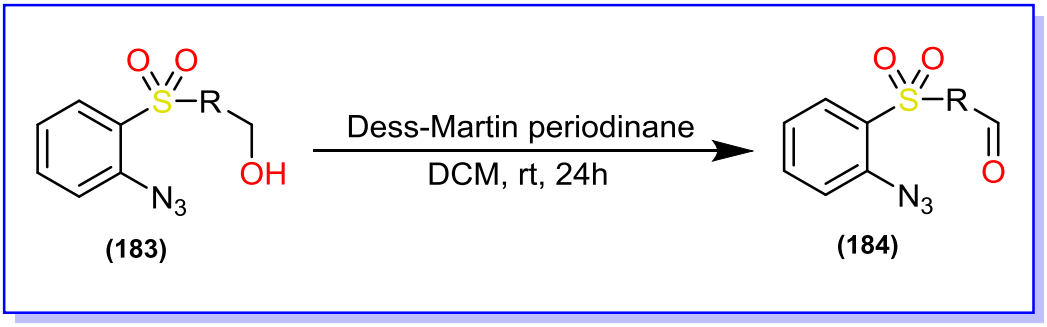
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.20 (2H, qd, J^1=16.5 Hz, J^2=4.1 Hz, CH_2CHCH_2), 1.42-1.53 (1H, m, CH_2CHCH_2), 1.71 (2H, dd, J^1=12.8 Hz, J^2=1.8 Hz, CH_2CHCH_2), 2.58 (2H, td, J^1=12.3 Hz, J^2=2.2 Hz, CH_2NCH_2), 2.68 (1H, br.s, O***H***), 3.38 (2H, d, *J*=6.4 Hz, CH_2NCH_2), 3.81 (2H, d, *J*=12.3 Hz, $HOCH_2$), 7.18 (1H, ddd, J^1=8.8 Hz, J^2=7.8 Hz, J^3=0.9 Hz, Ar***H***), 7.25 (1H, d, *J*= 8.0 Hz, Ar***H***), 7.53 (1H, ddd, J^1=8.8 Hz, J^2=7.8 Hz, J^3=1.3 Hz, Ar***H***), 7.83 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 28.54 (2 x CH_2), 37.96 (CH), 45.95 (2 x CH_2), 66.83 (CH_2), 120.04 (CH), 124.67 (CH), 128.98 (qC), 131.57 (CH), 134.01 (CH), 138.19 (qC) ppm.

HRMS (ESI^+): found 297.1026 $[M+H]^+$, $C_{12}H_{17}N_4O_3S$ requires 297.1016.

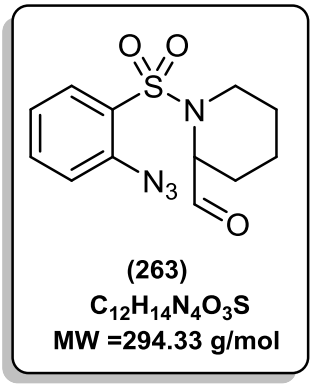
7.1.3. Conversion of the alcohols into the aldehydes.

General experimental:



To solution of the alcohol (1.0 mmol, 1.0 eq) in anhydrous dichloromethane (10 mL), Dess-Martin periodinane (466 mg, 1.1 mmol, 1.1 eq) was added at ambient temperature. The solution was stirred at ambient temperature under an atmosphere of dry nitrogen for 5 hours. The reaction mixture was then quenched with saturated aqueous solutions of $NaHCO_3$ (15 mL) and Na_2SO_3 (15 mL). The reaction mixture was filtered under vacuum through a pad of celite. The combined organic phase was dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure and purified by silica chromatography.

7.1.3.1. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-2-carbaldehyde.



(Eluent: petroleum ether/ethylacetate: 3/1, R_f = 0.35) to yield the product as an orange oil (76 %).

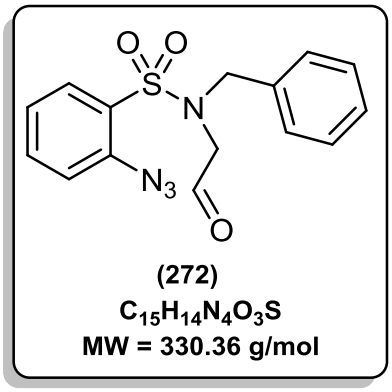
IR: υ_{max} (cm^{-1}): 732.4, 856.8, 963.7, 1070.3, 1184.3, 1334.6, 1471.0, 1574.3, 1731.8, 2098.8, 2859.1, 2944.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.21-1.31 (1H, m, CH***H***), 1.38-1.51 (1H, m, C***H***H), 1.56-1.66 (1H, m, CH***H***), 1.66-1.76 (2H, m, C**H$_2$**), 2.27 (1H, dd, J^1=13.0 Hz, J^2=1.9 Hz, C***H***H), 3.12 (1H, td, J^1=13.0 Hz, J^2=2.6 Hz, NC**H**), 3.86 (1H, d, J=13.5 Hz, NC***H***H), 4.66 (1H, d, J=5.1 Hz, NCH***H***), 7.25 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.32 (1H, d, J=8.0 Hz, Ar**H**), 7.60 (1H, app. td, J^1=7.8 Hz, J^2=1.3 Hz, Ar**H**), 8.01 (1H, dd, J^1=7.8 Hz, J^2=1.3 Hz, Ar**H**), 9.66 (1H, s, C**H**O).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.53 (CH_2), 24.12 (CH_2), 24.84 (CH_2), 44.17 (CH_2), 62.01 (CH), 119.95 (CH), 124.62 (CH), 130.76 (qC), 131.25 (CH), 134.00 (CH), 138.12 (qC), 200.94 (C=O).

HRMS (ESI$^+$): found 317.0680 [M+Na]+, $C_{12}H_{14}N_4O_3SNa$ requires 317.0679.

7.1.3.2. Synthesis of 2-azido-*N*-benzyl-*N*-(2-oxoethyl)benzenesulfonamide.



(272)
$C_{15}H_{14}N_4O_3S$
MW = 330.36 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.23) yielded the product as a white solid (83 %, m.p.=111-113 ^{o}C).

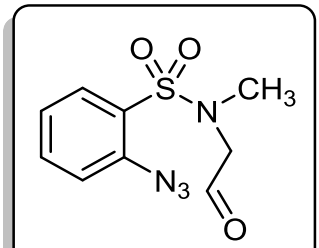
IR: υ_{max} (cm^{-1}): 795.8, 873.6, 959.2, 1000.0, 1105.7, 1125.9, 1143.8, 1294.3, 1321.0, 1454.2, 1474.5, 1585.9, 1715.6, 1748.4, 2102.1, 2898.5, 3030.3, 3075.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.06 (2H, s, Ph-C**H$_2$**), 4.54 (2H, s, NC**H$_2$**), 7.25-7.35 (7H, m, 7 x Ar**H**), 7.64 (1H, td, J^1= 8.0 Hz, J^2=1.4 Hz, Ar**H**), 8.06 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar**H**), 9.34 (1H, s, C**H**O) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 52.99 (CH_2), 59.31 (CH_2), 119.92 (CH), 124.78 (CH), 128.50 (CH), 128.83 (2CH), 128.95 (2CH), 130.18 (qC), 131.67 (CH), 134.32 (CH), 134.89 (qC), 138.33 (qC), 197.87 (CHO) ppm.

HRMS (ESI^+): found 369.0420 $[M+K]^+$, $C_{12}H_{14}N_4O_3SK$ requires 369.0418.

7.1.3.3. Synthesis of 2-azido-*N*-methyl-*N*-(2-oxoethyl)benzenesulfonamide.



(276)
$C_9H_{10}N_4O_3S$
MW =254.26 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.3) yielded the product as a dark brown oil (76 %).

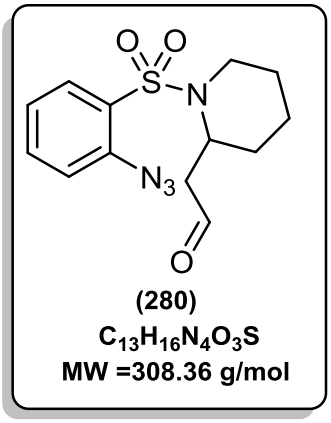
IR: υ_{max} (cm^{-1}): 727.7, 886.4, 978.1, 1059.2, 1155.7, 1287.8, 1331.1, 1442.6, 1471.0, 1574.6, 1731.1, 2100.3, 2945.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.88 (3H, s, C***H*****$_3$**), 4.17 (2H, s, C***H*****$_2$**), 7.20 (1H, ddd, J^1=8.5 Hz, J^2=7.9 Hz, J^3=1.2 Hz, Ar***H***), 7.27 (1H, dd, J^1= 8.0 Hz, J^2=1.2 Hz, Ar***H***), 7.57 (1H, ddd, J^1=8.5 Hz, J^2=7.8 Hz, J^3=1.5 Hz, Ar***H***), 7.92 (1H, dd, J^1=8.0 Hz, J^2=1.2 Hz, Ar***H***), 9.61(1H, s, C***H***O) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 36.05 (CH_3), 59.53 (CH_2), 119.99 (CH), 124.71 (CH), 129.13 (qC), 131.69 (CH), 134.32 (CH), 138.18 (qC), 197.73 (CHO) ppm.

HRMS (ESI^+): found 277.0373 $[M+Na]^+$, $C_9H_{10}N_4O_3SNa$ requires 277.0366.

7.1.3.4. Synthesis of 2-{1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}acetaldehyde.



(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.28) yielded the product as a light yellow oil (81 %).

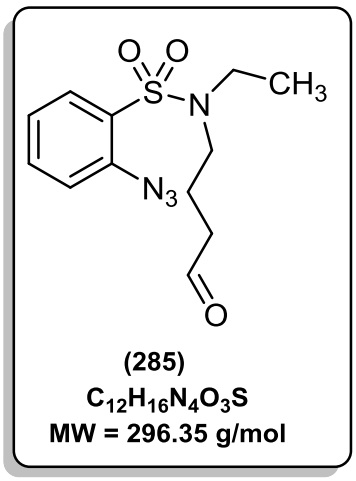
IR: υ_{max} (cm^{-1}): 759.5, 818.6, 932.4, 1071.2, 1122.1, 1157.1, 1288.5, 1326.4, 1443.6, 1471.2, 1574.7, 1721.0, 2099.4, 2863.2, 2941.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.14-1.76 (6H, m, 3 x C***H*****$_2$**), 2.72-2.84 (2H, m, C***H*****$_2$**-CHO), 3.02-3.09 (1H, m, C***H***), 3.89 (1H, dd, J^1=13.5 Hz, J^2=1.0 Hz, NCH***H***), 4.66 (1H, q, J=6.2 Hz, NC***H***H), 7.25 (1H, ddd, J^1=8.8 Hz, J^2=7.8 Hz, J^3=1.2 Hz, Ar***H***), 7.31 (1H, dd, J^1= 8.0 Hz, J^2=1.1 Hz, Ar***H***), 7.60 (1H, ddd, J^1=8.8 Hz, J^2=7.8 Hz, J^3=1.2 Hz, Ar***H***), 8.02 (1H, dd, J^1=8.0 Hz, J^2=1.5 Hz, Ar***H***), 9.62 (1H, t, J=2.0 Hz, C***H***O) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.39 (CH_2), 25.17 (CH_2), 28.62 (CH_2), 41.40 (CH_2), 44.49 (CH_2), 47.76 (CH), 119.92 (CH), 124.58 (CH), 130.98 (qC), 131.36 (CH), 133.88 (CH), 138.02 (qC), 199.87 (CHO) ppm.

HRMS (ESI^+): found 331.0832 $[M+Na]^+$, $C_{13}H_{16}N_4O_3SNa$ requires 331.0835.

7.1.3.5. Synthesis of 2-azido-*N*-ethyl-*N*-(4-oxobutyl)benzenesulfonamide.



(285)
$C_{12}H_{16}N_4O_3S$
MW = 296.35 g/mol

(Eluent: petroleum ether/ethylacetate: 3/2, R_f = 0.25) yielded the product as a light yellow oil (76 %).

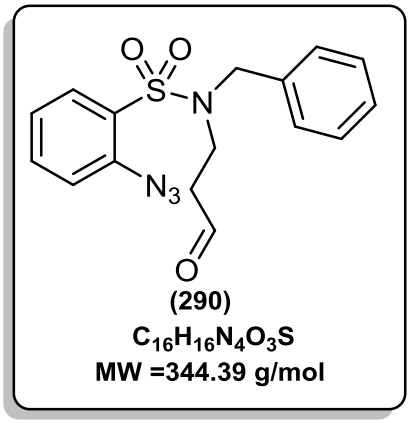
IR: υ_{max} (cm^{-1}): 737.3, 818.2, 915.7, 998.2, 1060.1, 1145.3, 1154.8, 1288.5, 1326.5, 1442.6, 1471.1, 1574.5, 1720.1, 2098.1, 2936.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.09 (3H, t, *J*=7.1 Hz, C***H*****$_3$**), 1.89 (2H, app. p, *J*=7.1 Hz, NCH_2C***H*****$_2$**), 2.57 (2H, t, *J*=7.1 Hz, C***H*****$_2$**-CHO), 3.31-3.42 (4H, m, C***H*****$_2$**NC***H*****$_2$**), 7.23 (1H, app. td, J^1=8.0 Hz, J^2=1.0 Hz, Ar***H***), 7.29 (1H, dd, J^1= 7.9 Hz, J^2=1.2 Hz, Ar***H***), 7.57 (1H, app. td, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 7.98 (1H, dd, J^1=7.9 Hz, J^2=1.2 Hz, Ar***H***), 9.79 (1H, s, C***H***O) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.89 (CH_3), 21.08 (CH_2), 40.69 (CH_2), 42.43 (CH_2), 49.65 (CH_2), 119.79 (CH), 124.66 (CH), 131.11 (qC), 131.59 (CH), 133.76 (CH), 137.95 (qC) 201.42 (CHO) ppm.

HRMS (ESI^+): found 297.1009 [M+H]+, $C_{12}H_{17}N_4O_3S$ requires 297.1016.

7.1.3.6. Synthesis of 2-azido-*N*-benzyl-*N*-(3-oxopropyl) benzenesulfonamide.



(290)
$C_{16}H_{16}N_4O_3S$
MW =344.39 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.3) yielded the product as a light yellow oil (77 %).

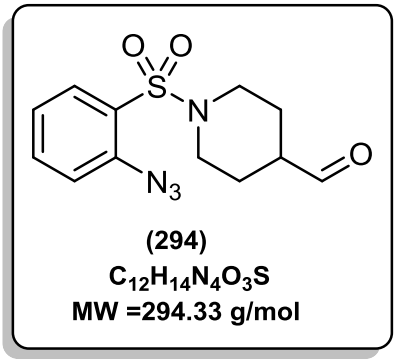
IR: υ_{max} (cm^{-1}): 577.3, 699.5, 726.6, 819.0, 908.2, 1059.1, 1123.6, 1156.4, 1288.2, 1329.8, 1454.9, 1471.1, 1573.8, 1584.4, 1633.5, 1722.0, 1866.0, 2100.0, 2917.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.56 (2H, ddd, J^1=7.4 Hz, J^2=7.0 Hz, J^3=0.8 Hz, NCH_2CH_2), 3.58 (2H, t, J=7.4 Hz, NCH_2CH_2), 4.53 (2H, s, Ph-CH_2), 7.25-7.36 (7H, m, 7 x Ar***H***), 7.62 (1H, td, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 8.03 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 9.53 (1H, s, C***H***O) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 41.68 (CH_2), 43.50 (CH_2), 53.08 (CH_2), 119.88 (CH), 124.75 (CH), 128.05 (CH), 128.31 (2 x CH), 128.77 (2 x CH), 130.43 (qC), 131.78 (CH), 134.12 (CH), 136.34 (qC), 138.21 (qC), 200.12 (CHO) ppm.

HRMS (ESI^+): found 345.1012 $[M+H]^+$, $C_{16}H_{17}N_4O_3S$ requires 345.1016.

7.1.3.7. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-4-carbaldehyde.



(294)
$C_{12}H_{14}N_4O_3S$
MW =294.33 g/mol

(Eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.31) yielded the product as a yellow oil (92 %).

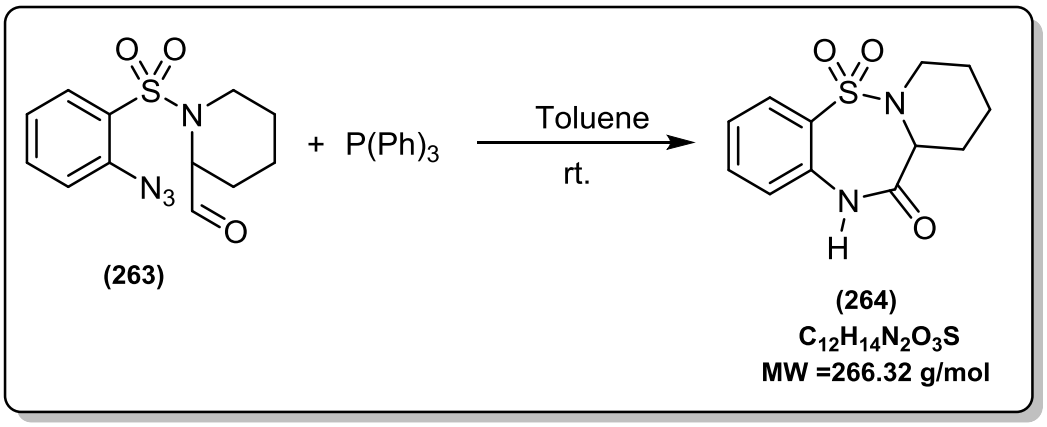
IR: υ_{max} (cm^{-1}): 739.2, 818.4, 929.8, 1042.9, 1068.5, 1124.2, 1158.0, 1265.8, 1288.5, 1325.8, 1442.7, 1471.3, 1573.6, 1723.0, 2098.6, 2856.3, 2926.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.61-1.71 (2H, m, CH_2CHCH_2), 1.89-1.97 (2H, m, CH_2CHCH_2), 2.30 (1H, septet, *J*=4.3 Hz, CH_2CHCH_2), 2.90 (2H, td, J^1=13.0 Hz, J^2=3.0 Hz, CH_2NCH_2), 3.61-3.67 (2H, m, CH_2NCH_2), 7.17 (1H, ddd, J^1=8.4 Hz, J^2=7.9 Hz, J^2=1.0 Hz, Ar***H***), 7.23 (1H, dd, J^1= 8.0 Hz, J^2=1.3 Hz, Ar***H***), 7.51 (1H, ddd, J^1=8.4 Hz, J^2=7.9 Hz, J^2=1.5 Hz, Ar***H***), 7.87 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar***H***), 9.58 (1H, s, C***H***O) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.23 (2 x CH_2), 44.98 (2 x CH_2), 47.04 (CH), 119.95 (CH), 124.70 (CH), 129.22 (qC), 131.73 (CH), 134.02 (CH), 138.29 (qC), 202.44 (CHO) ppm.

HRMS (ESI^+): found 295.0856 $[M+H]^+$, $C_{12}H_{15}N_4O_3S$ requires 295.0859.

7.1.4. Synthesis of 1,3,4,12a-tetrahydro-2*H*-benzo[*f*]pyrido[1,2-*b*][1,2,5]thiadiazepin-12(11*H*)-one 6,6-dioxide.



To a solution of 2-azidobenzyl benzoate (294 mg, 1.0 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added triphenylphosphine (314 mg, 1.2 mmol, 1.2 eq). The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using silica column chromatography [*petroleum ether*/ethyl acetate: 4/1, R_f = 0.22] to yield the product as a yellow- green oil (36 mg, 14 %).

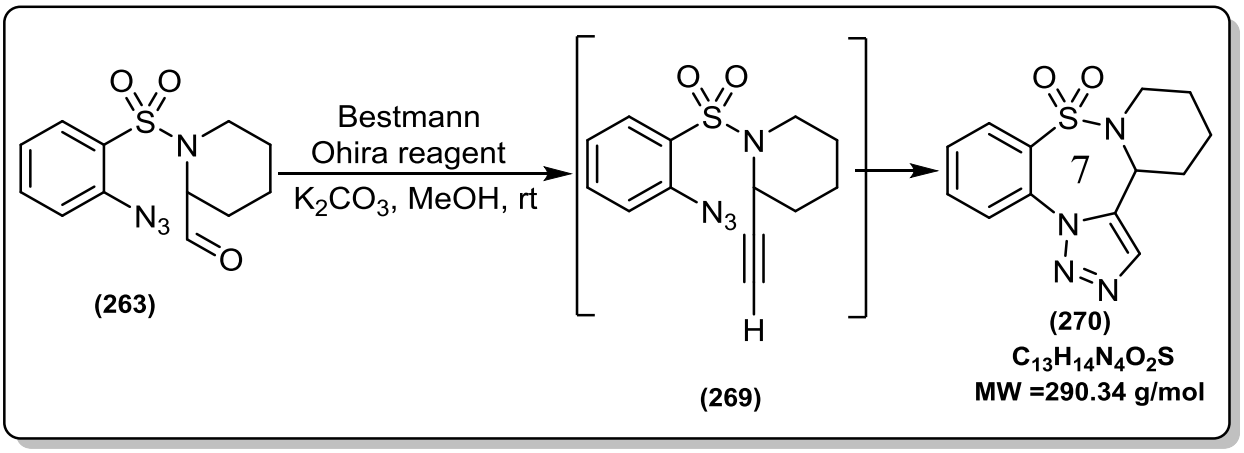
IR: υ_{max} (cm^{-1}): 580.7, 752.3, 882.3, 976.6, 1050.6, 1121.6, 1156.5, 1329.3, 1487.9, 1601.4, 1724.4, 2854.9, 2925.0, 3378.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.38-1.43 (1H, m, C***H***H), 1.77-1.87 (1H, m, C$\mathbf{H_2}$), 2.02-2.10 (1H, m, CH***H***), 2.41-2.48 (1H, m, C***H***H), 2.54-2.58 (1H, m, CH***H***), 3.12-3.19 (1H, m, NC***H***H), 3.57-3.65 (1H, m, NCH***H***), 5.42 (1H, br.s, NC***H***), 5.66-5.67 (1H, m, N***H***), 6.70 (1H, d, *J*=8.5 Hz, Ar**H**), 6.76 (1H, app. td, J^1=8.2 Hz, J^2=1.1 Hz, Ar**H**), 7.26 (1H, app. td, J^1=8.2 Hz, J^2=1.1 Hz, Ar**H**), 7.57 (1H, dd, J^1=8.5 Hz, J^2=1.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 26.25 (CH_2), 29.79 (CH_2), 39.60 (CH_2), 45.10 (CH_2), 73.60 (CH), 115.81 (CH), 118.40 (CH), 119.93 (qC), 125.37 (CH), 133.83 (CH), 140.47 (qC), 204.82 (C=O) ppm.

HRMS (ESI^+): found 266.0716 $[M]^+$, $C_{12}H_{14}N_2O_3S$ requires 266.0725.

7.1.5. Synthesis of 3b,4,6,7-tetrahydro-5*H*-benzo[*f*]pyrido[1,2-*b*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepine 9,9-dioxide.



The aldehyde (80 mg, 1.07 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (75 mg, 0.54 mmol, 2.0 eq) and the Bestmann-Ohira reagent[236] (78 µL, 62 mg, 0. 33 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography (petroleum ether/ethyl acetate: 1/1, R_f = 0.2) yielded the product as a pale yellow oil (56 mg, 71 %).

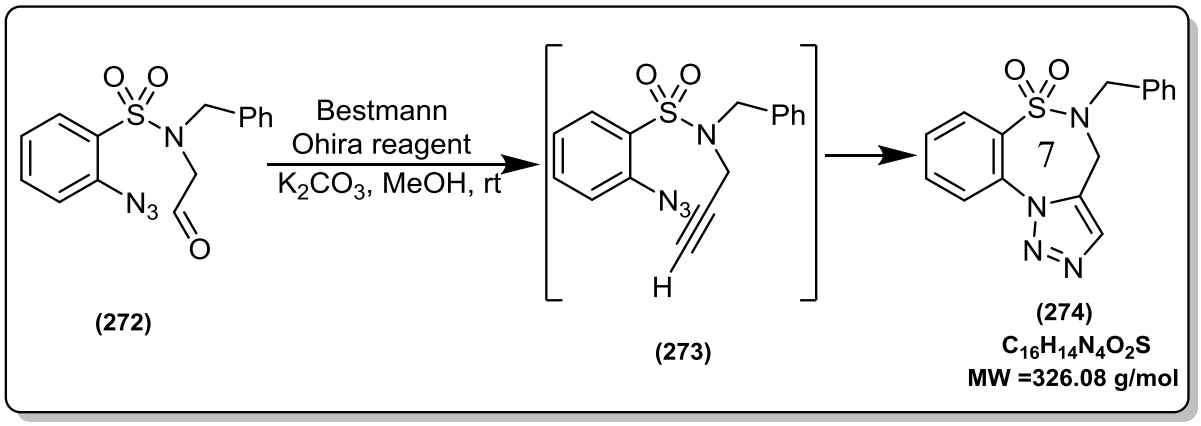
IR: υ_{max} (cm^{-1}): 728.3, 907.4, 955.3, 1096.5, 1127.9, 1170.3, 1346.2, 1488.0, 1593.0, 2854.9, 2926.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.33-1.45 (1H, m, CH***H***), 1.60-1.79 (2H, m, C**H$_2$**), 1.87-1.92 (1H, m, C***H***H), 2.02-2.15 (2H, m, C**H$_2$**), 2.66 (1H, td, J^1=11.8 Hz, J^2=2.6 Hz, NC***H***), 3.73 (1H, dd, J^1=9.7 Hz, J^2=2.6 Hz, NC***H***H), 3.86-3.89 (1H, m, NCH***H***), 7.58 (1H, app. td, J^1=7.6 Hz, J^2=0.7 Hz, Ar***H***), 7.68 (1H, br.s, Ar**H**), 7.75 (1H, dd, J^1=7.8 Hz, J^2=1.1 Hz, Ar**H**), 7.93 (1H, dd, J^1=7.8 Hz, J^2=1.1 Hz, Ar**H**), 9.97 (1H, d, J=7.6 Hz, Ar**H**).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 23.67 (CH_2), 25.07 (CH_2), 29.42 (CH_2), 48.80 (CH_2), 52.25 (CH), 125.02 (CH), 127.96 (CH), 129.70 (CH), 130.92 (qC), 132.86 (CH), 133.54 (qC), 134.48 (CH), 136.53 (qC) ppm.

HRMS (ESI^+): found 291.0909 $[M+H]^+$, $C_{13}H_{15}N_4O_2S$ requires 291.0910.

7.1.6. Synthesis of 5-benzyl-4,5-dihydrobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepine 6,6-dioxide.



The aldehyde (200 mg, 0.606 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (167 mg, 1.212 mmol, 2.0 eq) and the Bestmann-Ohira reagent (174 µL, 139 mg, 0. 727 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography (20 g) (petroleum ether/ethyl acetate: 1/1, R_f = 0.22) yielded the product as a orange oil (145 mg, 73 %).

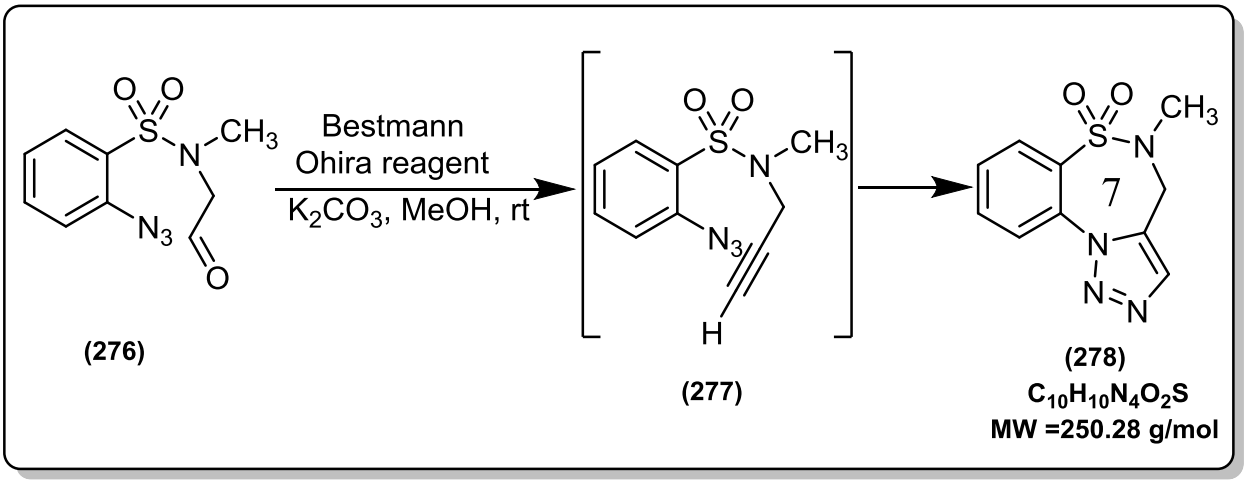
IR: υ_{max} (cm^{-1}): 697.1, 797.7, 908.5, 1059.1, 1089.9, 1139.7, 1167.7, 1343.9, 1454.0, 1485.7, 1591.8, 1650.8, 2924.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.26 (4H, d, *J*=7.1 Hz, 2 x C***H*$_2$**), 7.18-7.29 (5H, m, 5 x Ar***H***), 7.54 (2H, m, 2 x Ar***H***), 7.72 (1H, td, J^1=8.2 Hz, J^2=1.3 Hz, Ar***H***), 8.03 (1H, dd, J^1= 7.9 Hz, J^2=1.5 Hz, Ar***H***), 8.17 (1H, d, *J*=8.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 41.14 (CH_2), 54.12 (CH_2), 125.03 (CH), 128.36 (CH), 128.57 (2CH), 128.61 (CH), 129.04 (2CH), 129.18 (CH), 131.63 (qC), 132.85 (qC), 133.05 (CH), 133.94 (qC), 134.02 (qC), 134.41 (CH) ppm.

HRMS (ESI^+): found 327.0905 $[M+H]^+$, $C_{16}H_{15}N_4O_2S$ requires 327.1091.

7.1.7. Synthesis of 5-methyl-4,5-dihydrobenzo[*f*][1,2,3]triazolo[5,1-*d*][1,2,5]thiadiazepine 6,6-dioxide.



The aldehyde (180 mg, 0.708 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (195 mg, 1.416 mmol, 2.0 eq) and the Bestmann-Ohira reagent (203 µL, 163 mg, 0. 850 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography (petroleum ether/ethyl acetate: 1/2, R_f = 0.24) yielded the product as a pale yellow solid (120 mg, 68 %, m.p.=106-108 ^oC).

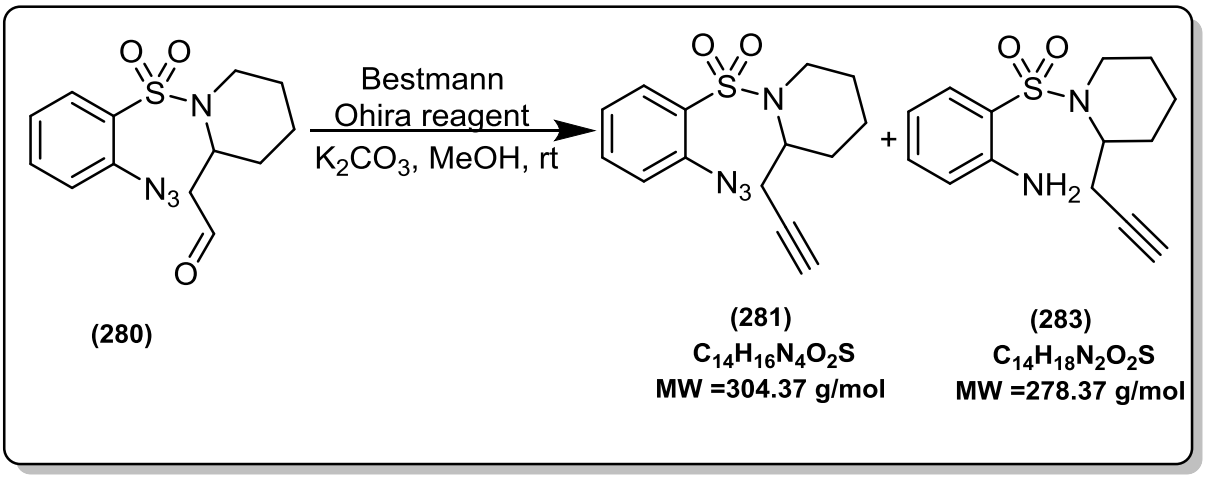
IR: υ_{max} (cm^{-1}): 727.9, 839.9, 910.8, 978.4, 1104.8, 1137.3, 1165.1, 1230.7, 1344.6, 1459.1, 1484.7, 1562.9, 2925.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.79 (3H, s, C***H*$_3$**), 4.30 (2H, s, C***H*$_2$**), 7.55 (1H, app. td, J^1=7.8 Hz, J^2= 1.0 Hz, Ar***H***), 7.68 (1H, s, =C***H***), 7.73 (1H, app. td, J^1= 7.8 Hz, J^2=1.4 Hz, Ar***H***), 7.96 (1H, dd, J^1=7.8 Hz, J^2=1.4 Hz, Ar***H***), 8.09 (1H, dd, J^1=8.1 Hz, J^2=0.9 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 38.03 (CH_3), 43.94 (CH_2), 125.04 (CH), 128.74 (CH), 129.38 (CH), 130.10 (qC), 132.60 (qC), 133.15 (qC), 134.04 (CH), 134.59 (CH) ppm.

HRMS (ESI^+): found 251.0612 $[M+H]^+$, $C_{10}H_{11}N_4O_2S$ requires 251.0597.

7.1.8. Attempted synthesis of 4,4a,5,6,7,8-hexahydrobenzo[*g*] pyrido[1,2-*b*][1,2,3]triazolo[5,1-*e*][1,2,6]thiadiazocine 10,10-dioxide.



The aldehyde (123 mg, 0.4 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (110 mg, 0.8 mmol, 2.0 eq) and the Bestmann-Ohira reagent (115µL, 92 mg, 0.48 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography to give two products:

First product (281): 1-[(2-azidophenyl)sulfonyl]-2-(prop-2-yn-1-yl) piperidine.

(Petroleum ether/ethyl acetate: 1/1, R_f = 0.21) yielded the product as a light yellow oil (80 mg, 66 %).

IR: υ_{max} (cm^{-1}): 576.3, 603.7, 647.2, 818.4, 867.8, 905.5, 964.9, 1071.6, 1124.9, 1156.5, 1265.8, 1327.1, 1444.2, 1471.9, 1575.5, 2099.6, 2125.8, 2943.5, 3307.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.16-1.60 (6H, m, 3 x C***H*$_2$**), 1.84 (1H, br.s, CH_2CC**H**), 1.88-1.93 (1H, m, HCC-CH***H***), 2.35 (1H, qd, J^1=16.0 Hz, J^2=2.6 Hz, HCCC***H***H), 2.95 (1H, td, J^1=13.8 Hz, J^2=2.3 Hz, NC***H***), 3.76 (1H, dd, J^1=13.9 Hz, J^2=3.9 Hz, NC***H***H), 4.15 (H, t, J=5.4 Hz, NCH***H***), 7.14 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar***H***), 7.21 (1H, app. td, J=7.9 Hz, Ar***H***), 7.49 (1H, app. td, J^1=7.8 Hz, J^2=1.4 Hz, Ar***H***), 7.91 (1H, dd, J^1=7.9 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.11 (CH_2), 20.05 (CH_2), 25.23 (CH_2), 26.74 (CH_2), 41.13 (CH_2), 51.87 (CH), 70.44 (CH), 80.81 (qC), 119.84 (CH), 124.54 (CH), 131.24 (CH), 131.34 (qC), 133.68 (CH), 137.99 (qC) ppm.

HRMS (ESI$^+$): found 305.1062 $[M+H]^+$, $C_{14}H_{17}N_4O_2S$ requires 305.1067.

Second product (283): 2-{[2-(prop-2-yn-1-yl)piperidin-1-yl]sulfonyl}aniline.

(Petroleum ether/ethyl acetate: 1/2, R_f = 0.21) yielded the product as a yellow oil (20 mg, 18 %).

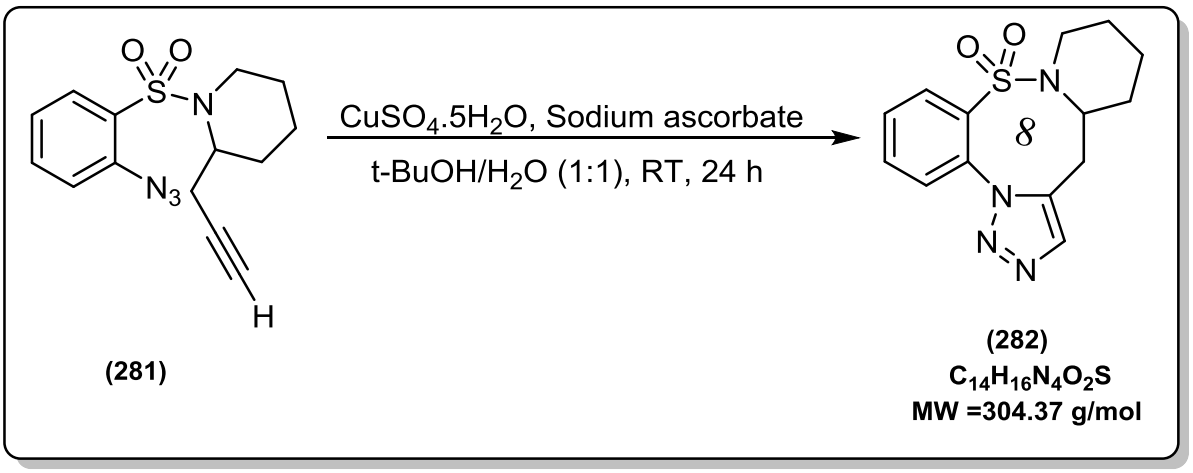
IR: υ_{max} (cm^{-1}): 839.0, 964.1, 1088.8, 1141.2, 1178.3, 1265.7, 1318.5, 1381.7, 1453.7, 1567.0, 1616.6, 2129.3, 2884.0, 2980.3, 3305.3, 3376.6, 3483.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.14-1.61 (6H, m, 3 x C***H*$_2$**), 1.83-1.97 (1H, m, HCC-CH***H***), 2.33.2.39 (1H, m, HCCC***H***H), 2.53-2.58 (1H, m, NC**H**), 2.85 (1H, td, J^1=13.8 Hz, J^2=2.3 Hz, CC***H***), 3.63 (1H, dd, J^1=13.9 Hz, J^2=3.9 Hz, NC***H***H), 4.13 (H, t, J=5.4 Hz, NCH***H***), 4.92 (2H, sb, N**H$_2$**), 7.23 (2H, d, J=8.2 Hz, 2 x Ar***H***), 7.74 (2H, d, J=8.2 Hz, 2 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.09 (CH_2), 19.58 (CH_2), 24.59 (CH_2), 26.19 (CH_2), 40.76 (CH_2), 51.66 (CH), 70.51 (CH), 80.99 (qC), 117.35 (CH), 124.55 (CH), 129.90 (CH), 133.90 (CH), 138.01 (qC), 145.31 (qC) ppm.

HRMS (ESI$^+$): found 278.1089 $[M+H]^+$, $C_{14}H_{18}N_2O_2S$ requires 278.1089.

7.1.9. Synthesis of 4,4a,5,6,7,8-hexahydrobenzo[*g*]pyrido[1,2-*b*][1,2,3]triazolo[5,1-*e*][1,2,6]thiadiazocine-10,10-dioxide.



A solution of sodium ascorbate (5 mg, 0.025 mmol, 0.1 eq) and $CuSO_4.5H_2O$ (1.22 mg, 0.0049 mmol, 0.02 eq) in water (2 mL) was added to a solution of 1-((2-azidophenyl)sulfonyl)-2-(prop-2-yn-1-yl)piperidine (75 mg, 0.25 mmol, 1.0 eq) in t-BuOH (2 mL). The whole was stirred at ambient temperature under nitrogen atmosphere for 48 hours and whilst being monitored by TLC. The reaction mixture was diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. Purified by silica column chromatography [petroleum ether/ethyl acetate: 1/5, R_f = 0.24] to yield the product as a light yellow oil (60 mg, 80 %).

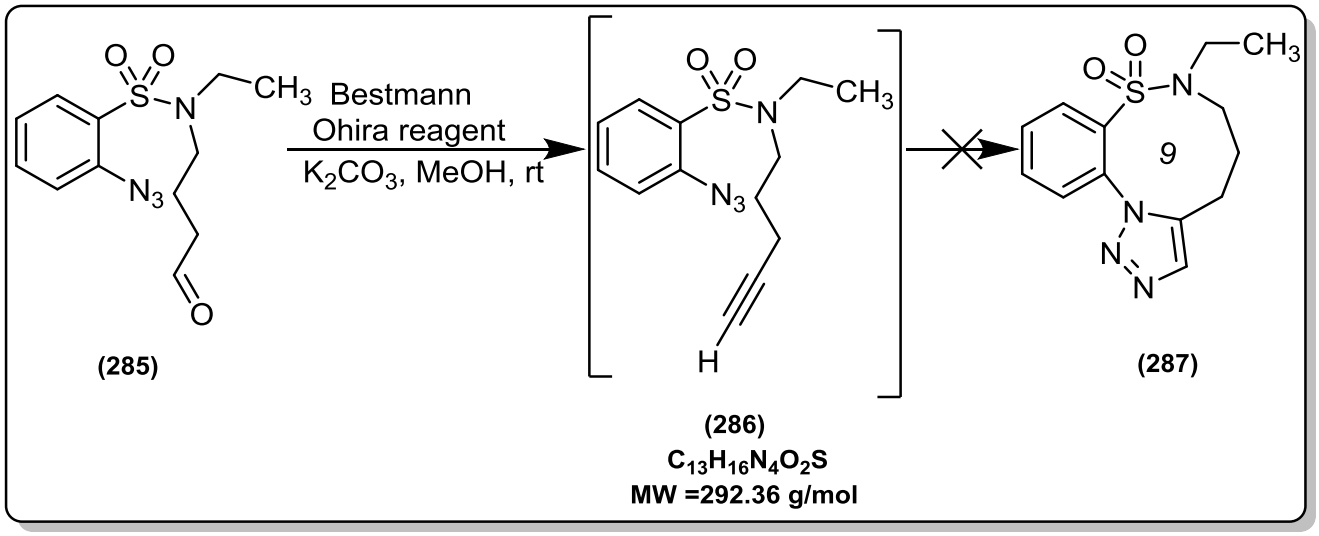
IR: υ_{max} (cm^{-1}): 772.7, 937.8, 1018.9, 1072.2, 1085.2, 1122.3, 1135.8, 1163.3, 1266.7, 1297.1, 1343.0, 1357.2, 1455.2, 1488.8, 1589.8, 2856.0, 2928.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.18-1.69 (6H, m, 3 x C***H*₂***), 1.87-1.96 (1H, m, C=C-CH***H***), 2.28 (1H, td, J^1=12.0 Hz, J^2=3.1 Hz, C=CC***H***H), 2.68-2.77 (1H, m, C***H***), 3.51 (1H, d, *J*=10.3 Hz, NC***H***H), 4.03-4.12 (1H, m, NCH***H***), 7.55-7.59 (2H, m, C=C***H*** + Ar***H***), 7.63 (1H, d, *J*=7.8 Hz, Ar***H***), 7.68 (1H, ddd, J^1=7.8 Hz, J^2=7.5 Hz, J^3=2.0 Hz, Ar***H***), 8.03 (1H, d, *J*=7.8 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.32 (CH_2), 23.07 (CH_2), 24.79 (CH_2), 32.38 (CH_2), 41.22 (CH_2), 54.68 (CH), 127.65 (CH), 128.00 (qC), 130.01 (CH), 130.30 (CH), 131.70 (CH), 132.90 (qC), 133.87 (CH), 133.93 (qC) ppm.

HRMS (ESI$^+$): found 305.1063 $[M+H]^+$, $C_{14}H_{17}N_4O_2S$ requires 305.1067.

7.1.10. Attempted synthesis of 7-ethyl-4,5,6,7-tetrahydrobenzo[*h*][1,2,3]triazolo[5,1-*f*][1,2,7]thiadiazonine 8,8-dioxide.



The aldehyde (200 mg, 0.675 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (186 mg, 1.35 mmol, 2.0 eq) and the Bestmann-Ohira reagent (194 µL, 155 mg, 0.81 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography (25 g) (petroleum ether/ethyl acetate: 1/1, R_f = 0.24) yielded the product as a dark brown oil (137 mg, 70 %).

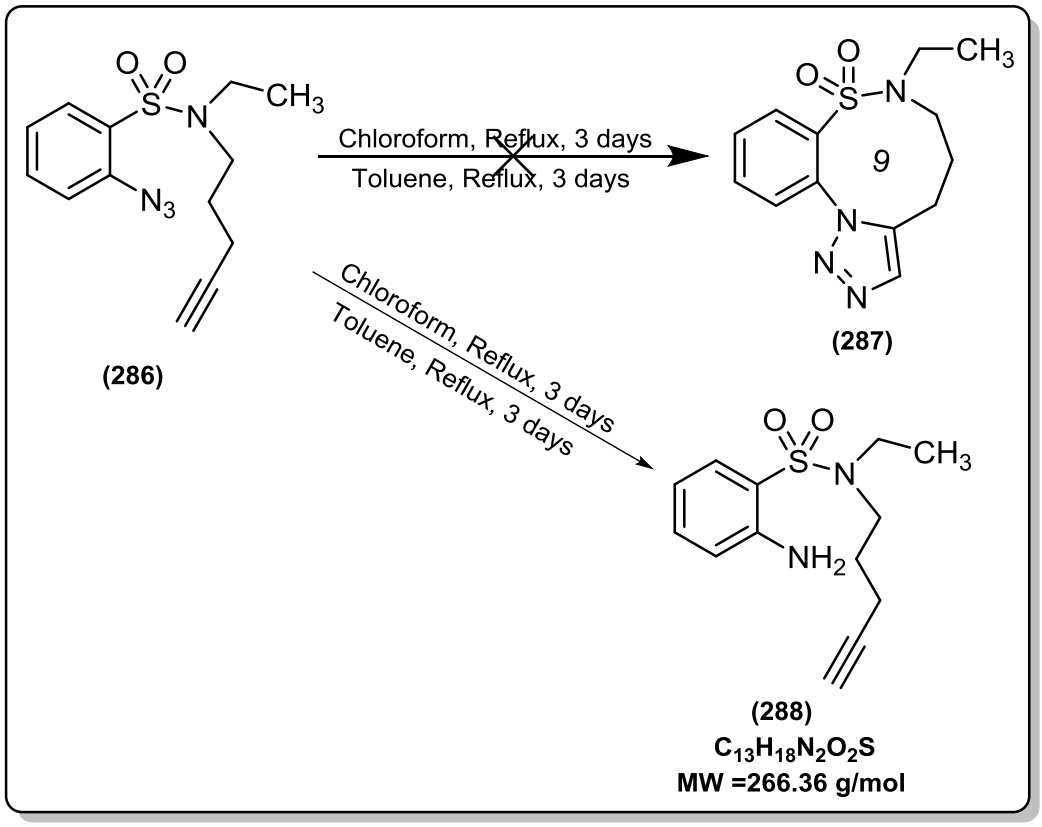
IR: υ_{max} (cm^{-1}): 750.4, 818.3, 936.4, 1002.5, 1063.9, 1155.4, 1264.7, 1327.7, 1443.0, 1471.3, 1574.9, 2101.1, 2232.0, 2849.3, 2920.2, 3281.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.03 (3H, t, *J*=7.1 Hz, C***H*$_3$**), 1.71 (2H, p, *J*=7.3 Hz, NCH_2C***H*$_2$**), 1.87 (1H, bs, C-***H***), 2.14 (2H, td, J^1=6.9 Hz, J^2=2.3 Hz, HCC-C***H*$_2$**), 3.29-3.37 (4H, m, C***H*$_2$NC***H*$_2$**), 7.15 (1H, dd, J^1=7.7 Hz, J^2=7.6 Hz, Ar***H***), 7.21 (1H, d, *J*= 7.6 Hz, Ar***H***), 7.49 (1H, dd, J^1=7.6 Hz, J^2=7.5 Hz, Ar***H***), 7.91 (1H, d, J^1=7.7 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.01 (CH_3), 15.81 (CH_2), 27.71 (CH_2), 42.67 (CH_2), 46.36 (CH_2), 68.98 (C-H), 83.18 (qC), 119.81 (CH), 124.61 (CH), 131.21 (qC), 131.57 (CH), 133.71 (CH), 137.98 (qC) ppm.

HRMS (ESI$^+$): found 293.1064 $[M+H]^+$, $C_{13}H_{17}N_4O_2S$ requires 293.1067.

7.1.11. Attempted synthesis of 7-ethyl-4,5,6,7-tetrahydrobenzo[*h*][1,2,3]triazolo[5,1-*f*][1,2,7]thiadiazonine 8,8-dioxide.



2-Azido-N-ethyl-N-(pent-4-yn-1-yl)benzenesulfonamide (100 mg, 0.34 mmol) in dry chloroform (10 mL) was heated at 80 ^oC under a nitrogen atmosphere for 3 days and monitored by TLC which showed no product. The solvent was removed and the remaining starting material was added to anhydrous toluene (10 mL). The reaction mixture was heated at reflux temperature for 3 days under an atmosphere of dry nitrogen whilst being monitored by TLC and concentrated. Purification by silica chromatography (petroleum ether/ ethyl acetate: 3/1, R_f = 0.23), yielded the product as a brown oil (91 mg, 75%).

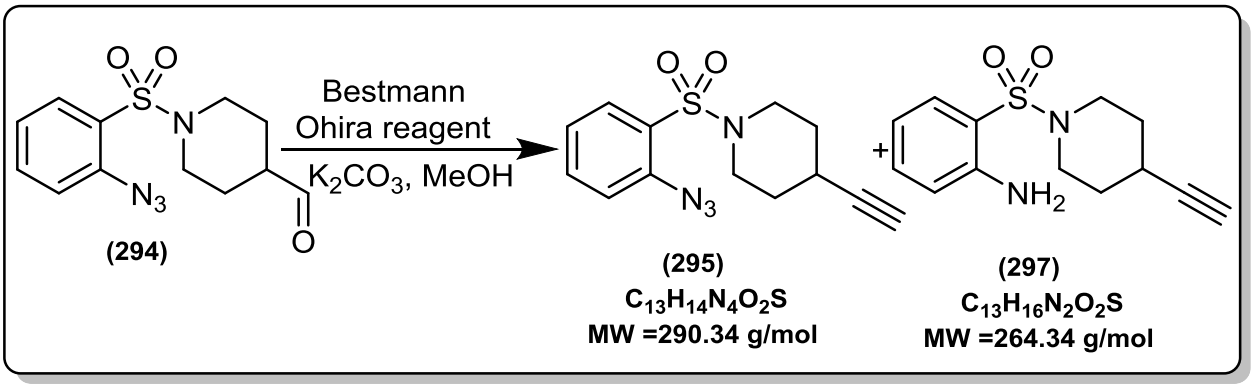
IR: υ_{max} (cm^{-1}): 839.6, 909.1, 1086.3, 1139.8, 1319.2, 1453.5, 1483.4, 1616.9, 2156.4, 2979.9, 3304.1, 3375.7, 3485.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.05 (3H, t, *J*=7.2 Hz, C***H*$_3$**), 1.66-1.73 (2H, m, NCH_2C***H*$_2$**), 1.87 (1H, t, *J*=2.6 Hz, C-***H***), 2.12 (2H, td, J^1=7.0 Hz, J^2=2.6 Hz, HCC-C***H*$_2$**), 3.19-3.24 (4H, m, C***H*$_2$**NC***H*$_2$**), 4.95 (2H, br.s, N***H*$_2$**), 6.63 (1H, d, *J*=8.0 Hz, Ar***H***), 6.67 (1H, d, *J*= 7.8 Hz, Ar***H***), 7.19 (1H, app. td, J^1=7.8 Hz, J^2=1.3 Hz, Ar***H***), 7.54 (1H, dd, J^1=8.0 Hz, J^2=1.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.63 (CH_3), 15.75 (CH_2), 27.39 (CH_2), 42.44 (CH_2), 45.83 (CH_2), 68.97 (C-H), 83.28 (qC), 117.32 (CH), 117.65 (CH), 121.36 (qC), 129.89 (CH), 133.87 (CH), 145.69 (qC) ppm.

HRMS (ESI^+): found 267.1167 $[M+H]^+$, $C_{13}H_{19}N_2O_2S$ requires 267.1162.

7.1.12. Attempted synthesis of 5,6-dihydro-4*H*-4,7-ethanobenzo[*h*][1,2,3]triazolo[5,1-*f*][1,2,7]thiadiazonine 8,8-dioxide.



The aldehyde (200 mg, 0.68 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (187 mg, 1.36 mmol, 2.0 eq) and the Bestmann-Ohira reagent (195 µL, 156 mg, 0. 816 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography gave two products:

First product (295): 1-[(2-azidophenyl)sulfonyl]-4-ethynylpiperidine.

(Petroleum ether/ethyl acetate: 1/2, R_f = 0.24) yielded the product as a light yellow oil (125 mg, 64 %).

IR: υ_{max} (cm^{-1}): 761.0, 817.6, 936.0, 1039.0, 1068.8, 1123.2, 1265.2, 1309.9, 1325.1, 1443.5, 1471.6, 1573.9, 1584.7, 2099.1, 2131.0, 2854.4, 2925.5, 3276.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.61-1.69 (2H, m, CH_2CHCH_2), 1.79-1.86 (2H, m, CH_2CHCH_2), 2.03 (1H, br.s, CC***H***), 2.49-2.54 (1H, m, CH_2CHCH_2), 3.08-3.14 (2H, m, CH_2NCH_2), 3.41-3.47 (2H, m, CH_2NCH_2), 7.16 (1H, dd, J^1=8.0 Hz, J^2=7.6 Hz, Ar***H***), 7.23 (1H, d, *J*= 8.0 Hz, Ar***H***), 7.51 (1H, app. td, J^1=8.0 Hz, J^2=1.0 Hz, Ar***H***), 7.87 (1H, d, *J*=8.0 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 29.00 (CH), 31.07 (2 x CH_2), 44.06 (2 x CH_2), 70.23 (CH), 85.55 (qC), 119.93 (CH), 124.65 (CH), 129.40 (qC), 131.72 (CH), 133.89 (CH), 138.29 (qC) ppm.

HRMS (ESI^+): found 291.0910 $[M+H]^+$, $C_{13}H_{15}N_4O_2S$ requires 291.0910.

Second product (297): 2-[(4-ethynylpiperidin-1-yl)sulfonyl]aniline.

(Petroleum ether/ethyl acetate: 1/1, R_f = 0.23) yielded the product as a yellow oil (25 mg, 14 %).

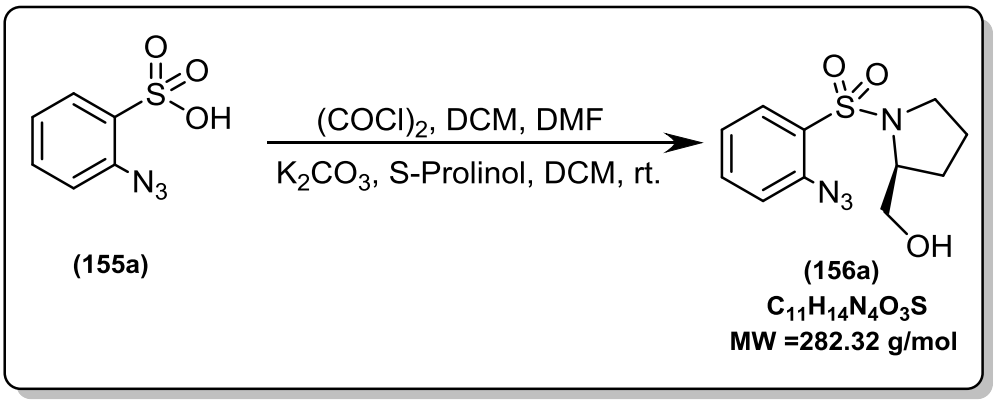
IR: υ_{max} (cm^{-1}): 732.9, 839.7, 928.4, 1039.0, 1087.4, 1113.2, 1142.2, 1248.3, 1320.7, 1338.0, 1452.3, 1483.3, 1566.4, 1615.6, 2124.0, 2851.6, 2925.7, 3285.3, 3377.1, 3481.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.59-1.68 (2H, m, CH_2CHCH_2), 1.78-1.84 (2H, m, CH_2CHCH_2), 1.99 (1H, d, *J*=2.3 Hz, CC***H***), 2.37-2.42 (1H, m, CH_2CHCH_2), 2.87 (2H, td, J^1=11.7 Hz, J^2=3.2 Hz, CH_2NCH_2), 3.32-3.37 (2H, m, CH_2NCH_2), 4.98 (2H, br.s, N***H***$_2$), 6.65 (1H, d, *J*=7.9 Hz, Ar***H***), 6.68(1H, d, *J*= 7.9 Hz, Ar***H***), 7.22 (1H, dd, J^1=7.9 Hz, J^2=6.7 Hz, Ar***H***), 7.48 (1H, d, *J*=7.9 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.94 (CH), 30.66 (2 x CH_2), 44.25 (2 x CH_2), 70.06 (CH), 85.59 (qC), 117.20 (CH), 117.66 (CH), 118.00 (qC), 130.24 (CH), 134.17 (CH), 146.23 (qC) ppm.

HRMS (ESI^+): found 265.1004 $[M+H]^+$, $C_{13}H_{17}N_2O_2S$ requires 265.1005.

7.1.13. Synthesis of (*S*)-[1-(2'-azidobenzenesulfonyl)pyrrolidin-2-yl] methanol.



2-Azidobenzenesulfonic acid (1.475 g, 7.425 mmol, 2.5 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in dichloromethane (7.4 mL, 14.8 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (1.65 g, 11.88 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of S-prolinol (300 mg, 2.970 mmol, 1.0 eq) in dichloromethane (10 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 1/10, Rf = 0.2] to yield the product as a yellow oil (600 mg, 72 %).

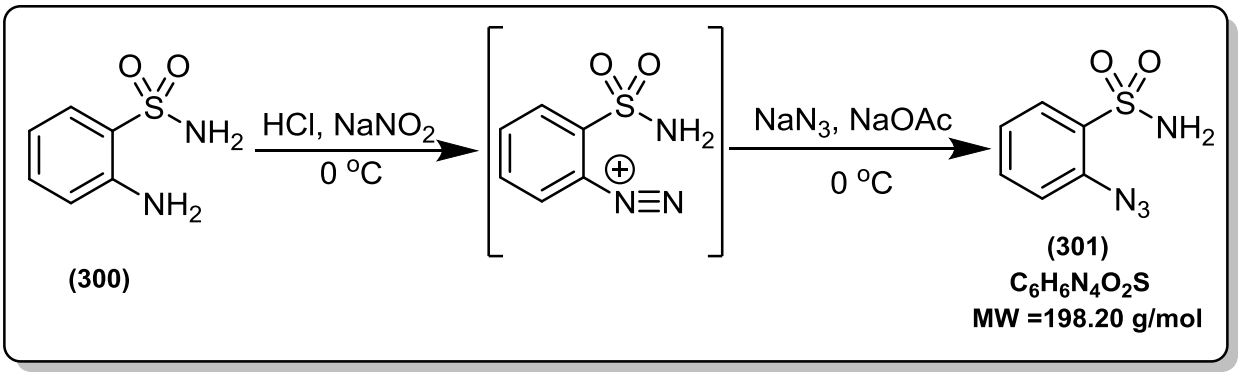
IR: υ_{max} (cm^{-1}): 575.3, 600.1, 649.3, 728.2, 769.4, 820.5, 864.2, 897.4, 997.5, 1018.6, 1064.6, 1141.8, 1198.1, 1305.1, 1466.5, 1572.5, 1581.5, 2101.4, 2872.4, 2963.4, 3081.6, 3438.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.68-1.77 (1H, m, C***H***H), 1.79-1.88 (1H, m, CH**H**), 1.90-2.00 (2H, m, C$\mathbf{H_2}$), 2.72 (1H, bs, CH_2O***H***), 3.30-3.49 (1H, m, NC***H***), 3.52-3.59 (1H, m, NCH***H***), 3.61-3.66 (1H, m, NC***H***H), 3.70-3.74 (1H, m, HOCH***H***), 4.02-4.08 (1H, m, HOC***H***H), 7.28 (1H, dd, J^1=8.1 Hz, J^2=7.0 Hz, Ar**H**), 7.33 (1H, dd, *J*= 8.0 Hz, Ar**H**), 7.62 (1H, ddd, J^1=8.1 Hz, J^2=7.0 Hz, J^3=1.1 Hz, Ar**H**), 8.04 (1H, dd, *J*=8.0 Hz, J=1.1 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 24.67 (CH_2), 29.05 (CH_2), 49.52 (CH_2), 61.83 (CH), 65.48 (CH_2), 119.91 (CH), 124.80 (CH), 129.04 (qC), 132.59 (CH), 134.21 (CH), 138.20 (qC) ppm.

HRMS (ESI$^+$): found 283.0855 $[M+H]^+$, $C_{11}H_{15}N_5O_3S$ requires 283.0859.

7.1.14. Synthesis of 2-azidobenzenesulfonamide.



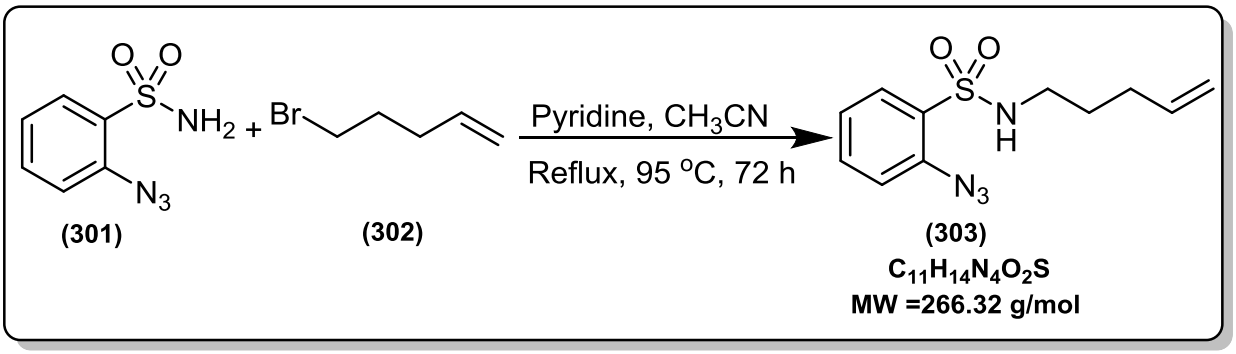
To a solution of 2-aminobenzenesulfonamide[237] (5 g, 29 mmol, 1.0 eq) in concentrated HCl (45 mL) and water (45 mL) at 0 °C, was added, with stirring, a solution of $NaNO_2$ (2.18 g, 31.97 mmol, 1.1 eq) in water (10 mL) cooled to 0 °C dropwise over 10 minutes and the whole stirred for a further hour before a cooled solution of NaN_3 (1.89 g, 29 mmol, 1.1 eq) and sodium acetate (60 g) in water (100 mL) was added dropwise over an hour. The precipitate formed was filtered by vacuum, washed thoroughly with water (60 mL) and dried in the oven at 80-100 °C to give the product as a fawn coloured solid (4.7 g, 82 %). (m.p. =182-184 °C, Lit. m.p.=176 °C[238]).

IR: υ_{max} (cm^{-1}): 767.3, 817.7, 884.2, 1064.1, 1080.8, 1155.0, 1282.6, 1331.4, 1446.6, 1555.9, 1577.9, 2095.6, 3252.7, 3354.1.

^{1}H NMR: δ_H (400 MHz, DMSO): 7.30-7.35 (3H, m, N**H$_2$**+ Ar**H**), 7.54 (1H, d, *J*= 7.8 Hz, Ar**H**), 7.66 (1H, app. td, J^1= 7.7 Hz, J^2=1.4 Hz, Ar**H**), 7.83 (1H, dd, J^1= 7.8 Hz, J^2= 1.4 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 121.20 (CH), 125.17 (CH), 128.45 (CH), 133.93 (CH), 134.23 (qC), 137.36 (qC) ppm.

7.1.15. Synthesis of 2-azido-*N*-(pent-4-en-1-yl)benzenesulfonamide.



To a solution of 2-azidobenzenesulfonamide (198 mg, 1.0 mmol, 1.0 eq) in CH_3CN (10 mL), 5-bromo-1-pentene (149 mg, 1.0 mmol, 1.0 eq) and pyridine (79 mg, 1.0 mmol, 1.0 eq) were added. The mixture was heated at 95 ^oC for 72 hours under a nitrogen atmosphere whilst being monitored by TLC. The reaction was diluted with water (10 mL) and the mixture was extracted with DCM (3 x 15 mL). The combined organic layer was dried over with anhydrous $MgSO_4$, filtered and concentrated. Purification by silica chromatography (eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.3) yielded the product as a light yellow oil (20 mg, 8 %).

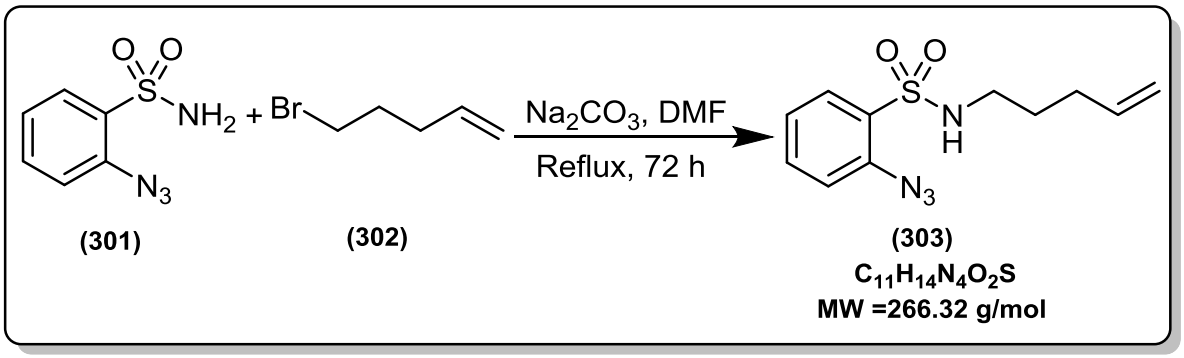
IR: υ_{max} (cm^{-1}): 731.0, 820.3, 914.7, 1067.1, 1125.3, 1161.5, 1290.8, 1329.0, 1415.2, 1471.4, 1575.0, 1640.5, 2133.4, 2854.3, 2926.5, 3073.9, 3299.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.52 (2H, p, *J*=7.2 Hz, C**H$_2$**), 2.00 (2H, q, *J*=7.0 Hz, C**H$_2$**), 2.83 (2H, q, *J*=6.8 Hz, C**H$_2$**), 4.88-4.96 (3H, m, N-**H**, =C**H$_2$**), 5.59-5.70 (1H, m, =C**H**), 7.18-7.24 (2H, m, 2 x Ar**H**), 7.53 (1H, app. td, J^1= 7.8 Hz, J^2=1.3 Hz, Ar**H**), 7.91 (1H, dd, J^1= 7.8 Hz, J^2=1.1 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 28.66 (CH_2), 30.67 (CH_2), 42.79 (CH_2), 115.62 (CH_2), 119.36 (CH), 124.91 (CH), 129.92 (qC), 130.76 (CH), 133.96 (CH), 137.19 (CH), 137.46 (qC) ppm.

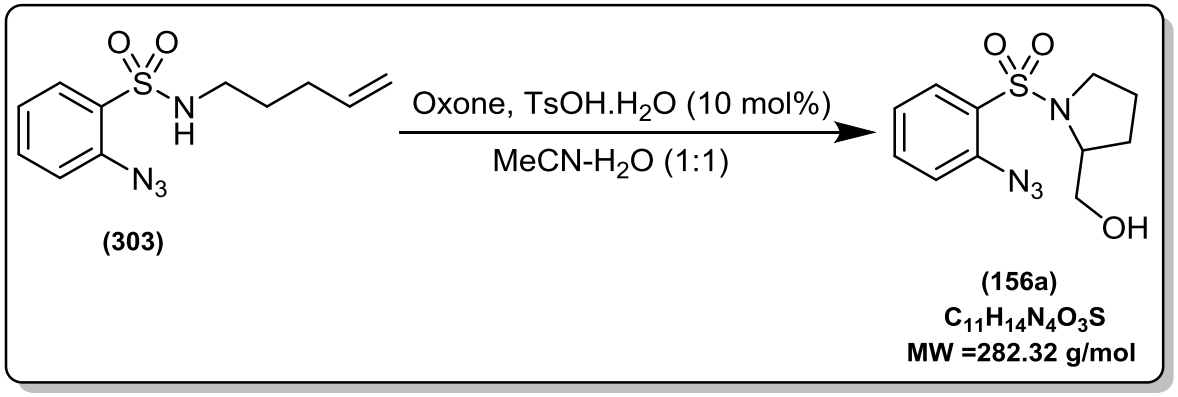
HRMS (ESI$^+$): found 289.0730 $[M+Na]^+$, $C_{11}H_{14}N_4O_2SNa$ requires 289.0730.

7.1.16. Synthesis of 2-azido-*N*-(pent-4-en-1-yl)benzenesulfonamide.



To a solution of 2-azidobenzenesulfonamide (198 mg, 1.0 mmol, 1.0 eq) in DMF (10 mL) cooled to 0 ^{o}C, 5-bromo-1-pentene (149 mg, 1.0 mmol, 1.0 eq) and Na_2CO_3 (212 mg, 2.0 mmol, 1.0 eq) were added. The mixture was heated at reflux temperature for 72 hours under a nitrogen atmosphere whilst being monitored by TLC. The reaction was diluted with $NaCl_{(aq)}$ (20 mL) and the mixture was extracted with DCM (3 x 15 mL). The combined organic layer was dried over with anhydrous $MgSO_4$, filtered and concentrated. Purification by silica chromatography (eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.3) yielded the product as a light yellow oil (8 mg, 3 %), with data identical to that above.

7.1.17. Synthesis of {1-[(2-azidophenyl)sulfonyl]pyrrolidin-2-yl}methanol.



To a solution of 2-azido-N-(pent-4-en-1-yl)benzenesulfonamide (20 mg, 0.075 mmol, 1.0 eq) and Oxone (35 mg, 0.113 mmol, 1.5 eq) in a 1:1 mixture (5 mL) of acetonitrile and water was added p-toluenesulfonic acid monohydrate (2.9 mg, 0.015 mmol, 0.2 eq). The whole was heated at reflux temperature for 12 hours, whilst being monitored by TLC. To this solution,

saturated aqueous $NaHCO_3$ solution (15 mL) was added and the product was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Purification by silica chromatography (eluent: petroleum ether/ethyl acetate: 1/10, R_f = 0.2) yielded the product as a yellow oil (20 mg, 95 %).

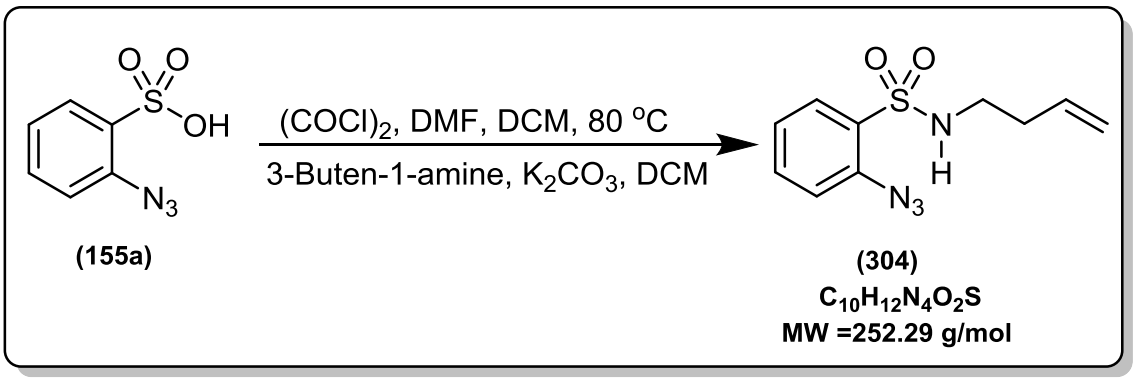
IR: υ_{max} (cm^{-1}): 732.2, 820.0, 1018.6, 1064.6, 1141.8, 1199.8, 1305.1, 1472.0, 1574.6, 1581.5, 2101.4, 2872.4, 2963.4, 3081.6, 3525.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.61-1.68 (1H, m, C***H***H), 1.72-180 (1H, m, CH***H***), 1.81-1.98 (2H, m, C**H$_2$**), 2.70 (1H, bs, CH_2O***H***), 3.28-3.34 (1H, m, NC***H***), 3.44-3.50 (1H, m, NCH***H***), 3.53-3.60 (1H, m, NC***H***H), 3.62-3.66 (1H, m, HOCH***H***), 3.94-4.00 (1H, m, HOC***H***H), 7.28 (1H, dd, J^1=8.1 Hz, J^2=7.0 Hz, Ar**H**), 7.33 (1H, dd, *J*= 8.0 Hz, Ar**H**), 7.62 (1H, ddd, J^1=8.1 Hz, J^2=7.0 Hz, J^3=1.1 Hz, Ar**H**), 8.04 (1H, dd, *J*=8.0 Hz, J=1.1 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 24.67 (CH_2), 29.06 (CH_2), 49.53 (CH_2), 61.84 (CH), 65.49 (CH_2), 119.90 (CH), 124.80 (CH), 129.08 (qC), 132.59 (CH), 134.20 (CH), 138.22 (qC) ppm.

HRMS (ESI^+): found 305.0674 $[M+Na]^+$, $C_{11}H_{14}N_5O_3SNa$ requires 305.0679.

7.1.18. Synthesis of 2-azido-*N*-(but-3-en-1-yl)benzenesulfonamide.



2-Azidobenzenesulfonic acid (2.462 g, 12.37 mmol, 2.2 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in dichloromethane (14.06 mL, 28.12 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was allowed to reach room

temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (3.109 g, 22.50 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of 4-amino-1-butene (400 mg, 5.624 mmol, 1.0 eq) in dichloromethane (10 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 3/1, R_f = 0.25] to yield the product as a pale yellow oil (1.0 g, 78 %).

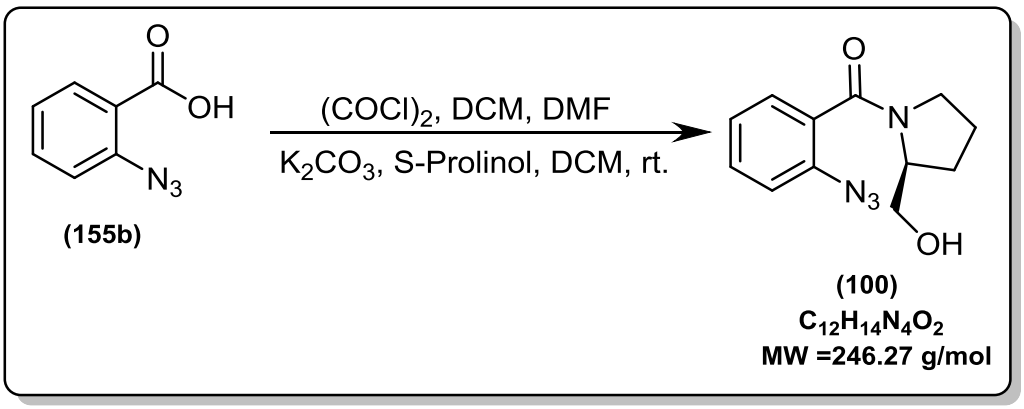
IR: υ_{max} (cm^{-1}): 756.4, 819.0, 916.1, 1066.1, 1124.3, 1243.8, 1288.4, 1326.9, 1411.6, 1443.7, 1470.8, 1574.4, 1641.1, 2129.9, 2980.1, 3076.5, 3303.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.25 (2H, app. q, *J*=6.6 Hz, C**H**$_2$), 2.99 (2H, app. q, *J*=6.5 Hz, C**H**$_2$), 5.00-5.14 (3H, m, NH, =C**H**$_2$), 5.61-5.72 (1H, m, =C**H**), 7.28 (1H, d, *J*=7.7 Hz, Ar**H**), 7.32 (1H, d, *J*= 7.7 Hz, Ar**H**), 7.63 (1H, ddd, J^1= 7.7 Hz, J^2=7.0 Hz, J^3=1.3 Hz, Ar**H**), 8.00 (1H, d, *J*= 7.7 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 33.52 (CH_2), 42.39 (CH_2), 118.04 (CH_2), 119.38 (CH), 124.89 (CH), 129.85 (qC), 130.73 (CH), 133.99 (CH), 134.28 (CH), 137.51 (qC) ppm.

HRMS (ESI$^+$): found 275.0574 $[M+Na]^+$, $C_{10}H_{12}N_4O_2SNa$ requires 275.0573.

7.1.19. Synthesis of (2-azidophenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone.



2-Azidobenzoic acid (358 mg, 2.2 mmol, 2.2 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in dichloromethane (2.5 mL, 5.0 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude 2-azidobenzoyl chloride as a dark brown solid.

A solution of potassium carbonate (552 mg, 4.0 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of S-prolinol (101 mg, 1.0 mmol, 1.0 eq) in dichloromethane (10 mL). The 2-azidobenzoyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 1/2, Rf = 0.23] to yield the product as a light yellow solid (200 mg, 81 %, m.p.=100-101 ^oC, lit. m.p.=98-100 ^oC[120]).

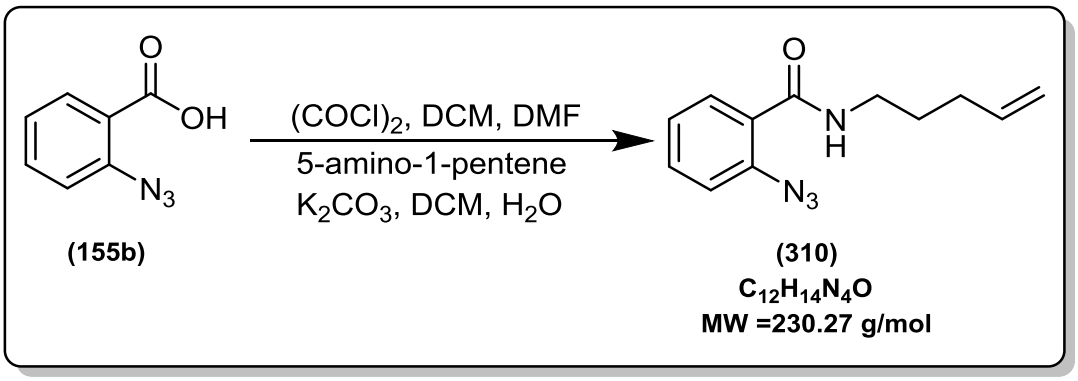
IR: υ_{max} (cm^{-1}): 769.2, 945.4, 1032.0, 1083.8, 1169.3, 1210.1, 1290.8, 1454.6, 1597.1, 2089.8, 2980.8, 3291.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.66-1.93 (3H, m, C***H*****$_2$** + C***H***H), 2.15-2.23 (1H, m, CH***H***), 3.23-3.34 (2H, m, N-C***H*****$_2$**), 3.72-3.77 (1H, m, HO-C***H***H), 3.84-3.87 (1H, m, HO-CH***H***), 4.36 (1H, dq, J^1=10.1 Hz, J^2=2.7 Hz, NC***H***), 3.83 (1H, bs, O***H***), 7.10-7.22 (2H, m, 2 x Ar***H***), 7.32 (1H, dd, J^1=8.1 Hz, J^2=1.3 Hz, Ar***H***), 7.45 (1H, app. dt, J^1=8.1 Hz, J^2=1.6 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 24.51 (CH_2), 28.62 (CH_2), 49.64 (CH_2), 61.35 (CH), 66.63 (CH_2OH), 118.53 (CH), 125.27 (CH), 127.77 (CH), 129.32 (qC), 130.68 (CH), 136.07 (qC), 169.05 (C=O) ppm.

HRMS (ESI^+): found 247.1185 $[M+ H]^+$, $C_{12}H_{15}N_4O_2$ requires 247.1190.

7.1.20. Synthesis of 2-azido-*N*-(pent-4-en-1-yl)benzamide



2-Azidobenzenesulfonic acid (717mg, 4.4 mmol, 2.2 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in dichloromethane (5.0 mL, 10.0 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude 2-azidobenzoyl chloride as a dark brown solid.

A solution of potassium carbonate (1.104 g, 8.0 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of 5-amino-1-pentene[188] (170 mg, 2.0 mmol, 1.0 eq) in dichloromethane (10 mL). The 2-azidobenzoyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 1/4, R_f = 0.25] to yield the product as ayellow oil (330 mg, 72 %).

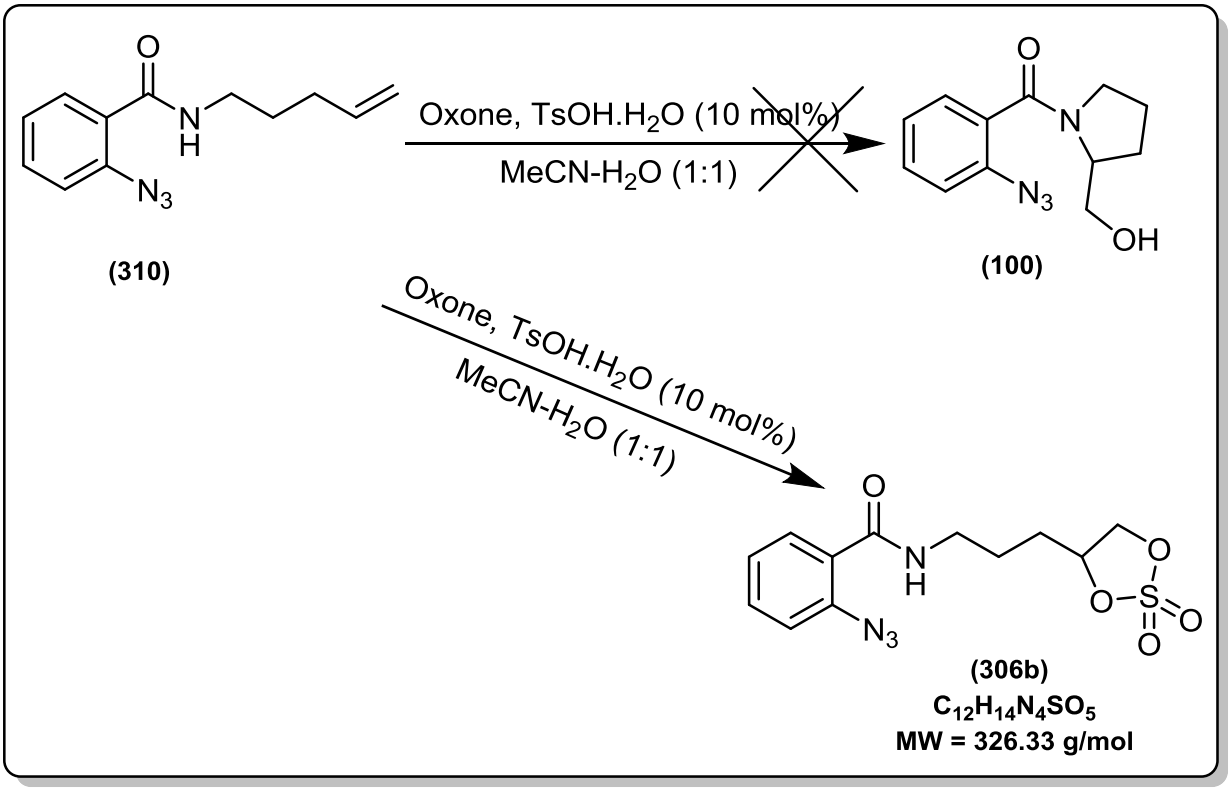
IR: υ_{max} (cm^{-1}): 785.7, 943.8, 993.5, 1164.2, 1293.5, 1444.8, 1480.3, 1536.2, 1577.2 1638.5, 1712.4, 2124.9, 2863.6, 2930.4, 3075.9, 3293.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.66 (2H, p, *J*=7.2 Hz, -$CH_2C\boldsymbol{H_2}CH_2$-), 2.09 (2H, q, *J*=7.3 Hz, $C\boldsymbol{H_2}CH{=}CH_2$), 3.37-3.42 (2H, m, $NHC\boldsymbol{H_2}$), 4.92 (1H, dd, J^1=10.2 Hz, J^2=1.6 Hz, CH=C***H***H), 4.99 (1H, J^1= 17.1 Hz, J^2=1.6 Hz, CH=CH***H***), 5.70-5.82 (1H, m, C***H***=CH_2), 7.10 (1H, dd, J^1=7.8 Hz, J^2=0.8 Hz, Ar***H***), 7.14 (1H, ddd, J^1=7.8 Hz, J^2=7.4 Hz, J^3=1.6 Hz, Ar**H**), 7.40 (2H, ddd, J^1=7.8 Hz, J^2=7.4 Hz, J^3=1.6 Hz, 2 x Ar**H**), 8.04 (1H, dd, J^1= 7.8 Hz, J^2=1.6 Hz, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 28.64 (CH_2), 31.25 (CH_2), 39.54 (CH_2), 115.22 (=CH_2), 118.37 (CH), 125.17 (CH), 125.26 (qC), 132.17 (CH), 132.19 (CH), 136.82 (qC), 137.79 (CH), 164.58 (C=O) ppm.

HRMS (ESI$^+$): found 231.1238 $[M+H]^+$, $C_{12}H_{15}N_4O$ requires 231.1240.

7.1.21. Attempted synthesis of (2-azidophenyl)(2-(hydroxymethyl)pyrrolid-in-1-yl)methanone.



To a solution of 2-azido-N-(pent-4-en-1-yl)benzamide (100 mg, 0.434mmol, 1.0 eq) and Oxone (200 mg, 0.652 mmol, 1.5 eq) in a 1:1 mixture (10 mL) of acetonitrile and water was added p-toluenesulfonic acid monohydrate (17 mg, 0.087 mmol, 0.2 eq). The whole was heated at reflux temperature for 12 hours, whilst being monitored by TLC. To this solution, saturated aqueous $NaHCO_3$ solution (15 mL) was added and the product was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by using silica chromatography (eluent: petroleum ether/ethyl acetate: 1/2, R_f = 0.2) yielded the product as a light yellow oil (64 mg, 60 %).

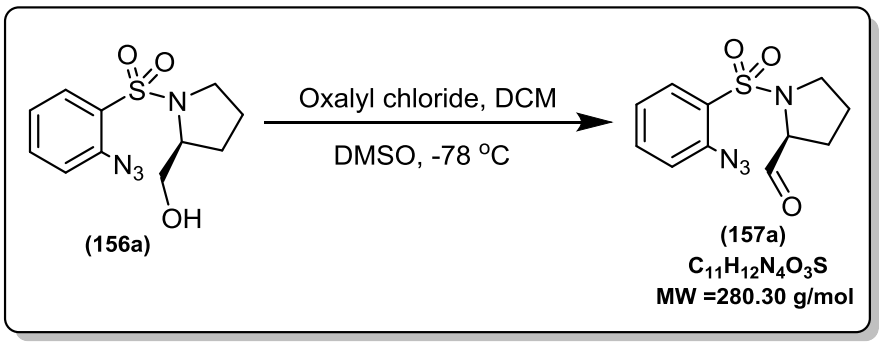
IR: υ_{max} (cm^{-1}): 752.7, 1090.0, 1164.4, 1291.6, 1444.5, 1480.2, 1537.4, 2597.2, 1632.6, 1712.4, 2125.8, 2928.3, 3360.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.50-1.99 (4H, m, 2 x C***H*$_2$**), 3.32-3.56 (4H, m, 2 x C**H**$_2$), 3.76-3.83 (2H, m, O-C***H***), 7.12 (1H, d, *J*=7.7 Hz, Ar***H***), 7.16 (1H, dd, J^1= 7.7 Hz, J^2=7.5 Hz, Ar***H***), 7.42 (1H, dd, J^1=7.8 Hz, J^2=1.1 Hz, Ar***H***), 7.51 (1H, bs, NH), 8.03 (1H, d, *J*=7.8 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.93 (CH_2), 32.12 (CH_2), 50.20 (CH_2), 58.24 (OCH), 67.04 (OCH_2), 71.12 (CH), 118.42 (CH), 125.00 (qC), 125.22 (CH), 132.17 (CH), 132.37 (CH), 136.92 (qC), 164.94 (C=O) ppm.

HRMS (ESI^+): found 326.0375 $[M]^+$, $C_{12}H_{14}N_4O_5S$ requires 326.0378.

7.1.22. Synthesis of [1-(2'-azidobenzenesulfonyl)pyrrolidin-2-yl]carbalde-hyde.



A 2M solution of oxalyl chloride in dichloromethane (0.94 mL, 1.68 mmol, 1.2 eq) was diluted with dichloromethane (5 mL) and cooled to -78 ^{o}C under nitrogen. DMSO (0.26 mL, 265 mg, 3.40 mmol, 2.4 eq) in dichloromethane (5 mL) and the alcohol (400 mg, 1.42 mmol, 1 eq) in dichloromethane (2.5 mL) were added respectively, each over 10 mins. The whole was maintained at -78 ^{o}C for 30 minutes before dropwise addition of triethylamine (1.09 mL, 0.78 g, 7.09 mmol, 5 eq) and the whole was allowed to reach room temperature. The reaction was quenched with a mixture of diethyl ether (5 mL) and water (5 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtrered, concentrated and purified on silica (20g)

(petroleum ether/ethyl acetate: 3/2, Rf = 0.2) to yield the product as a white solid (383 mg, 96 %, m.p.=103 - 105 °C).

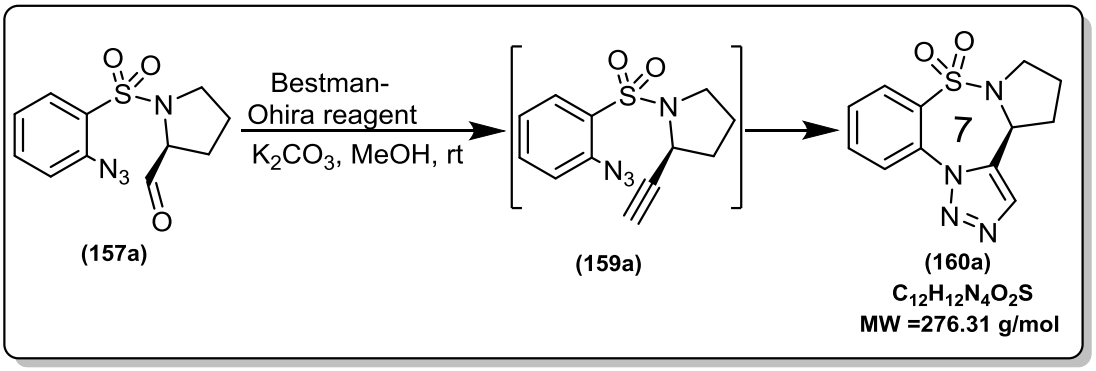
IR: υ_{max} (cm^{-1}): 716.5, 771.1, 1079.4, 1150.6, 1323.1, 1434.8, 1468.9, 1572.3, 1731.7, 2122.2, 2887.6, 2976.8, 3100.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.81-1.95 (2H, m, C**H**$_2$), 2.00-2.09 (1H, m, C***H***H), 2.14-2.23 (1H, m, CH***H***), 3.38-3.44 (1H, m, NC***H***H), 3.55-3.60 (1H, m, CH***H***), 4.46-4.49 (1H, m, NC**H**), 7.28 (1H, ddd, J^1=7.5 Hz, J^2=7.1 Hz, J^3=1.5 Hz, Ar**H**), 7.34 (1H, d, J=8.0 Hz, Ar**H**), 7.64 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar**H**), 8.04 (1H, d, J=8.0 Hz, Ar**H**), 9.7 (1H, s, C**H**O).

^{13}C NMR δ_c (100 MHz, DMSO): 24.99 (CH_2), 27.70 (CH_2), 48.80 (CH_2), 67.08 (CH), 119.88 (CH), 124.86 (CH), 128.97 (qC), 132.50 (CH), 134.38 (CH), 138.24 (qC), 200.42 (CH).

HRMS (ESI^+): found 281.0697 [M+H]+, $C_{11}H_{13}N_4O_3S$ requires 281.0703.

7.1.23. Synthesis of (*S*)-pyrrolo[1,2-*b*][1,2,3]triazolo[5,1-*d*][1,2,5] benzothiadiazepin 8,8-dioxide.



The aldehyde (300 mg, 1.07 mmol, 1 eq) was dissolved in dry methanol (5 mL); potassium carbonate (296 mg, 2.14 mmol, 2 eq) and the Bestmann-Ohira reagent (209 µL, 247 mg, 1.29 mmol, 1.2 eq) were added and the whole was stirred for 22 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an

orange solid. Purification by silica chromatography (20 g) (petroleum ether/ethyl acetate: 1/3, Rf = 0.22) yielded the product as a yellow solid (207 mg, 70 %, m.p.= 208-210 ^{o}C).

IR: υ_{max} (cm^{-1}): 745.8, 809.4, 998.4, 1050.2, 1195.3, 1242.7, 1336.2, 1482.9, 1592.3, 2870.1, 2991.8, 3108.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.53-1.63 (1H, m, C***H***H), 1.77-1.85 (1H, m, CH***H***), 1.87-1.98 (1H, m, C***H***H), 2.14-2.21 (1H, m, CH***H***), 2.98-3.04 (1H,m, C***H***H), 3.54-3.59 (1H, m, CH***H***), 5.06-5.10 (1H, m, NCH), 7.51 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.67 (1H, s, C***H***NN), 7.72 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.99 (1H, d, *J*=7.8 Hz, Ar**H**), 8.05 (1H, d, *J*=7.8 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.42 (CH_2), 35.45 (CH_2), 49.96 (CH_2), 55.09 (CH), 125.41 (CH), 128.61 (CH), 129.32 (CH), 130.94 (qC),133.54 (qC), 134.03 (CH), 134.37 (CH), 136.77 (qC) ppm.

HRMS (ESI^+): found 277.0754 $[M+H]^+$, $C_{12}H_{13}N_4O_2S$ requires 277.0754.

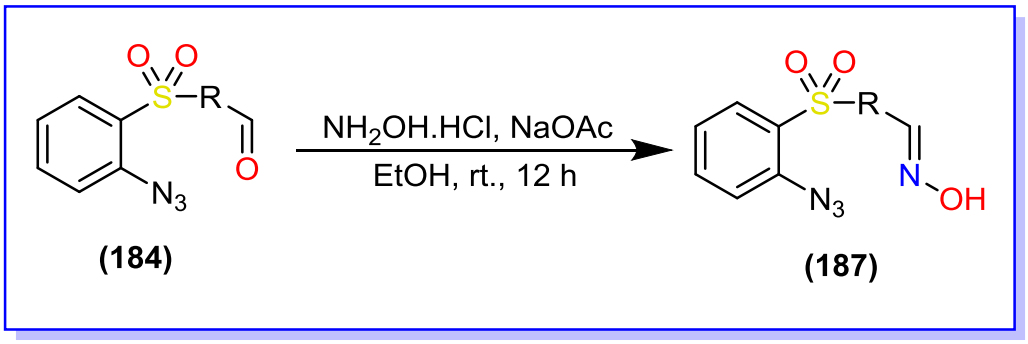
Chapter 7:

7-Experimental: Triazolo and Tetrazolobenzothiadiazepines and benzodiazepines.

7.2. The synthesis of Tetrazolobenzothiadiazepines.

7.2.1. Conversion of the aldehydes into the oximes.

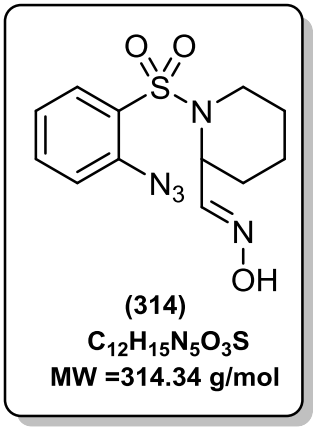
General experimental:



(184) (187)

To a mixture of hydroxylamine hydrochloride (278 mg, 4.0 mmol, 4.0 eq) and sodium acetate (492 mg, 6.0 mmol, 6.0 eq) in ethanol (25 mL) was added, at room temperature with vigorous stirring, the aldehyde (1.0 mmol, 1.0 eq). The reaction mixture was stirred for 5 hours, filtered in vacuo to remove the precipitate and the solvent was evaporated off. The residue was extracted with dichloromethane (2 x 15 mL), washed with water (2 x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered in vacuo and the solvent evaporated off and purified by silica chromatography.

7.2.1.1. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-2-carbaldehyde oxime.



(314)
$C_{12}H_{15}N_5O_3S$
MW =314.34 g/mol

(Eluent: Petroleum ether/ethylacetate: 3/2, R_f = 0.2) yielded the product as a light yellow oil (68 %).

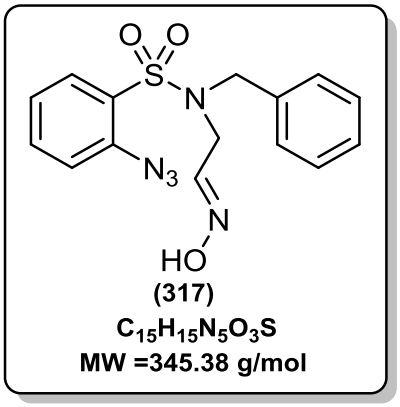
IR: υ_{max} (cm^{-1}): 753.3, 921.3, 945.1, 1070.3, 1158.1, 1289.9, 1334.2, 1471.5, 1575.0, 2100.3, 2860.0, 2941.9, 3021.4, 3244.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.26 (1H, t, *J*=7.2 Hz, CH***H***), 1.36-1.42 (1H, m, C***H***H), 1.54-1.61 (1H, m, C***H***H), 1.66-1.74 (3H, m, CH**H** + C**H$_2$**), 2.12 (1H, d, *J*=12.0 Hz, NC***H***), 3.16 (1H, td, J^1=13.5 Hz, J^2=2.3 Hz, NC***H***H), 3.93 (1H, d, *J*=13.5 Hz, NCH***H***), 6.84 (1H, d, *J*=5.7 Hz, =C***H***), 7.21 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar***H***), 7.28 (1H, d, *J*=7.8 Hz, Ar**H**), 7.57 (1H, ddd, J^1=8.0 Hz, J^2=7.5 Hz, J^3=1.4 Hz, Ar**H**), 7.96 (1H, dd, J^1=8.0 Hz, J^2= 1.3 Hz, Ar**H**), 9.01 (1H, br.s, O**H**).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.73 (CH_2), 25.54 (CH_2), 28.00 (CH_2), 42.83 (CH_2), 49.33 (CH), 119.85 (CH), 124.57 (CH), 130.40 (qC), 131.42 (CH), 134.02 (CH), 138.03 (qC), 149.71 (CH) ppm.

HRMS (ESI^+): found 332.0788 $[M+Na]^+$, $C_{12}H_{15}N_5O_3SNa$ requires 332.0788.

7.2.1.2. Synthesis of 2-azido-*N*-benzyl-*N*-[2-(hydroxyimino)ethyl] benzenesulfonamide.



(Eluent: Petroleum ether/ethylacetate: 2/1, R_f = 0.25) yielded the product as a white solid (96 %, m.p.=129-130 ^oC).

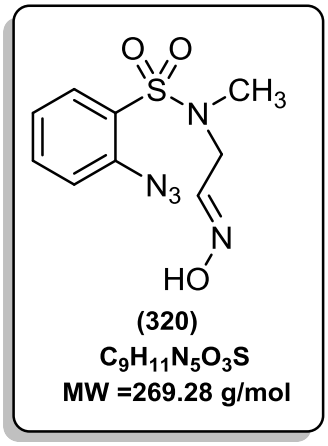
IR: υ_{max} (cm^{-1}): 763.1, 911.6, 932.5, 1148.0, 1163.0, 1336.5, 1349.3, 1471.5, 2098.5, 3213.7.

^{1}H NMR: δ_H (400 MHz, DMSO): 4.05 (2H, d, *J*=2.4 Hz, N=CH-C***H*$_2$**), 4.54 (2H, br.s, NC***H*$_2$**), 6.43 (1H, dd, J^1=3.7 Hz, J^2=1.1 Hz, N=C***H***), 7.22-7.38 (6H, m, 6 x Ar***H***), 7.58 (1H, d, *J*=8.3 Hz, Ar***H***), 7.74 (1H, t, *J*= 7.7 Hz, Ar***H***), 7.92 (1H, d, *J*=7.7 Hz, Ar***H***), 11.14 (1H, d, *J*=1.80 Hz, O***H***) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 46.3 (CH_2), 52.54 (CH_2), 121.52 (CH), 125.44 (CH), 128.25 (CH), 128.71 (2CH), 129.06 (2CH), 130.46 (qC), 131.26 (CH), 135.12 (CH), 136.79 (qC), 138.20 (qC), 147.42 (CH) ppm.

HRMS (ESI^+): found 346.0970 $[M+H]^+$, $C_{15}H_{16}N_5O_3S$ requires 346.0968.

7.2.1.3. Synthesis of 2-azido-*N*-[2-(hydroxyimino)ethyl]-*N*-methylbenzenesulfonamide.



(320)
$C_9H_{11}N_5O_3S$
MW =269.28 g/mol

(Eluent: Petroleum ether/ethylacetate: 2/1, R_f = 0.23) yielded the product as a light yellow oil (78 %).

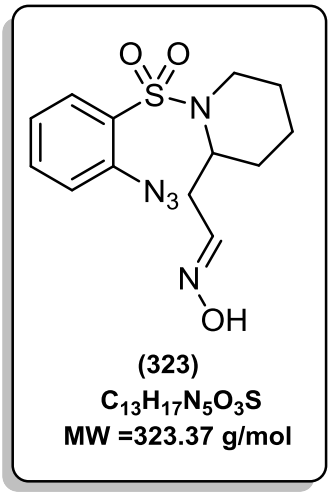
IR: υ_{max} (cm^{-1}): 724.2, 906.9, 939.9, 1059.0, 1144.6, 1257.7, 1288.2, 1330.8, 1471.6, 1575.1, 2129.7, 3427.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.82 (3H, s, C***H*$_3$***), 4.17 (2H, d, *J*=4.4 Hz, C***H*$_2$***), 7.17 (1H, app. td, J^1=7.7 Hz, J^2=1.0 Hz, Ar***H***), 7.23 (1H, ddd, J^1=8.0 Hz, J^2=7.7 Hz, J^3=2.2 Hz, Ar***H***), 7.31 (1H, t, *J*= 6.0 Hz, =C***H***), 7.53 (1H, dd, J^1=7.7 Hz, J^2=1.6 Hz, Ar***H***), 7.89 (1H, app. dt, J^1=8.0 Hz, J^2=1.6 Hz, Ar***H***), 8.77 (1H, br.s, O***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 34.53 (CH_3), 45.29 (CH_2), 119.93 (CH), 124.74 (CH), 129.11 (qC), 131.82 (CH), 134.26 (CH), 138.24 (qC), 147.22 (CH) ppm.

HRMS (ESI^+): found 270.0659 $[M+H]^+$, $C_9H_{12}N_5O_3S$ requires 270.0655.

7.2.1.4. Synthesis of 2-{1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}acetaldehyde oxime.



(323)
$C_{13}H_{17}N_5O_3S$
MW =323.37 g/mol

(Eluent: Petroleum ether/ethylacetate: 1/1, R_f = 0.3) yielded the product as a light yellow oil (88 %).

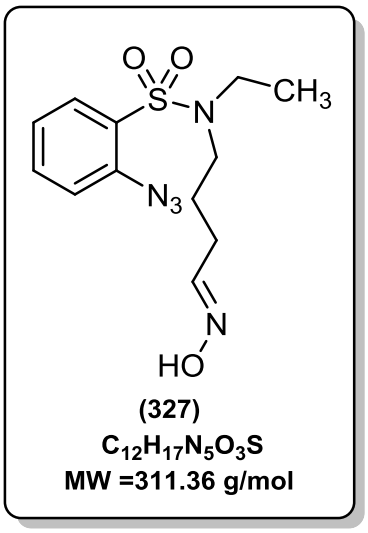
IR: υ_{max} (cm^{-1}): 725.9, 817.1, 948.1, 1069.3, 1121.3, 1155.6, 1183.0, 1265.4, 1288.3, 1322.5, 1443.1, 1470.9, 1574.5, 2098.7, 2942.7, 3247.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.16-1.66 (6H, m, 3 x C***H*₂**), 2.30-2.37 (1H, m, N=CH-C***H***H), 2.50-2.62 (1H, m, N=CH-CH***H***), 3.02 (1H, p, *J*=12.8 Hz, C***H***), 3.75-3.81 (1H, m, NCH***H***), 4.13-4.18 (1H, m, NC***H***H), 6.55 (1H, t, *J*=5.5 Hz, HO-N=C***H***), 7.14 (1H, ddd, J^1=8.3 Hz, J^2=7.9 Hz, J^3=1.5 Hz, Ar***H***), 7.21 (1H, d, *J*= 7.9 Hz, Ar***H***), 7.41-7.51 (1H, m, Ar***H***), 7.90 (1H, app. qd, J^1=7.9 Hz, J^2=1.3 Hz, Ar***H***), 8.75 (1H, br.s, O***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.26 (CH_2), 25.34 (CH_2), 27.95 (CH_2), 30.32 (CH_2), 41.00 (CH_2), 50.46 (CH), 120.00 (CH), 124.43 (CH), 131.04 (CH), 131.28 (qC), 133.71 (CH), 137.91 (qC), 148.79 (CH) ppm.

HRMS (ESI^+): found 324.1120 $[M+H]^+$, $C_{13}H_{18}N_5O_3S$ requires 324.1125.

7.2.1.5. Synthesis of 2-azido-*N*-ethyl-*N*-[4-(hydroxyimino)butyl] benzenesulfonamide.



(327)
$C_{12}H_{17}N_5O_3S$
MW =311.36 g/mol

(Eluent: Petroleum ether/ethylacetate: 3/2, R_f = 0.2) yielded the product as a light yellow oil (92 %).

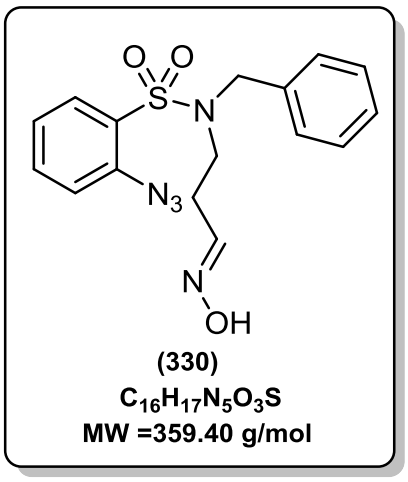
IR: υ_{max} (cm^{-1}): 682.1, 818.4, 907.9, 1005.4, 1060.2, 1144.8, 1155.4, 1288.4, 1329.0, 1443.0, 1471.4, 1575.1, 2098.5, 2936.8, 3446.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.03 (3H, p, *J*=7.0 Hz, C***H*****$_3$**), 1.70 (2H, p, *J*=7.4 Hz, NCH_2C***H*****$_2$**), 2.14 (1H, dd, J^1=13.5 Hz, J^2=7.4 Hz, NCH_2CH***H***), 2.27-2.32 (1H, m, NCH_2C***H***H), 3.28 (4H, app. p, *J*=7.4 Hz, C***H*****$_2$**NC***H*****$_2$**), 7.15 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar***H***), 7.21 (1H, d, *J*= 7.9 Hz, Ar***H***), 7.34 (1H, t, *J*=5.7 Hz, N=C***H***), 7.49 (1H, ddd, J^1=7.9 Hz, J^2=7.5 Hz, J^3=1.4 Hz, Ar***H***), 7.91 (1H, d, *J*=7.8 Hz, Ar***H***), 8.26 (1H, bs, O***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.00 (CH_3), 22.27 (CH_2), 25.60 (CH_2), 42.51 (CH_2), 46.64 (CH_2), 119.82 (CH), 124.61 (CH), 131.15 (qC), 131.53 (CH), 133.74 (CH), 137.97 (qC), 150.30 (C=N) ppm.

HRMS (ESI^+): found 312.1124 [M+H]+, $C_{12}H_{18}N_5O_3S$ requires 312.1125.

7.2.1.6. Synthesis of 2-azido-*N*-benzyl-*N*-[3-(hydroxyimino) propyl]benzene-sulfonamide.



(330)
$C_{16}H_{17}N_5O_3S$
MW =359.40 g/mol

(Eluent: *Pe*troleum ether/ethylacetate: 3/2, R_f = 0.2) yielded the product as a yellow oil (93 %).

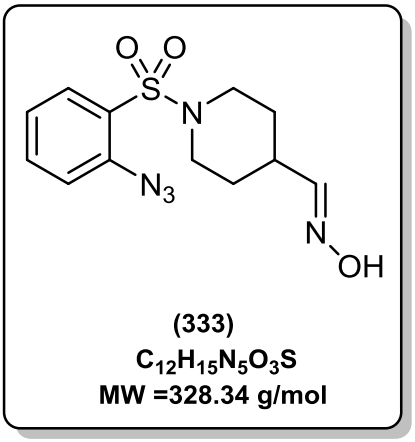
IR: υ_{max} (cm^{-1}): 726.3, 819.2, 999.4, 1064.0, 1123.9, 1157.2, 1288.2, 1329.5, 1471.7, 1495.4, 1575.1, 2101.2, 2923.8, 3258.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.47 (2H, app. q, *J*=6.4 Hz, $NCH_2C\boldsymbol{H_2}$), 3.39-3.47 (2H, m, $NC\boldsymbol{H_2}CH_2$), 4.57 (2H, s, Ph-$C\boldsymbol{H_2}$), 7.02 (1H, t, *J*=5.9 Hz, N=C**H**), 7.20-7.33 (7H, m, 7 x Ar***H***), 7.58 (1H, td, J^1=8.0 Hz, J^2=1.5 Hz, Ar***H***), 8.01 (1H, dq, J^1=8.0 Hz, J^2=1.5 Hz, Ar***H***), 9.41 (1H, br.s, O***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 28.58 (CH_2), 43.69 (CH_2), 51.45 (CH_2), 119.95 (CH), 124.62 (CH), 127.90 (CH), 128.28 (2 x CH), 128.68 (2 x CH), 130.66 (qC), 131.45 (CH), 134.02 (CH), 136.12 (qC), 138.16 (qC), 148.49 (CH=N) ppm.

HRMS (ESI^+): found 360.1120 $[M+H]^+$, $C_{16}H_{18}N_5O_3S$ requires 360.1125.

7.2.1.7. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-4-carbaldehyde oxime.



(333)
$C_{12}H_{15}N_5O_3S$
MW =328.34 g/mol

(Eluent: Petroleum ether/ethylacetate: 2/1, R_f = 0.2) yielded the product as a white solid (85 %, m.p.=151-153 ^oC).

IR: υ_{max} (cm^{-1}): 770.2, 923.2, 1043.0, 1074.0, 1122.4, 1146.4, 1247.2, 1308.6, 1334.0, 1437.4, 1471.2, 1584.7, 2097.8, 2849.1, 2933.3, 3255.6.

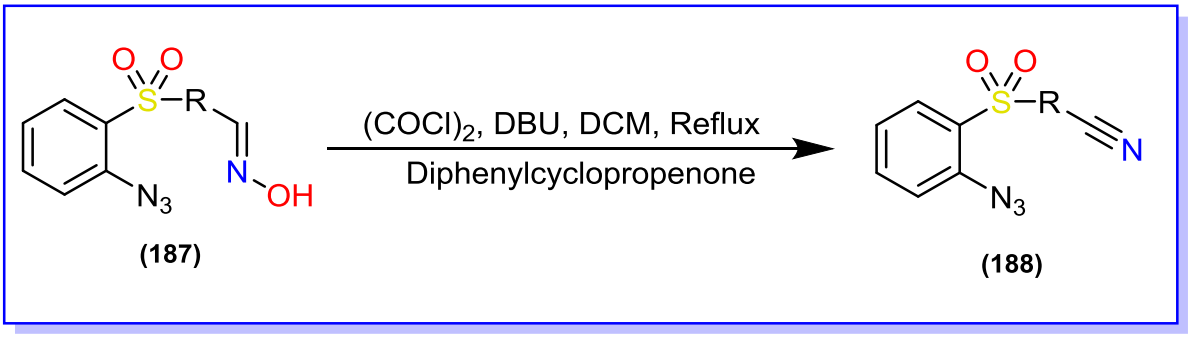
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.43-1.59 (2H, m, $CH_2CHC\boldsymbol{H_2}$), 1.76-1.81 (2H, m, $C\boldsymbol{H_2}CHCH_2$), 2.20-2.29 (1H, m, $CH_2C\boldsymbol{H}CH_2$), 2.72 (2H, td, J^1=12.4 Hz, J^2=2.6 Hz, $CH_2NC\boldsymbol{H_2}$), 3.77-3.82 (2H, m, $C\boldsymbol{H_2}NCH_2$), 7.17 (1H, ddd, J^1=8.0 Hz, J^2=7.6 Hz, J^3=1.0 Hz, Ar***H***), 7.23 (1H, dd, J^1= 8.0 Hz, J^2=0.7 Hz, Ar***H***), 7.27 (1H, d, J=5.6 Hz, N=C***H***), 7.51 (1H, ddd, J^1=7.9 Hz, J^2=7.6 Hz, J^3=1.4 Hz, Ar***H***), 7.87 (1H, dd, J^1=7.9 Hz, J^2=1.4 Hz, Ar***H***), 9.58 (1H, s, O**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 29.12 (2 x CH_2), 36.10 (CH), 45.38 (2 x CH_2), 119.93 (CH), 124.67 (CH), 129.29 (qC), 131.77 (CH), 133.94 (CH), 138.32 (qC), 153.69 (CH) ppm.

HRMS (ESI^+): found 310.0967 $[M+H]^+$, $C_{12}H_{16}N_5O_3S$ requires 310.0968.

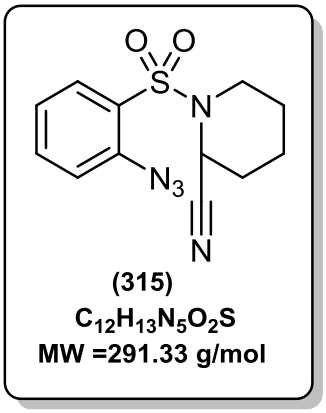
7.2.2. Conversion of the oximes into the nitriles.

General experimental:



To a stirred mixture of diphenylcyclopropenone (19 mg, 0.09 mmol, 5 mol%) and aldoxime (289 mg, 0.935 mmol, 1.0 eq) in DCM (10 mL) was added a solution of $(COCl)_2$ (118 mg, 0.935 mmol, 1.0 eq) in DCM (1.0 mL) by using a syringe pump over 1h and then to this was added by slow addition DBU (426 mg, 2.8 mmol, 3.0 eq) in DCM (3 mL). The mixture was heated at reflux whilst being monitored by TLC. The reaction mixture was diluted with DCM and washed with water (3 x 25 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, concentrated under reduced pressure and purified by silica column chromatography.

7.2.2.1. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-2-carbonitrile.



[Eluent: petroleum ether/ethyl acetate: 3/1, R_f = 0.3] to yield the product as a dark brown oil (86 %).

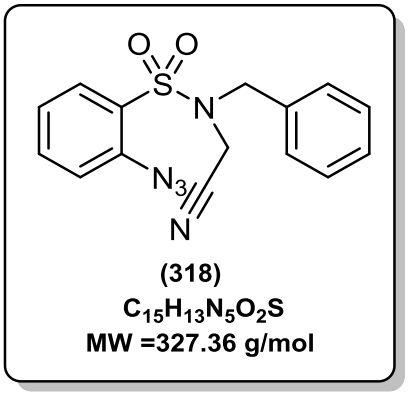
IR: υ_{max} (cm^{-1}): 746.7, 905.9, 1069.4, 1120.5, 1161.1, 1288.9, 1443.3, 1506.6, 1575.4, 2100.4, 2257.0, 2862.7, 2948.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.46-1.59 (1H, m, CH***H***), 1.61-1.71 (2H, m, C**H$_2$**), 1.78-1.87 (2H, m, C**H$_2$**), 1.91-1.96 (1H, m, C***H***H), 2.91 (1H, td, J^1=13.0 Hz, J^2= 2.3 Hz, NCH***H***), 3.77 (1H, d, *J*=13.4 Hz, NC***H***H), 5.09 (1H, br.s, NC***H***), 7.18 (1H, ddd, J^1=7.9 Hz, J^2=7.6 Hz, J^3=1.4 Hz, Ar***H***), 7.25 (1H, d, *J*=8.0 Hz, Ar**H**), 7.54 (1H, ddd, J^1=8.0 Hz, J^2=7.6 Hz, J^3=1.3 Hz, Ar**H**), 7.87 (1H, d, *J*=7.9 Hz, Ar**H**).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.01 (CH_2), 24.93 (CH_2), 29.63 (CH_2), 43.49 (CH_2), 46.16 (CH), 116.35 (qC), 120.05 (CH), 124.71 (CH), 128.46 (qC), 131.55 (CH), 134.70 (CH), 138.65 (qC) ppm.

HRMS (ESI$^+$): found 309.1140 $[M+NH_4]^+$, $C_{12}H_{17}N_6O_2S$ requires 309.1128.

7.2.2.2. Synthesis of 2-azido-*N*-benzyl-*N*-(cyanomethyl)benzenesulfonamide.



(318)
$C_{15}H_{13}N_5O_2S$
MW =327.36 g/mol

[Eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.23] to yield the product as a light yellow solid (84 %, m.p.= 107-109 ^oC).

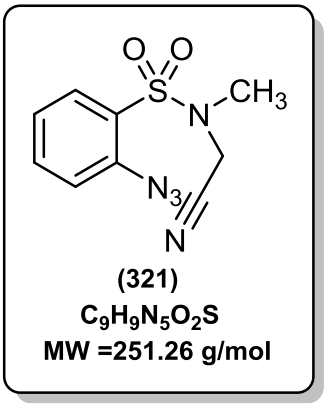
IR: υ_{max} (cm^{-1}): 744.2, 893.2, 924.9, 1067.7, 1096.0, 1123.4, 1206.0, 1290.0, 1325.1, 1471.8, 1585.3, 2104.9, 2248.8, 2948.6, 2989.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.16 (2H, s, CN-C***H$_2$***), 4.37 (2H, bs, N-C***H$_2$***), 7.22 (1H, dd, J^1=8.0 Hz, J^2=7.5 Hz, Ar***H***), 7.26-7.31 (6H, m, 6 x Ar***H***), 7.59 (1H, td, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 7.97 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δc (100 MHz, $CDCl_3$): 34.88 (CH_2), 51.02 (CH_2), 114.29 (CN), 119.99 (CH), 124.87 (CH), 128.77 (3 x CH), 128.84 (qC), 129.11 (2 x CH), 131.80 (CH), 133.53 (qC), 134.91 (CH), 138.63 (qC) ppm.

HRMS (ESI$^+$): found 350.0685 $[M+Na]^+$, $C_{15}H_{13}N_5O_2SNa$ requires 350.0682.

7.2.2.3. Synthesis of 2-azido-*N*-(cyanomethyl)-*N*-methylbenzenesulfonamide.



(321)
$C_9H_9N_5O_2S$
MW =251.26 g/mol

[Eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.3] to yield the product as a yellow oil (71 %).

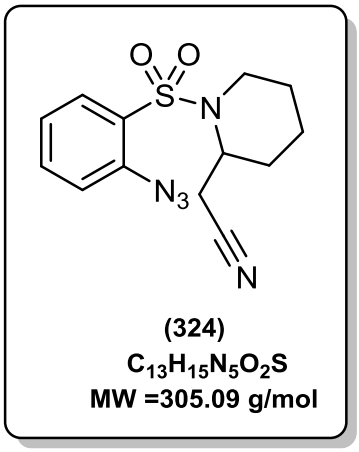
IR: υ_{max} (cm^{-1}): 729.4, 819.5, 921.6, 1005.7, 1058.5, 1122.0, 1222.4, 1265.7, 1287.3, 1308.9, 1333.5, 1442.3, 1471.1, 1574.5, 2125.2, 2261.1, 2927.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.85 (3H, s, C***H*$_3$***), 3.37 (2H, s, C***H*$_2$***), 7.20 (1H, dd, J^1=8.0 Hz, J^2=7.7 Hz, Ar***H***), 7.26 (1H, d, J= 8.0 Hz, Ar***H***), 7.57 (1H, ddd, J^1=8.0 Hz, J^2=7.8 Hz, J^3=1.2 Hz, Ar***H***), 7.90 (1H, dd, J^1=8.0 Hz, J^2=1.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 34.61 (CH_3), 38.71 (CH_2), 114.50 (CN), 119.98 (CH), 124.81 (CH), 127.98 (qC), 131.93 (CH), 134.87 (CH), 138.56 (qC) ppm.

HRMS (ESI$^+$): found 269.0812 $[M+NH_4]^+$, $C_9H_{13}N_6O_2S$ requires 269.0815.

7.2.2.4. Synthesis of 2-{1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}acetonitrile.



[Eluent: petroleum ether/ethyl acetate: 3/1, R_f= 0.29] to yield the product as a light yellow oil (81 %).

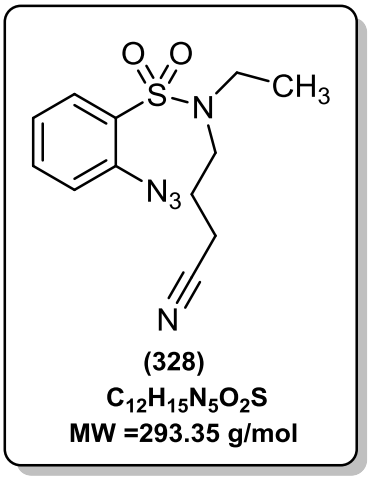
IR: υ_{max} (cm^{-1}): 818.0, 911.6, 962.1, 988.3, 1070.8, 1118.9, 1209.9, 1287.3, 1328.3, 1443.8, 1471.1, 1574.6, 2098.5, 2253.7, 2866.0, 2944.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.18-1.65 (6H, m, 3 x C***H*$_2$**), 2.59-2.77 (2H, m, CN-C***H*$_2$**), 2.94 (1H, t, *J*=13.2 Hz, N-C***H***), 3.73 (1H, d, *J*=13.8 Hz, NCH***H***), 4.34 (1H, bs, NC***H***H), 7.17 (1H, ddd, J^1=7.9 Hz, J^2=7.4 Hz, J^3=0.6 Hz, Ar**H**), 7.22-7.24 (1H, m, Ar***H***), 7.53 (1H, ddd, J^1= 7.8 Hz, J^2=7.5, J^3=1.5 Hz, Ar***H***), 7.90 (1H, d, J^1=7.8 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 17.94 (CH_2), 19.32 (CH_2), 24.78 (CH_2), 27.27 (CH_2), 41.97 (CH_2), 49.49 (CH), 117.34 (CN), 120.07 (CH), 124.64 (CH), 130.31 (qC), 131.25 (CH), 134.19 (CH), 138.13 (qC) ppm.

HRMS (ESI^+): found 323.1294 $[M+NH_4]^+$, $C_{13}H_{19}N_6O_2S$ requires 323.1285.

7.2.2.5. Synthesis of 2-azido-*N*-(3-cyanopropyl)-*N*-ethylbenzenesulfonamide.



(328)
$C_{12}H_{15}N_5O_2S$
MW =293.35 g/mol

[Eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.24] to yield the product as a yellow oil (81 %).

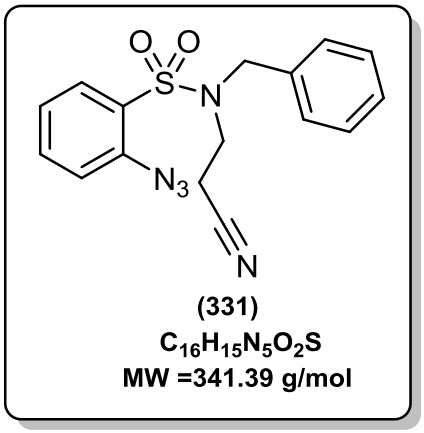
IR: υ_{max} (cm^{-1}): 729.0, 818.8, 913.2, 934.2, 1001.5, 1145.9, 1155.4, 1288.2, 1327.9, 1442.8, 1471.1, 1574.5, 2099.0, 2246.5, 2937.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.02 (3H, t, *J*=7.2 Hz, C***H*****$_3$**), 1.89 (2H, app. p, *J*=7.1 Hz, NCH_2C***H*****$_2$**), 2.37 (2H, t, *J*=7.1 Hz, C***H*****$_2$**-CN), 3.25 (2H, q, *J*=7.2 Hz, NC***H*****$_2$**CH_3), 3.40 (2H, t, *J*=6.9 Hz, NC***H*****$_2$**CH_2), 7.17 (1H, dd, J^1=7.9 Hz, J^2=7.5 Hz, Ar***H***), 7.22 (1H, d, *J*= 8.0 Hz, Ar***H***), 7.52 (1H, ddd, J^1=7.9 Hz, J^2=7.5 Hz, J^3=1.4 Hz, Ar***H***), 7.91 (1H, dd, J^1=8.0 Hz, J^2= 1.3 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.92 (CH_3), 14.56 (CH_2), 25.24 (CH_2), 42.96 (CH_2), 46.48 (CH_2), 119.21 (CN), 119.60 (CH), 124.77 (CH), 130.57 (qC), 131.65 (CH), 134.06 (CH), 137.96 (qC) ppm.

HRMS (ESI^+): found 311.1286 $[M+NH_4]^+$, $C_{12}H_{19}N_6O_2S$ requires 311.1285.

7.2.2.6. Synthesis of 2-azido-*N*-benzyl-*N*-(2-cyanoethyl) benzenesulfonamide.



[Eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.25] to yield the product as a bronze-coloured solid (77 %, m.p. = 78 - 80 ^{o}C).

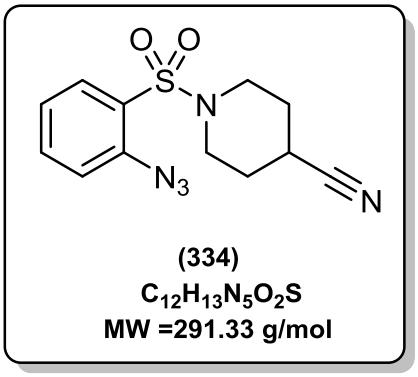
IR: υ_{max} (cm^{-1}): 755.8, 820.1, 945.6, 981.7, 1099.4, 1123.7, 1147.4, 1266.0, 1289.1, 1334.3, 1471.9, 1495.7, 1584.1, 2102.2, 2250.7, 2929.5, 3031.2, 3066.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.30 (2H, t, *J*=7.3 Hz, $NCH_2C\boldsymbol{H_2}$), 3.50 (2H, t, *J*=7.3 Hz, $NC\boldsymbol{H_2}CH_2$), 4.45 (2H, s, Ph-$C\boldsymbol{H_2}$), 7.17-7.27 (7H, m, 7 x Ar***H***), 7.55 (1H, td, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***), 7.95 (1H, dd, J^1=8.0 Hz, J^2=1.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.08 (CH_2), 43.87 (CH_2), 52.99 (CH_2), 117.34 (CN), 119.97 (CH), 124.84 (CH), 128.41 (2 x CH), 128.44 (CH), 129.00 (2 x CH), 130.06 (qC), 131.79 (CH), 134.44 (CH), 135.54 (qC), 138.39 (qC) ppm.

HRMS (ESI^+): found 364.0836 $[M+Na]^+$, $C_{16}H_{15}N_5O_2SNa$ requires 364.0839.

7.2.2.7. Synthesis of 1-[(2-azidophenyl)sulfonyl]piperidine-4-carbo nitrile.



(334)
$C_{12}H_{13}N_5O_2S$
MW =291.33 g/mol

[Eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.24] to yield the product as a light yellow oil (85 %).

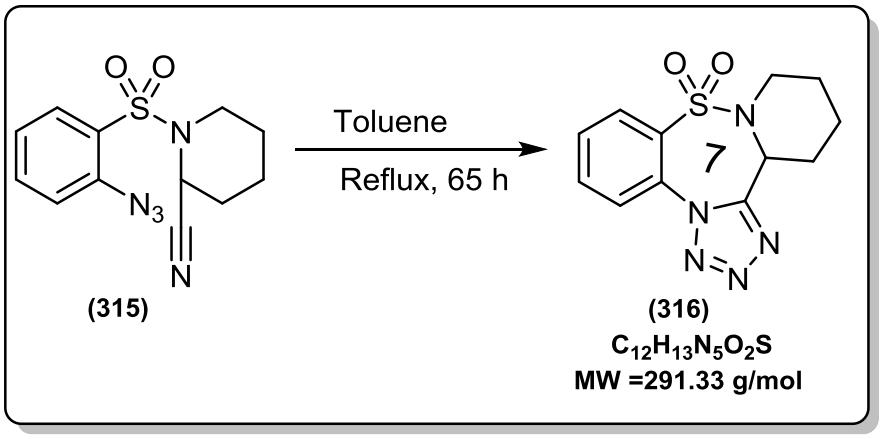
IR: υ_{max} (cm^{-1}): 723.8, 908.7, 950.0, 1035.5, 1067.0, 1123.2, 1158.7, 1253.1, 1288.2, 1324.8, 1341.2, 1443.2, 1471.5, 1574.0, 2098.6, 2254.0, 2969.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.81-1.96 (4H, m, C***H*****$_2$**CHC***H*****$_2$**), 2.77 (1H, septet, *J*=4.0 Hz, CH_2C***H***CH_2), 3.28-3.38 (4H, m, C***H*****$_2$**NC***H*****$_2$**), 7.17 (1H, dd, J^1=7.9 Hz, J^2=7.5 Hz, Ar***H***), 7.24 (1H, d, *J*= 7.9 Hz, Ar***H***), 7.53 (1H, ddd, J^1=7.9 Hz, J^2=7.7 Hz, J^3=1.4 Hz, Ar***H***), 7.86 (1H, d, *J*=7.9 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.63 (CH), 28.43 (2 x CH_2), 43.74 (2 x CH_2), 120.06 (CH), 120.58 (CN), 124.78 (CH), 128.84 (qC), 131.67 (CH), 134.28 (CH), 138.32 (qC) ppm.

HRMS (ESI^+): found 292.0857 $[M+H]^+$, $C_{12}H_{14}N_5O_2S$ requires 292.0863.

7.2.3. Synthesis of 12,13,14,14a-tetrahydro-11*H*-benzo[*f*]pyrido [1,2-*b*]tetrazolo[5,1-*d*][1,2,5]thiadiazepine 9,9-dioxide.



1-[(2-Azidophenyl)sulfonyl]piperidine-2-carbonitrile (180 mg, 0.619 mmol) was heated at reflux in dry toluene (10 mL) under a nitrogen atmosphere for 65 hours. The solvent was removed in vacuo and the crude product was purified by silica chromatography (petroleum ether/ ethyl acetate: 1/1, R_f = 0.24), to yield the product as a white solid (122 mg, 68 %, m. p.= 179-181 ^oC).

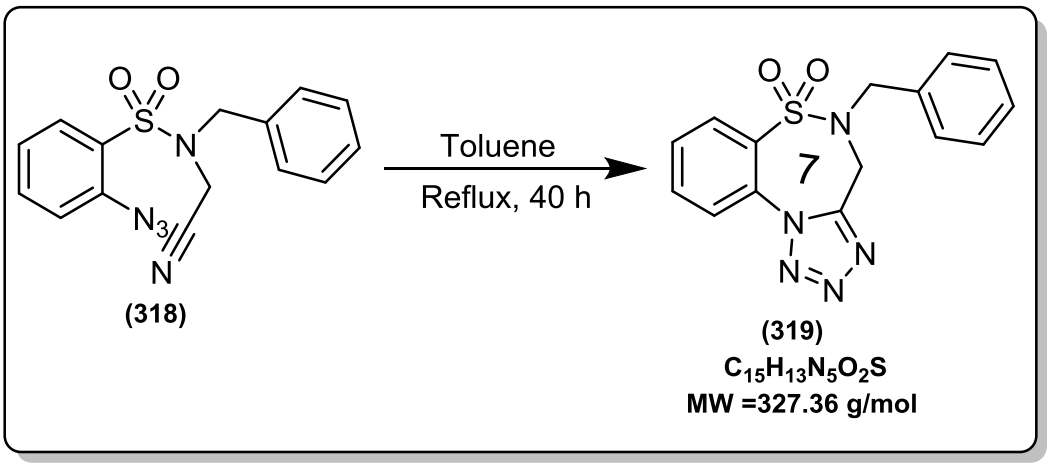
IR: υ_{max} (cm^{-1}): 649.0, 1039.2, 1097.0, 1170.0, 1351.3, 1442.5, 1477.4, 1590.8, 1979.9, 2953.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.43-1.50 (1H, m, CH***H***), 1.66-1.85 (3H, m, C**H**H + C**H$_2$**), 2.24-2.32 (1H, m, C***H***H), 2.71-2.82 (2H, m, CH***H*** + NC***H***H), 3.35-3.39 (1H, m, NCH***H***), 5.23 (1H, br.s, NC***H***), 7.67 (1H, dd, J^1=7.7 Hz, J^2=7.6 Hz, Ar***H***), 7.84 (1H, ddd, J^1=8.3 Hz, J^2=8.0 Hz, J^3=0.5 Hz, Ar**H**), 8.16 (1H, d, J=7.7 Hz, Ar**H**), 8.47 (1H, d, J=8.3 Hz, Ar**H**).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.62 (CH_2), 24.27 (CH_2), 28.97 (CH_2), 45.37 (CH_2), 51.81 (CH), 124.48 (CH), 129.46 (CH), 129.74 (CH), 130.37 (qC), 130.67 (qC), 134.64 (CH), 154.24 (qC) ppm.

HRMS (ESI^+): found 292.0866 $[M+H]^+$, $C_{12}H_{14}N_5O_2S$ requires 292.0863.

7.2.4. Synthesis of 5-benzyl-4,5-dihydrobenzo[*f*]tetrazolo[5,1-*d*] [1,2,5]thiadiazepine 6,6-dioxide.



2-Azido-*N*-benzyl-*N*-(cyanomethyl) benzenesulfonamide (150 mg, 0.459 mmol) was heated at reflux in dry toluene (10 mL) under a nitrogen atmosphere for 40 hours. The solvent was removed in vacuo and the crude product was purified by silica chromatography (petroleum ether/ ethyl acetate: 2/1, R_f = 0.24), to yield the product as a dark yellow (109 mg, 73 %, m.p.= 150-152 ^oC).

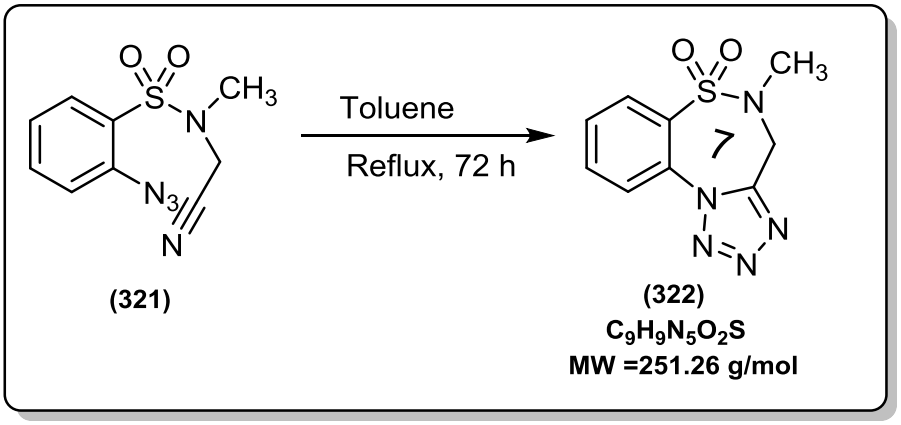
IR: υ_{max} (cm^{-1}): 728.2, 748.5, 905.9, 1066.9, 1093.9, 1138.6, 1171.6, 1356.5, 1448.1, 1480.0, 1587.6, 3032.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.22 (2H, br.s, C***H*****$_2$**), 4.99 (2H, br.s, C***H*****$_2$**), 7.19-7.21 (2H, m, 2 x Ar***H***), 7.28-3.32 (3H, m, 3 x Ar***H***), 7.68 (1H, ddd, J^1=8.0 Hz, J^2=7.7 Hz, J^3=1.3 Hz, Ar***H***), 7.84 (1H, ddd, J^1= 8.5 Hz, J^2=8.0 Hz, J^3=1.3 Hz, Ar**H**), 8.22 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar***H***), 8.40 (1H, d, J=8.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 43.27 (CH_2), 53.25 (CH_2), 124.76 (CH), 128.51 (2 x CH), 128.91 (CH), 129.09 (2 x CH), 129.27 (CH), 129.52 (CH), 130.54 (qC), 131.86 (qC), 133.05 (qC), 134.71 (CH), 151.75 (qC) ppm.

HRMS (ESI^+): found 328.0866 $[M+H]^+$, $C_{15}H_{14}N_5O_2S$ requires 328.0863.

7.2.5. Synthesis of 5-methyl-4,5-dihydrobenzo[*f*]tetrazolo[5,1-*d*][1,2,5]thiadiazepine 6,6-dioxide.



2-Azido-*N*-(cyanomethyl)-*N*-methylbenzenesulfonamide (85 mg, 0.339 mmol) was heated at reflux in dry toluene (10 mL) under a nitrogen atmosphere for 72 hours. The solvent was removed in vacuo and the crude product was purified by silica chromatography (petroleum ether/ ethyl acetate: 1/1, R_f = 0.28), to yield the product as a dark yellow oil (76 mg, 89 %).

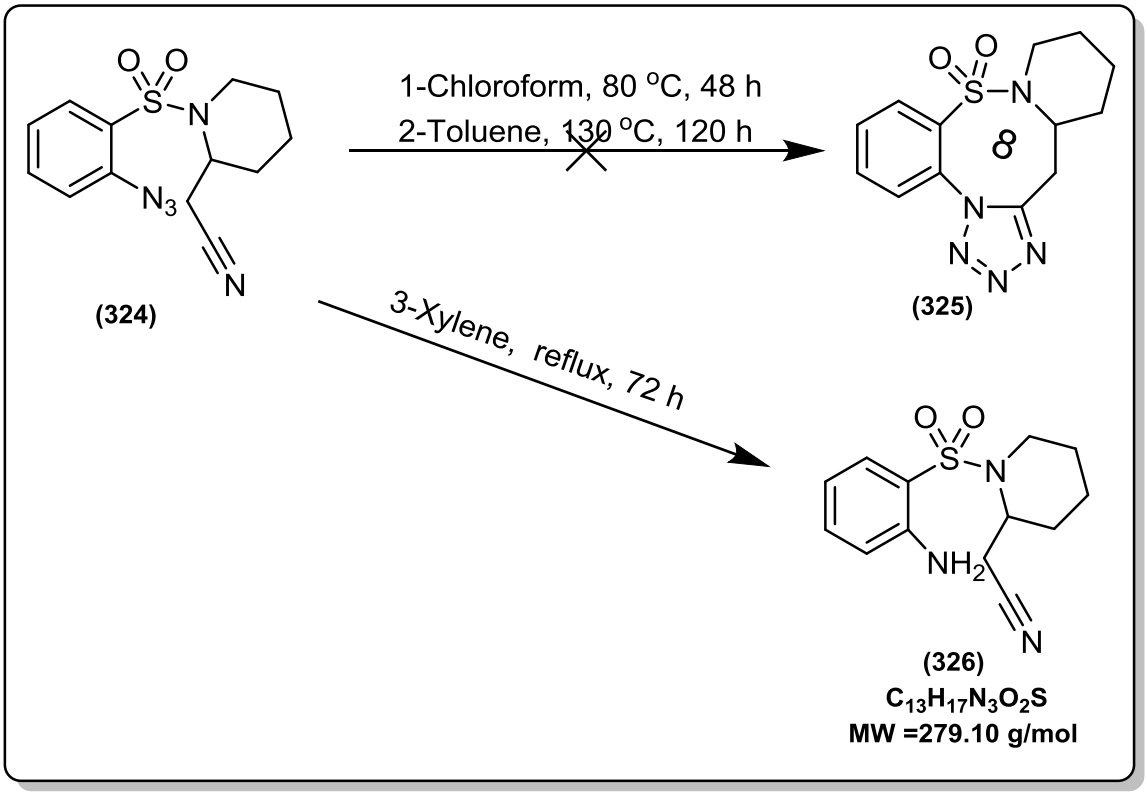
IR: υ_{max} (cm^{-1}): 758.7, 927.8, 1038.1, 1064.6, 1140.3, 1168.4, 1353.6, 1451.8, 1480.8, 1588.5, 2925.0, 2980.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.77 (3H, s, C***H*****$_3$**), 4.66 (2H, s, C***H*****$_2$**), 7.59 (1H, ddd, J^1=7.9 Hz, J^2=7.6 Hz, J^3=1.1 Hz, Ar***H***), 7.78 (1H, ddd, J^1= 8.3 Hz, J^2=7.9 Hz, J^3=1.5 Hz, Ar***H***), 8.07 (1H, dd, J^1=7.9 Hz, J^2=1.5 Hz, Ar***H***), 8.34 (1H, dd, J^1=8.3 Hz, J^2=0.9 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 37.08 (CH_3), 46.70 (CH_2), 124.72 (CH), 129.67 (CH), 129.90 (CH), 130.19 (qC), 130.46 (qC), 134.86 (CH), 151.72 (qC) ppm.

HRMS (ESI^+): found 252.0555 $[M+H]^+$, $C_9H_{10}N_5O_2S$ requires 252.0550.

7.2.6. Attempted synthesis of 11,12,13,14,14a,15-hexahydrobenzo [*g*]pyrido[1,2-*b*]tetrazolo[5,1-*e*][1,2,6]thiadiazocine 9,9-dioxide.



2-{1-[(2-Aminophenyl)sulfonyl]piperidin-2-yl}acetonitrile (100 mg, 0.33 mmol) in dry chloroform (7 mL) was heated at 80 °C under a nitrogen atmosphere for 48 hours and monitored by TLC which showed no product. The solvent was removed and to the remaining starting material was added anhydrous toluene (7 mL). The reaction mixture was heated at reflux temperature under a nitrogen atmosphere for 72 hours and monitored by TLC which showed no product. The solvent removed and the remaining crude material had dry xylene (7 mL) added. The reaction mixture was heated at reflux temperature for 3 days under an atmosphere of dry nitrogen whilst being monitored by TLC and concentrated. Purification by silica chromatography (petroleum ether/ ethyl acetate: 2/1, R_f = 0.23), yielded compound **(326)** as a yellow oil (62 mg, 68%).

IR: υ_{max} (cm^{-1}): 867.9, 950.3, 1061.5, 1141.0, 1232.0, 1319.2, 1452.3, 1483.4, 1566.1, 1617.6, 2856.7, 2926.6, 3374.7, 3475.8.

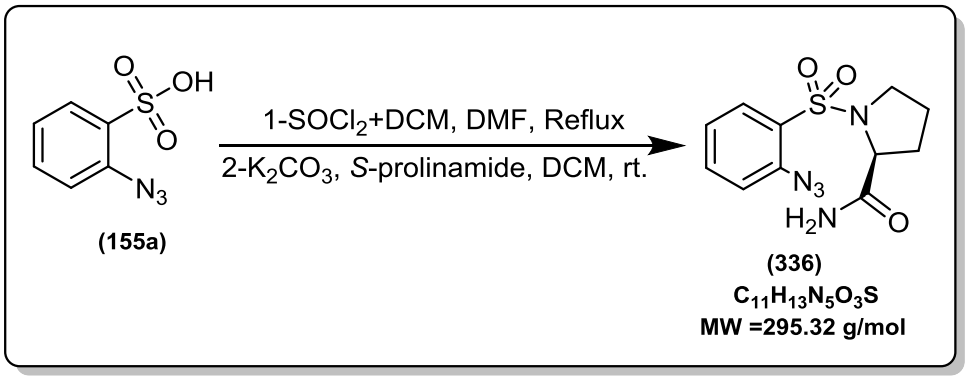
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.20-1.66 (6H, m, 3 x C***H***$_2$), 2.54-2.73 (2H, m, CN-C***H***$_2$), 2.81 (1H, td, J^1=15.3 Hz, J^2=2.8 Hz, N-C***H***), 3.67 (1H, d, J=14.0 Hz, NCH***H***), 4.29-4.33 (1H, m, NC***H***H), 4.89 (2H, bs, N***H***$_2$), 6.66 (1H, d, J=8.3 Hz, Ar***H***), 6.70 (1H, ddd, J^1=8.0 Hz,

J^2=7.7 Hz, J^3=0.8 Hz, Ar***H***), 7.24 (1H, ddd, J^1=8.3 Hz, J^2=8.0 Hz, J^3=1.4 Hz, Ar***H***), 7.58 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.00 (CH_2), 18.55 (CH_2), 24.32 (CH_2), 26.88 (CH_2), 40.69 (CH_2), 49.29 (CH), 117.43 (CN), 117.72 (CH), 117.83 (CH), 121.05 (qC), 129.93 (CH), 134.39 (CH), 145.36 (qC) ppm.

HRMS (ESI$^+$): found 280.1109 $[M+H]^+$, $C_{13}H_{18}N_3O_2S$ requires 280.1114.

7.2.7. Synthesis of 1-(2'-Azidobenzenesulfonyl)-2-prolin amide.



To 2-azidobenzenesulfonic acid (1.80 g, 9.04 mmol, 2.6 eq) was added a 2M solution of thionyl chloride in dichloromethane (12 mL, 24.00 mmol, 6.85 eq) followed by the addition of DMF (100 µL). The resultant mixture was heated to reflux for 15 hours under nitrogen at 80 ^{o}C. The excess thionyl chloride was removed in vacuo and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (2.64 g, 19.14 mmol, 5.5 eq) in water (20 mL) was added in one portion to *S*-prolinamide (400 mg, 3.50 mmol, 1 eq) in dichloromethane (20 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added dropwise to this solution. The reaction was allowed to stir at room temperature for 20 hours before the organic layer was separated and the aqueous layer washed with DCM (2 x 20 mL). The combined organic phases were dried over magnesium sulfate, filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 1/10, Rf = 0.2] to yield the product as a yellow powder (764 mg, 74 %, m. p.= 139 - 141 ^{o}C).

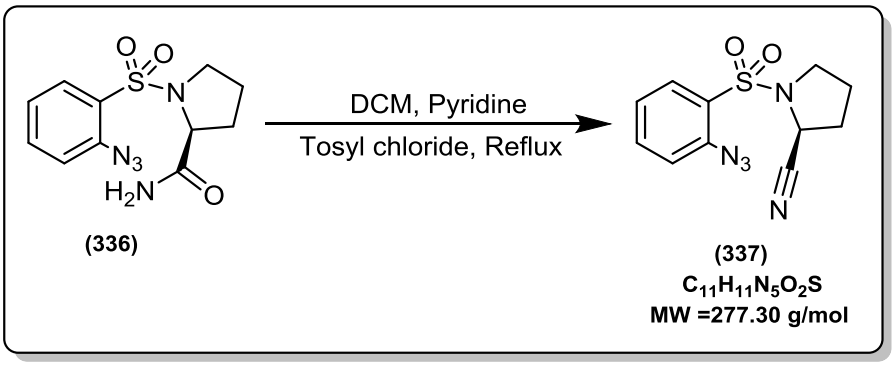
IR: υ_{max} (cm^{-1}): 757.5 (m), 1154.3 (m), 1196.6 (s), 1332.2 (m), 1473.2 (s), 1574.1 (m), 1668.5 (s), 2126.6 (N_3), 2952.9 (m), 2977.3 (m), 3153.2 (m), 3447.6 (m).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.71-1.99 (3H, m, CH_2+C***H***H), 2.23-2.30 (1H, m, CH***H***), 3.21-3.28 (1H, m, NC***H***H), 3.38-3.43 (1H, m, NCH***H***), 4.56-4.59 (1H, m, NCH), 5.68 (1H, bs, N***H***H), 6.83 (1H, bs, NH***H***), 7.23-7.28 (2H, m, 2 x Ar**H**), 7.57 (1H, dd, J^1=7.7 Hz, J^2=7.4 Hz, Ar**H**), 7.96 (1H, dd, J^1=8.0 Hz, J^2= 8.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 24.67 (CH_2), 30.14 (CH_2), 49.10 (CH_2), 62.29 (CH), 119.97 (CH), 124.95 (CH), 127.74 (qC), 133.00 (CH), 134.74 (CH), 138.39 (qC), 174.26 (qC) ppm.

HRMS (ESI^+): found 296.0818 [M+H]+, $C_{11}H_{14}N_5O_3S$ requires 296.0812.

7.2.8. Synthesis of (*S*)-1-(2'-azidobenzenesulfonyl)pyrrolidine-2-carbonitrile.



To a solution of the (*S*)-*N*-(2-azidobenzenesulfonyl)-2-prolinamide (180 mg, 0.61 mmol) in DCM (5 mL) at room temperature was added pyridine (371 mg, 378 µL, 4.69 mmol, 7.7 eq) followed by neat tosyl chloride (755 mg, 3.69 mmol, 6.5 eq). The resultant mixture was heated to reflux under a nitrogen atmosphere for 6 hours at 50 ^oC. The solvent was removed in vacuo and the crude product purified by column chromatography (petroleum ether/ ethyl acetate: 1/1, R_f = 0.35) to yield the product as a brown oil (148 mg, 79 %).

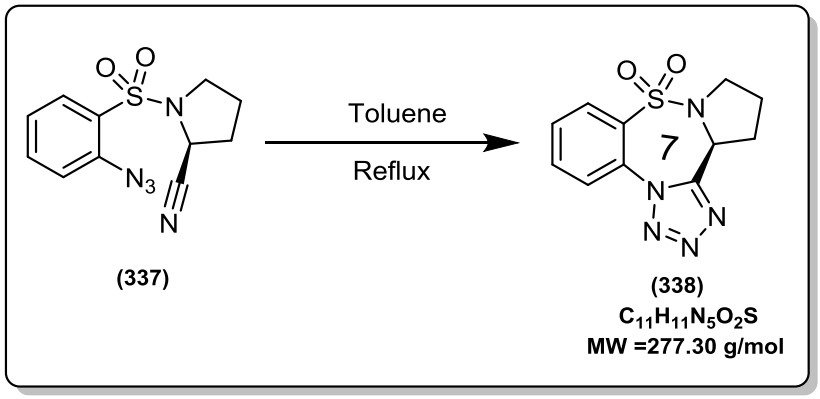
IR: υ_{max} (cm^{-1}): 770.2 (s), 1150.5 (m), 1260.8 (m), 1320.2 (m), 1434.8 (m), 1467.2 (m), 1571.9 (m), 2098.6 (m), 2250.2 (m), 2885.1 (s), 2980.4 (m), 3096.7 (s).

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.03-2.36 (4H, m, 2 x C**H$_2$**), 3.44-3.51 (1H, m, NC***H***H), 3.59-3.64 (1H, m, NCH***H***), 4.94-4.97 (1H, dd, NC**H**), 7.29 (H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.33-7.35 (1H, d, *J*=7.9 Hz, Ar**H**), 7.66 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 8.04 (1H, d, *J*=7.9 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.92 (CH_2), 32.31 (CH_2), 47.82 (CH_2), 48.90 (CH), 118.29 (qC), 119.88 (CH), 124.79 (CH), 129.07 (qC), 131.80 (CH), 134.67 (CH), 138.55 (qC) ppm.

HRMS (ESI$^+$): found 278.0710 $[M+H]^+$, $C_{11}H_{12}N_5O_2S$ requires 278.0706.

7.2.9. 11,12,13,13a-tetrahydrobenzo[*f*]pyrrolo[1,2-*b*]tetrazolo[5,1-*d*][1,2,5]thiadiazepine 9,9-dioxide



(*S*)-*N*-(2-azidobenzenesulfonyl)-pyrrolidine-2-carbonitrile (100 mg, 0.361 mmol) was heated at reflux in dry toluene (10 mL) under a nitrogen atmosphere for 72 hours. The solvent removed in vacuo and the crude product was purified by silica chromatography (petroleum ether/ ethyl acetate: 2/1, Rf = 0.3), to yield the product as a white solid (60 mg, 60 %, m. p.= 179-181 ^{o}C).

IR: υ_{max} (cm^{-1}): 777.4, 829.7, 1175.2, 1359.9, 1455.8, 1485.8, 1588.7, 2878.5, 2980.8, 3080.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.68-1.77 (1H, m, C***H***H), 1.84-1.93 (1H, m, CH***H***), 1.94-2.06 (1H, m, C***H***H), 2.52-2.58 (1H, m, CH***H***), 2.93-3.00 (1H, m, C***H***H), 3.49-3.59 (1H, m, CH***H***), 5.52 (1H, t, J=7.1 Hz, NC**H**), 7.57 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar**H**), 7.76 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, Ar**H**), 8.05 (1H, d, *J*=7.8 Hz, Ar**H**), 8.09 (1H, d, *J*=7.8 Hz, Ar**H**) ppm.

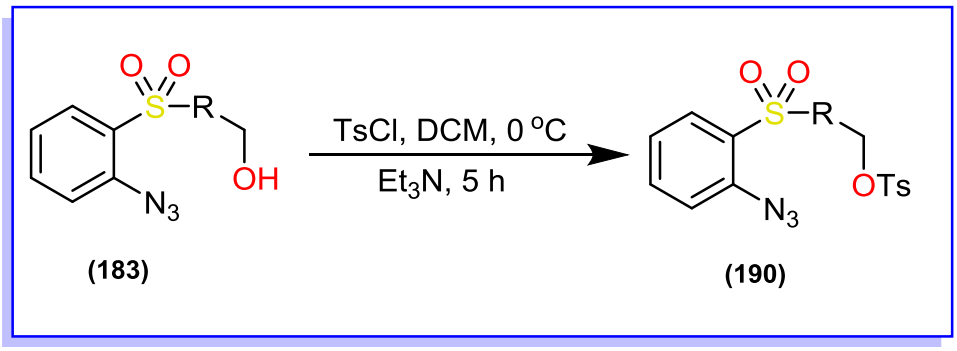
^{13}C NMR δ_c (100 MHz, DMSO): 24.61 (CH_2), 34.64 (CH_2), 49.33 (CH_2), 56.19 (CH), 125.20 (CH), 129.38 (CH), 129.75 (CH), 130.82 (qC), 131.16 (qC), 134.61 (CH), 155.50 (qC) ppm.

HRMS (ESI$^+$): found 278.0703 $[M+H]^+$, $C_{11}H_{12}N_5O_2S$ requires 278.0706.

7.3. Attempted synthesis of Tetrazolobenzothiadiazepines and Benzodiazepines.

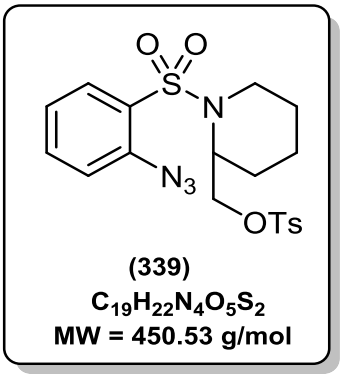
7.3.1. Tosylation of the alcohol.

General experimental:



To a stirred solution the alcohol (1.0 mmol, 1.0 eq) and p-toluenesulfonyl chloride (1.5 mmol, 1.5 eq) in dichloromethane (10 mL) at 0 °C, triethylamine (505 mg, 5.0 mmol, 5.0 eq) was added dropwise. The mixture was stirred at room temperature over 5 h whilst being monitored by TLC. The reaction mixture was diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with dichloromethene (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), with brine (2 x 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed in *vacuo*. Purification was by silica chromatography.

7.3.1.1. Synthesis of {1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}methyl 4-methylbenzenesulfonate.



(Eluent: petroleum ether/ethylacetate: 4/1, R_f = 0.23) yielded the product as a yellow oil (98 %).

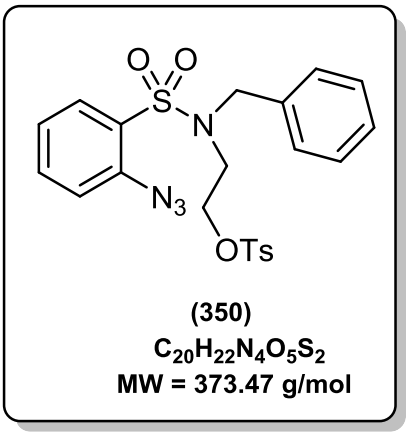
IR: υ_{max} (cm^{-1}): 725.6, 813.8, 973.7, 1159.2, 1175.8, 1327.2, 1360.5, 1471.4, 1597.5, 2099.0, 2945.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.20-1.34 (2H, m, C**H**$_2$), 1.47-1.52 (3H, m, C**H**$_2$), 1.62-1.69 (1H, m, CH***H***), 2.34 (3H, br.s, C**H**$_3$), 2.86 (1H, td, J^1=13.1 Hz, J^2=2.1 Hz, NC***H***), 3.72 (1H, d, J=13.9 Hz, NC***H***H), 3.97 (1H, dd, J^1=9.5 Hz, J^2=1.3 Hz, NCH***H***), 4.01-4.05 (1H, m, C***H***H), 4.14 (1H, q, J=5.9 Hz, CH***H***), 7.10 (1H, td, J^1=8.0 Hz, J^2=0.8 Hz, Ar***H***), 7.17 (1H, dd, J^1= 8.0 Hz, J^2= 0.5 Hz, Ar***H***), 7.22-7.25 (2H, m, 2 x Ar***H***), 7.47 (1H, ddd, J^1=8.0 Hz, J^2=7.7 Hz, J^3=1.4 Hz, ArH), 7.60 (2H, d, J= 8.3 Hz, 2 x Ar***H***), 7.82 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.24 (CH_2), 21.63 (CH_3), 24.89 (CH_2), 24.92 (CH_2), 41.97 (CH_2), 50.58 (CH), 67.09 (CH_2), 120.10 (CH), 124.44 (CH), 127.83 (2 x CH), 129.97 (2 x CH), 130.70 (qC), 131.05 (CH), 132.44 (qC), 133.89 (CH), 137.94 (qC) 145.12 (qC) ppm.

HRMS (ESI^+): found 468.1365 $[M+NH_4]^+$, $C_{19}H_{26}N_5O_5S_2$ requires 468.1370.

7.3.1.2. Synthesis of 2-[(2-azido-*N*-benzylphenyl)sulfonamido]ethyl 4-methylbenzenesulfonate.



(350)
$C_{20}H_{22}N_4O_5S_2$
MW = 373.47 g/mol

(Eluent: petroleum ether/ethylacetate: 3/1, R_f = 0.22) yielded the product as a light yellow solid (98 %, mp.=92-94 ^oC).

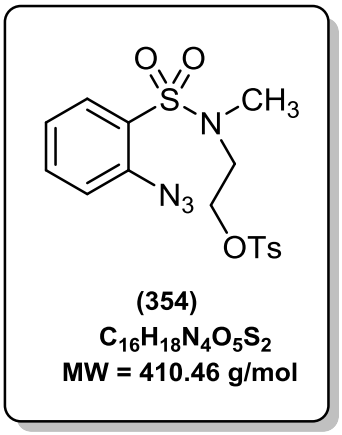
IR: υ_{max} (cm^{-1}): 756.4, 816.2, 976.2, 1095.9, 1159.4, 1337.0, 1171.6, 1356.5, 1448.1, 1480.0, 1587.6, 2129.5, 3032.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.47 (3H, br.s, C***H*****$_3$**), 3.49-3.54 (2H, m, NCH_2 C***H*****$_2$**-O), 3.89 (2H, q, *J*=6.3 Hz, NC***H*****$_2$**CH_2O), 4.55 (2H, d, *J*=14.8 Hz, N-C***H*****$_2$**), 7.20-7.34 (9H, m, 9 x Ar***H***), 7.57-7.70 (3H, m, 3 x Ar***H***), 8.00 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 21.68 (CH_3), 45.54 (CH_2), 52.65 (CH_2), 67.59 (CH_2), 119.99 (CH), 124.62 (CH), 127.88 (2 x CH), 128.45 (2 x CH), 128.76 (2 x CH), 129.92 (2 x CH), 130.44 (qC), 131.53 (CH), 132.16 (CH), 132.41 (qC), 134.12 (CH), 135.78 (qC), 138.33 (qC), 145.06 (qC) ppm.

HRMS (ESI^+): found 509.0910 $[M+Na]^+$, $C_{22}H_{22}N_4O_5S_2Na$ requires 509.0924.

7.3.1.3. Synthesis of 2-[(2-azido-*N*-methylphenyl)sulfonamido]ethyl 4-methylbenzenesulfonate.



(354)
$C_{16}H_{18}N_4O_5S_2$
MW = 410.46 g/mol

(Eluent: petroleum ether/ethylacetate: 3/2, R_f = 0.25) yielded the product as a yellow oil (88 %).

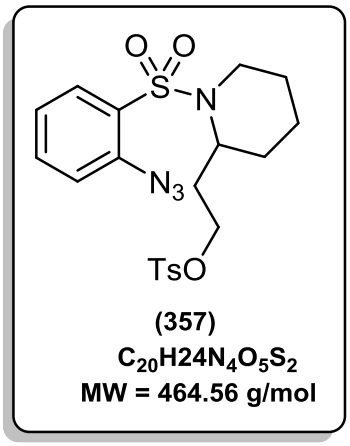
IR: υ_{max} (cm^{-1}): 723.8, 815.5, 972.7, 1096.1, 1146.7, 1157.2, 1175.5, 1289.0, 1336.3, 1443.5, 1472.0, 1575.4, 2100.5, 2954.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.42 (3H, bs, Ar-C***H*****$_3$**), 2.84 (3H, s, N-C***H*****$_3$**), 3.56 (2H, t, *J*=5.5 Hz, NC***H*****$_2$**CH_2O), 4.14 (2H, t, *J*=5.5 Hz, NCH_2C***H*****$_2$**O), 7.19 (1H, dd, J^1=7.9 Hz, J^2=7.6 Hz, Ar***H***), 7.26 (1H, d, *J*=8.0 Hz, Ar***H***), 7.33 (2H, d, *J*= 8.2 Hz, 2 x Ar***H***), 7.56 (1H, ddd, J^1=7.9 Hz, J^2=7.6 Hz, J^3=1.3 Hz, Ar***H***), 7.73 (2H, d, *J*=8.2 Hz, 2 x Ar***H***), 7.88 (1H, ddd, J^1=7.9 Hz, J^2= 7.6 Hz, J^3=1.1 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 21.65 (CH_3), 36.07 (CH_3), 49.14 (CH_2), 68.82 (CH_2), 119.99 (CH), 124.64 (CH), 127.87 (2 x CH), 129.19 (qC), 130.04 (2 x CH), 131.75 (CH), 132.42 (qC), 134.19 (CH), 138.09 (qC), 145.22 (qC) ppm.

HRMS (ESI$^+$): found 428.1063 $[M+NH_4]^+$, $C_{16}H_{22}N_5O_5S_2$ requires 428.1057.

7.3.1.4. Synthesis of 2-{1-[(2-azidophenyl)sulfonyl]piperidin-2-yl}ethyl4-methylbenzenesulfonate.



(357)
$C_{20}H24N_4O_5S_2$
MW = 464.56 g/mol

(Eluent: petroleum ether/ethylacetate: 3/1, R_f = 0.24) yielded the product as a light yellow oil (84 %).

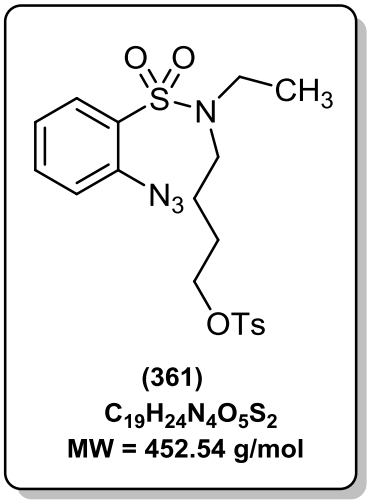
IR: υ_{max} (cm^{-1}): 759.3, 956.1, 1019.4, 1068.7, 1096.1, 1157.0, 1174.2, 1188.2, 1306.1, 1326.8, 1443.3, 1470.9, 1494.6, 1574.2, 1597.3, 2098.1, 2866.1, 2942.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.17-1.55 (6H, m, 3 x C***H*****$_2$**), 1.76 (1H, m, O-CH_2CH***H***-), 1.96-2.08 (1H, m, O-CH_2C***H***H-), 2.36 (3H, bs, C***H*****$_3$**), 2.90 (1H, m, C***H***), 3.74 (1H, dd, J^1=14.2 Hz, J^2=3.4 Hz, NC***H***H), 3.82-3.88 (1H, m, NCH***H***), 3.92-4.04 (2H, m, O-C***H*****$_2$**CH_2-), 7.12 (1H, ddd, J^1=7.9 Hz, J^2=7.5 Hz, J^3=0.9 Hz, Ar***H***), 7.19 (1H, dd, J^1=7.9 Hz, J^2=0.9 Hz, Ar***H***), 7.26 (2H, d, J=8.1 Hz, 2 x Ar***H***), 7.49 (1H, ddd, J^1=7.9 Hz, J^2=7.5 Hz, J^3=1.5 Hz, Ar***H***), 7.67 (2H, d, J=8.1, 2 x Ar***H***), 7.86 (1H, dd, J^1=7.9 Hz, J^2=1.5 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.34 (CH_2), 21.65 (CH_3), 25.06 (CH_2), 28.26 (CH_2), 29.52 (CH_2), 40.89 (CH_2), 49.76 (CH), 67.95 (CH_2), 119.96 (CH), 124.63 (CH), 127.89 (2 x CH), 129.88 (2 x CH), 131.20 (qC), 131.24 (CH), 132.90 (qC), 133.78 (CH), 137.75 (qC), 144.84 (qC) ppm.

HRMS (ESI$^+$): found 465.1269 $[M+H]^+$, $C_{20}H_{25}N_4O_5S_2$ requires 465.1261.

7.3.1.5. Synthesis of 4-[(2-azido-*N*-ethylphenyl)sulfonamido]butyl 4-methylbenzenesulfonate.



(361)
$C_{19}H_{24}N_4O_5S_2$
MW = 452.54 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.33) yielded the product as a dark brown oil (97 %).

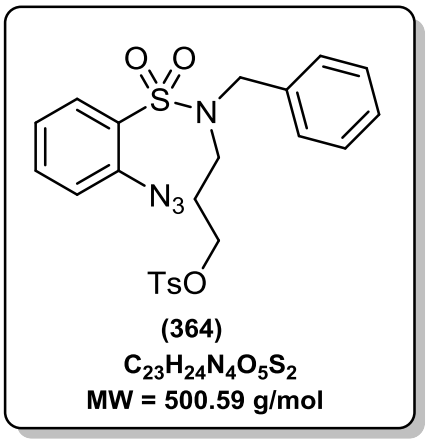
IR: υ_{max} (cm^{-1}): 749.2, 816.1, 949.8, 1010.7, 1097.0, 1122.4, 1155.9, 1290.0, 1329.7, 1471.4, 1574.8, 1597.3, 2129.0, 2979.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.06 (3H, t, *J*=7.2 Hz, $CH_2C\boldsymbol{H_3}$), 1.58-1.73 (4H, m, $NCH_2C\boldsymbol{H_2}C\boldsymbol{H_2}$), 2.46 (3H, br.s, Ph-C$\boldsymbol{H_3}$), 3.28-3.36 (4H, m, C$\boldsymbol{H_2}$-NCH-C$\boldsymbol{H_2}$), 4.04 (2H, t, *J*=6.0 Hz, O-C$\boldsymbol{H_2}$), 7.23 (1H, ddd, J^1=7.7 Hz, J^2=7.4 Hz, J^3=1.2 Hz, Ar***H***), 7.28-7.30 (1H, m, Ar***H***), 7.36 (2H, d, *J*= 8.1 Hz, 2 x Ar***H***), 7.57 (1H, ddd, J^1=7.7 Hz, J^2=7.4 Hz, J^3=1.2 Hz, Ar***H***), 7.79 (2H, d, *J*=8.1 Hz, 2 x Ar***H***), 7.97 (1H, dd, J^1=8.0 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.89 (CH_3), 21.66 (CH_3), 24.78 (CH_2), 25.97 (CH_2), 42.30 (CH_2), 46.72 (CH_2), 70.00 (CH_2), 119.81 (CH), 124.63 (CH), 127.88 (2 x CH), 129.90 (2 x CH), 131.19 (qC), 131.52 (CH), 132.97 (qC), 133.73 (CH), 137.94 (qC), 144.84 (qC) ppm.

HRMS (ESI$^+$): found 453.1264 $[M+H]^+$, $C_{19}H_{25}N_4O_5S_2$ requires 453.1261.

7.3.1.6. Synthesis of 3-[(2-azido-*N*-benzylphenyl)sulfonamido]propyl 4-methyl-benzenesulfonate.



(364)
$C_{23}H_{24}N_4O_5S_2$
MW = 500.59 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.33) yielded the product as a brown oil (89 %).

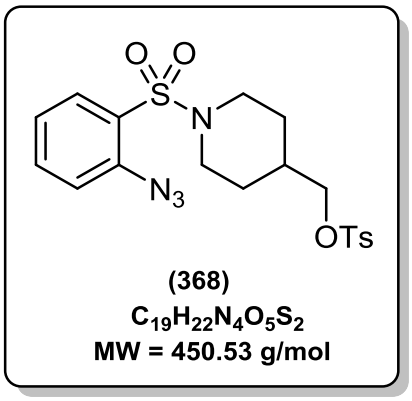
IR: υ_{max} (cm^{-1}): 728.0, 814.7, 972.2, 1020.3, 1096.2, 1123.2, 1157.0, 1174.7, 1288.5, 1332.5, 1471.5, 1494.9, 1597.3, 2128.0, 2979.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.71 (2H, p, *J*=7.3 Hz, $NCH_2C\boldsymbol{H_2}$), 2.45 (3H, s, $C\boldsymbol{H_3}$), 3.30 (2H, t, *J*=7.3 Hz, $NC\boldsymbol{H_2}CH_2$), 3.87 (2H, t, *J*=6.2 Hz, O-$C\boldsymbol{H_2}$), 4.47 (2H, s, Ph-$C\boldsymbol{H_2}$), 7.21-7.33 (9H, m, 9 x Ar***H***), 7.60 (1H, d, *J*=7.9 Hz, Ar***H***), 7.70 (2H, d, *J*=8.3 Hz, 2 x Ar***H***), 7.99 (1H, dd, J^1=7.9 Hz, J^2=1.5 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 21.66 (CH_3), 28.09 (CH_2), 44.64 (CH_2), 52.51 (CH_2), 67.84 (CH_2), 119.90 (CH), 124.77 (CH), 127.85 (2 x CH), 127.93 (CH), 128.27 (2 x CH), 128.68 (2 x CH), 129.90 (2 x CH), 130.62 (qC), 131.64 (CH), 132.73 (CH), 134.08 (CH), 136.29 (qC), 138.08 (qC), 144.92 (qC) ppm.

HRMS (ESI^+): found 501.1266 $[M+H]^+$, $C_{23}H_{25}N_4O_5S_2$ requires 501.1261.

7.3.1.7. Synthesis of {1-[(2-azidophenyl)sulfonyl]piperidin-4-yl}methyl 4-methylbenzenesulfonate.



(368)
$C_{19}H_{22}N_4O_5S_2$
MW = 450.53 g/mol

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.30) yielded the product as a brown oil (89 %).

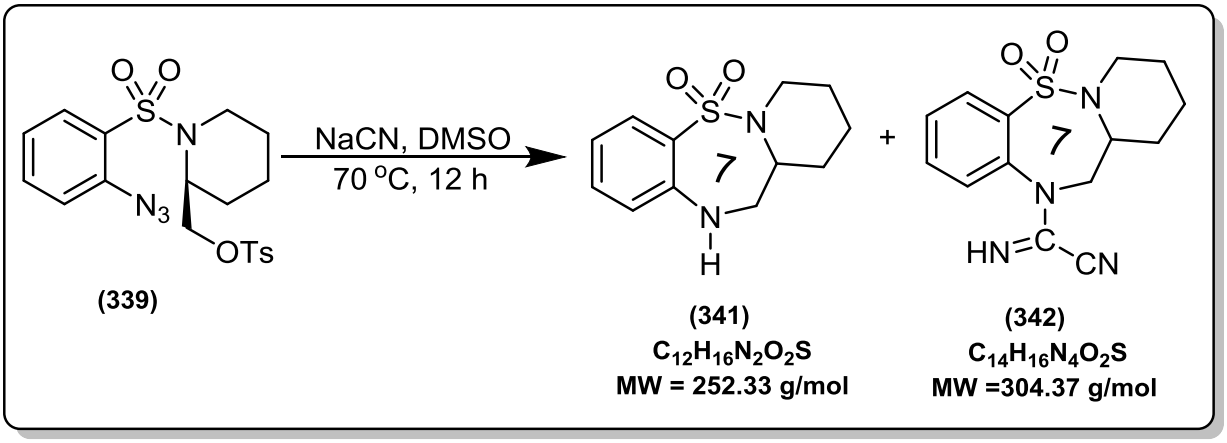
IR: υ_{max} (cm^{-1}): 725.7, 841.9, 909.1, 1065.9, 1173.8, 1188.6, 1287.5, 1308.8, 1353.7, 1443.5, 1471.4, 1574.0, 2130.6, 2980.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.10-1.20 (2H, m, C***H***$_2$CHCH$_2$), 1.61-1.71 (3H, m, CH$_2$C***H***C***H***$_2$), 2.35 (3H, s, C***H***$_3$), 2.54 (2H, td, J^1=14.0 Hz, J^2=1.6 Hz, C***H***$_2$CHCH$_2$), 3.11-3.15 (4H, m, C***H***$_2$NC***H***$_2$), 7.13 (1H, dd, J^1=7.9 Hz, J^2=7.4 Hz, Ar***H***), 7.20 (1H, d, *J*=7.9 Hz, Ar***H***), 7.26 (2H, d, *J*=8.2 Hz, 2 x Ar***H***), 7.49 (1H, ddd, J^1= 7.9 Hz, J^2=7.5 Hz, J^3=1.3 Hz, Ar***H***), 7.66 (2H, d, *J*=8.2 Hz, 2 x Ar***H***), 7.80 (1H, dd, J^1=7.9 Hz, J^2=1.3 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 21.64 (CH_3), 28.13 (2 x CH_2), 35.11 (CH), 45.46 (2 x CH_2), 73.61 (CH_2), 120.04 (CH), 124.68 (CH), 127.81 (2 x CH), 129.05 (qC), 129.97 (2 x CH), 131.59 (CH), 132.61 (CH), 134.05 (qC), 138.19 (qC), 145.05 (qC) ppm.

HRMS (ESI^+): found 451.1108 $[M+H]^+$, $C_{19}H_{23}N_4O_5S_2$ requires 451.1104.

7.3.2. Attempted Synthesis of 11,12,13,14,14a,15-hexahydrobenzo[*g*]pyrido-[1,2-*b*]tetrazolo[5,1-*e*][1,2,6]thiadiazocine 9,9-dioxide.



To a stirred solution of the tosylate (450 mg, 1.0 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (98 mg, 2.0 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 °C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography gave two products:

Synthesis of 1,3,4,11,12,12a-hexahydro-2*H*-benzo[*f*]pyrido[1,2-*b*][1,2,5]thiadia-zepine 6,6-dioxide (341).

[Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.28) yielded the product as a light yellow solid (159 mg, 63 %, m.p.=127-129 °C)].

IR: υ_{max} (cm^{-1}): 758.5, 910.7, 959.2, 1074.0, 1153.2, 1247.0, 1314.7, 1477.9, 1595.8, 2855.7, 2925.9, 2945.7, 3348.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.23-1.33 (1H, m, C***H***H), 1.43-1.51 (1H, m, CH***H***), 1.52-1.61 (2H, m, C**H$_2$**), 1.62-1.69 (1H, m, CH***H***), 1.71-1.80 (1H,m, C***H***H), 2.75-2.79 (1H, m, NC***H***), 3.05 (1H, d, *J*=14.1 Hz, HNCH***H***), 3.29-3.38 (2H, m, HNC***H***H + NCH***H***), 3.99-4.03 (1H, m, NC***H***H), 4.47 (1H, br.s, N**H**), 6.79 (1H, d, *J*=8.0 Hz, Ar**H**), 6.86 (1H, ddd, J^1=8.0 Hz,

J^2=7.8 Hz, J^3=0.8 Hz, Ar**H**), 7.20 (1H, ddd, J^1=8.0 Hz, J^2=7.8 Hz, J^3=1.5 Hz, Ar**H**), 7.69 (1H, dd, J^1=8.0 Hz, J^2=1.5, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 19.88 (CH_2), 25.04 (CH_2), 28.87 (CH_2), 41.77 (CH_2), 45.29 (CH_2), 55.76 (CH), 120.44(CH), 121.26(CH), 127.78 (qC), 129.51 (CH), 133.31 (CH), 146.44 (qC) ppm.

HRMS (ESI$^+$): found 252.0931 $[M]^+$, $C_{12}H_{16}N_2O_2S$ requires 252.0932.

Synthesis of 1,2,3,4,12,12a-hexahydro-11*H*-benzo[*f*]pyrido [1,2-*b*][1,2,5]thiadia-zepine-11-carbimidoyl cyanide 6,6-dioxide (342).

[Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.22)] yielded the product as a light yellow solid (95 mg, 31 %, m.p.=167-169 ^{o}C).

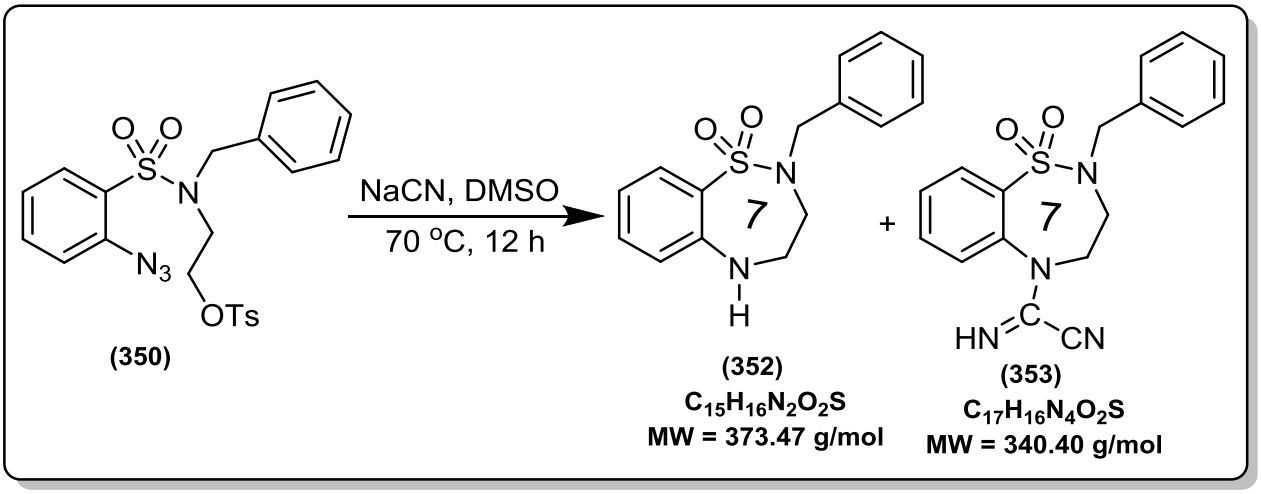
IR: υ_{max} (cm^{-1}): 647.8, 960.2, 1073.5, 1158.5, 1315.0, 1475.7, 1606.6, 2252.6 2857.9, 2946.8, 3346.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.55-1.84 (6H, m, 3 x C**H$_2$**), 2.24-2.29 (1H, m, N-C***H***), 3.31 (1H, br.s, N-C***H***H-CH), 3.44 (1H, d, *J*=10.7 Hz, N-CH***H***-CH), 4.29 (1H, d, *J*=12.4 Hz, NC***H***H), 4.55 (1H, br.s, NCH***H***), 7.40 (1H, d, *J*=7.0 Hz, Ar**H**), 7.50 (1H, dd, J^1=7.2 Hz, J^2=6.6 Hz, Ar**H**), 7.60 (1H, dd, J^1=7.2 Hz, J^2=6.6 Hz, Ar**H**), 7.91 (1H, d, *J*=7.0 Hz, Ar**H**), 8.22 (1H, br.s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.60 (CH_2), 24.72 (CH_2), 27.76 (CH_2), 41.01 (CH_2), 43.36 (CH_2), 50.68 (CH), 110.36 (CN), 129.74 (CH), 130.50 (CH), 130.71 (CH), 134.19 (CH), 138.12 (qC), 138.45 (qC) 141.06 (qC) ppm.

HRMS (ESI$^+$): found 304.0998 $[M]^+$, $C_{14}H_{16}N_4O_2S$ requires 304.0994.

7.3.3. Attempted synthesis of 6-benzyl-5,6-dihydro-4*H*-benzo[*g*] tetrazolo[5,1-*e*][1,2,6]thiadiazocine 7,7-dioxide.



To a stirred solution of the tosylate (300 mg, 0.62 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (61 mg, 1.24 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 °C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography gave two products:

2-Benzyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepine 1,1-dioxide (352).

(Eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.38) yielded the product as a brown oil (150 mg, 84 %).

IR: υ_{max} (cm^{-1}): 604.4, 697.5, 724.8, 907.4, 1152.8, 1325.7, 1352.9, 1477.4, 1594.0, 2979.8, 3370.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 3.32 (4H, s, 2 x C***H*****$_2$**), 4.19 (2H, 2, C***H*****$_2$**), 4.32 (1H, br.s, N***H***), 6.79 (1H, dd, J^1=8.0 Hz, J^2=1.0 Hz, Ar***H***), 6.92 (1H, dd, J^1= 7.8 Hz, J^2=7.4 Hz, Ar***H***), 7.18-7.28 (6H, m, 6 x Ar***H***), 7.81 (1H, dd, J^1=8.0 Hz, J^2=1.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 43.28 (CH_2), 48.23 (CH_2), 51.48 (CH_2), 120.76 (CH), 120.87 (CH), 127.90 (CH), 128.36 (2 x CH), 128.71 (2 x CH), 128.82 (qC), 129.73 (CH), 133.26 (CH), 135.93 (qC), 146.10 (qC) ppm.

HRMS (ESI$^+$): found 289.1007 $[M+H]^+$, $C_{15}H_{17}N_2O_2S$ requires 289.1005.

2-Benzyl-3,4-dihydrobenzo[*f*][1,2,5]thiadiaze pine-5(2*H*)-carbimidoyl cyanide 1,1-dioxide (353).

(Eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.19) yielded the product as a light yellow oil (18 mg, 9 %).

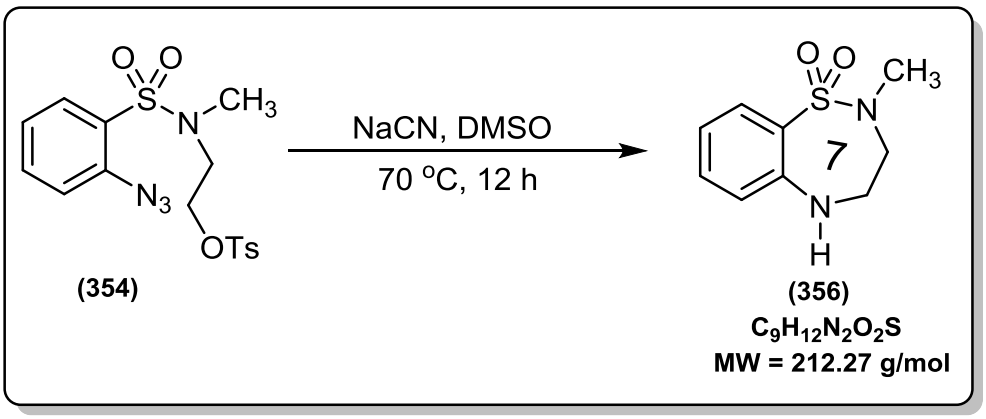
IR: υ_{max} (cm^{-1}): 724.6, 906.4, 1010.6, 1128.2, 1153.6, 1249.4, 1327.3, 1370.8, 1475.5, 1606.7, 2248.7, 2931.1, 3378.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.91 (1H, m, C***H***H), 3.29 (2H, m, C**H$_2$**), 3.58 (1H, bs, CH***H***), 4.57 (1H, m, C***H***H), 4.50 (1H, d, *J*=14.5 Hz, CH***H***), 7.17-7.26 (3H, m, 3 x Ar***H***), 7.41 (1H, d, *J*=7.5 Hz, Ar***H***), 7.50 (1H, dd, J^1=7.5 Hz, J^2=7.3 Hz, Ar***H***), 7.59 (1H, dd, J^1=7.5 Hz, J^2=7.3 Hz, Ar**H**), 7.78 (2H, d, *J*=7.5 Hz, 2 x Ar**H**), 7.98 (1H, d, *J*=7.5 Hz, Ar**H**), 8.20 (1H, sb, N**H**) ppm.

^{13}C NMR δc (100 MHz, $CDCl_3$): 28.44 (CH_2), 50.58 (CH_2), 51.46 (CH_2), 110.37 (CN), 120.92 (qC), 127.90 (CH), 128.30 (2 x CH), 128.88 (2 x CH), 129.67 (CH), 129.77 (CH), 130.88 (CH), 134.18 (CH), 135.03 (qC), 140.87 (qC), 146.20 (qC) ppm.

HRMS (ESI$^+$): found 341.1065 $[M+H]^+$, $C_{17}H_{17}N_4O_2S$ requires 341.1067.

7.3.4. Attempted synthesis of 6-methyl-5,6-dihydro-4*H*-benzo[*g*] tetrazolo[5,1-*e*][1,2,6]thiadiazocine 7,7-dioxide.



To a stirred solution of the tosylate (300 mg, 0.73 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (72 mg, 1.46 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 ^{o}C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.28) yielded the product as a pale yellow (135 mg, 87 %, m.p.=140-142 ^{o}C).

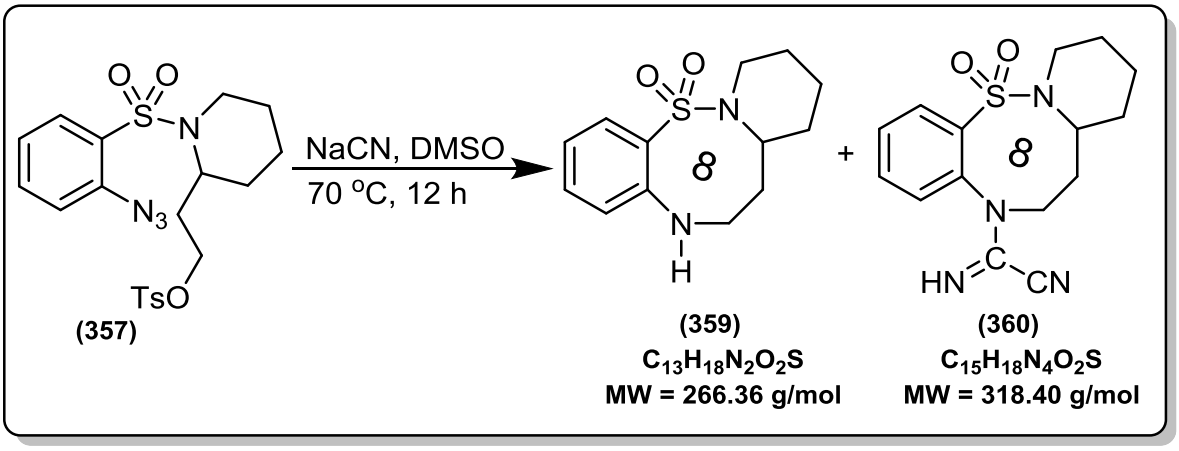
IR: υ_{max} (cm^{-1}): 761.4, 883.8, 911.3, 1028.2, 1045.2, 1130.7, 1148.7, 1251.3, 1316.2, 1369.9, 1476.9, 1476.9, 1509.2, 1593.2, 2939.7, 3370.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.82 (3H, s, C***H*$_3$**), 3.35 (2H, t, *J*=4.5 Hz, NCH$_2$C***H*$_2$**NH), 3.56-3.58 (2H, m, NC***H*$_2$**CH$_2$NH), 4.38 (1H, br.s, N***H***), 6.89 (1H, d, *J*=8.0 Hz, Ar***H***), 7.01 (1H, ddd, J^1= 8.0 Hz, J^2= 7.7 Hz, J^3=1.5 Hz, Ar***H***), 7.33 (1H, ddd, J^1=8.0 Hz, J^2=7.7 Hz, J^3=1.5 Hz, Ar***H***), 7.85 (1H, dd, J^1=8.0 Hz, J^2=1.5 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 35.73 (CH_3), 42.64 (CH_2), 52.41 (CH_2), 120.97 (CH), 121.10 (CH), 127.72 (qC), 130.33 (CH), 133.35 (CH), 146.02 (qC) ppm.

HRMS (ESI$^+$): found 213.0694 $[M+H]^+$, $C_9H_{13}N_2O_2S$ requires 213.0692.

7.3.5. Attempted synthesis of 10,10a,11,12,13,14-hexahydro-9*H*-benzo[*h*]-pyrido[1,2-*b*]tetrazolo[5,1-*f*][1,2,7]thiadiazonine 16,16-dioxide.



To a stirred solution of the tosylate (250 mg, 0.538 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (53 mg, 1.076 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 ^{o}C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography gave two products:

5,6,7,7a,8,9,10,11-Octahydrobenzo[*g*]pyrido[1,2-*b*][1,2,6]thiadiazocine 13,13-dioxide (359).

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.32) yielded the product as a light yellow oil (88 mg, 61 %).

IR: υ_{max} (cm^{-1}): 781.9, 854.3, 911.3, 1087.0, 1105.6, 1136.4, 1150.0, 1246.1, 1295.1, 1310.9, 1331.9, 1463.1, 1488.2, 1595.2, 2864.5, 2938.4, 3365.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.15-1.33 (2H, m, C***H*$_2$**), 1.48-1.61 (4H, m, 2 x C***H*$_2$**), 1.76-1.93 (2H, m, C***H*$_2$**), 2.24-2.31 (1H, m, C***H***H), 3.24-3.34 (1H, m, HNCH***H***), 3.23-3.34 (2H, m, HNC***H***H+NC***H***), 3.40-3.43 (1H, m, NCH***H***), 4.20 (1H, bs, NC***H***H), 4.96 (1H, bs, N***H***), 6.97 (1H, dd, J^1=7.9 Hz, J^2=7.6 Hz, Ar***H***), 7.06 (1H, d, J= 8.0 Hz, Ar***H***), 7.34 (1H, ddd, J^1=7.9 Hz, J^2=7.6 Hz, J^3=1.0 Hz, Ar***H***), 7.73 (1H, dd, J^1=8.0 Hz, J^2=0.9 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.64 (CH_2), 25.33 (CH_2), 29.00 (CH_2), 32.89 (CH_2), 40.31 (CH_2), 50.06 (CH_2), 52.95 (CH), 121.97 (CH), 125.65 (CH), 129.72 (CH), 132.36 (qC), 133.40 (CH), 147.08 (qC) ppm.

HRMS (ESI^+): found 267.1167 $[M+H]^+$, $C_{13}H_{19}N_2O_2S$ requires 267.1162.

7,7a,8,9,10,11-Hexahydrobenzo[*g*]pyrido[1,2-*b*][1,2,6]thiadiazocine-5(6*H*)-carbimidoyl cyanide 13,13-dioxide (360).

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.2) yielded the product as a yellow oil (50 mg, 29 %).

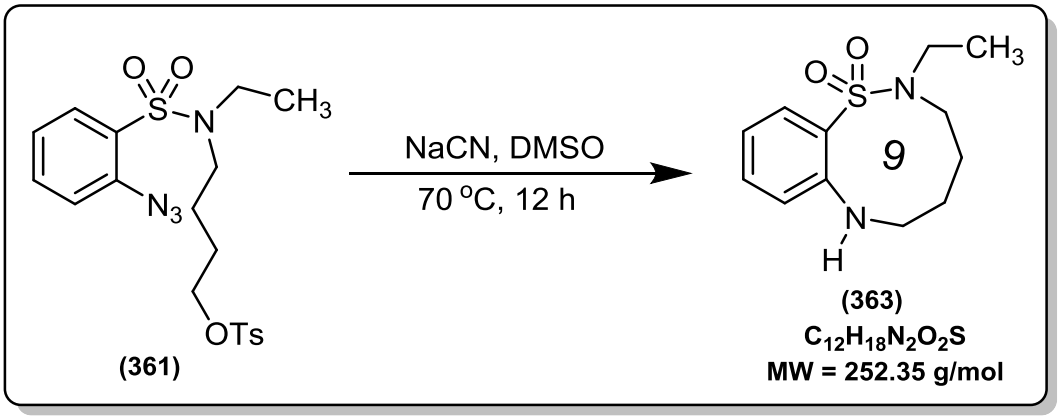
IR: υ_{max} (cm^{-1}): 772.1, 872.4, 954.1, 1054.9, 1089.2, 1191.4, 1226.9, 1306.5, 1326.2, 1444.3, 1474.6, 1584.5, 1607.4, 2255.2, 2857.0, 2930.2, 3314.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.18-1.22 (1H, m, C***H***H), 1.41-1.66 (4H, m, 2 x C$\mathbf{H_2}$), 1.76-1.85 (1H, m, C***H***H), 1.90-1.99 (1H, m, CH***H***), 2.07 (1H, d, *J*=5.0 Hz, C***H***H), 2.48 (1H, td, J^1=12.9 Hz, J^2=4.3 Hz, CH***H***), 2.91 (1H, bs, C***H***H), 3.61-3.65 (1H, m, C***H***), 4.31-4.43 (2H, m, NC$\boldsymbol{H_2}$), 7.25 (1H, d, *J*=7.7 Hz, Ar***H***), 7.47 (1H, ddd, J^1= 7.7 Hz, J^2=7.5 Hz, J^3= 0.9 Hz, Ar***H***), 7.56 (1H, ddd, J^1=7.7 Hz, J^2=7.5 Hz, J^3=1.4 Hz, Ar***H***), 7.99 (1H, dd, J^1=7.7 Hz, J^2=1.4 Hz, Ar***H***), 8.09 (1H, bs, N***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.78 (CH_2), 25.66 (CH_2), 26.10 (CH_2), 30.19 (CH_2), 40.72 (CH_2), 49.51 (CH_2), 50.57 (CH), 110.76 (CN), 129.60 (CH), 130.30 (CH), 130.84 (CH), 133.80 (CH), 140.51 (qC), 142.13 (qC), 158.19 (C=N) ppm.

HRMS (ESI$^+$): found 319.1228 $[M+H]^+$, $C_{15}H_{19}N_4O_2S$ requires 319.1223.

7.3.6. Synthesis of 2-ethyl-2,3,4,5,6,7-hexahydrobenzo[*h*][1,2,7]thiadiazonine 1,1-dioxide.



To a stirred solution of the tosylate (250 mg, 0.553 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (54 mg, 1.11 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 ^{o}C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.26) yielded the product as a yellow oil (85 mg, 60 %).

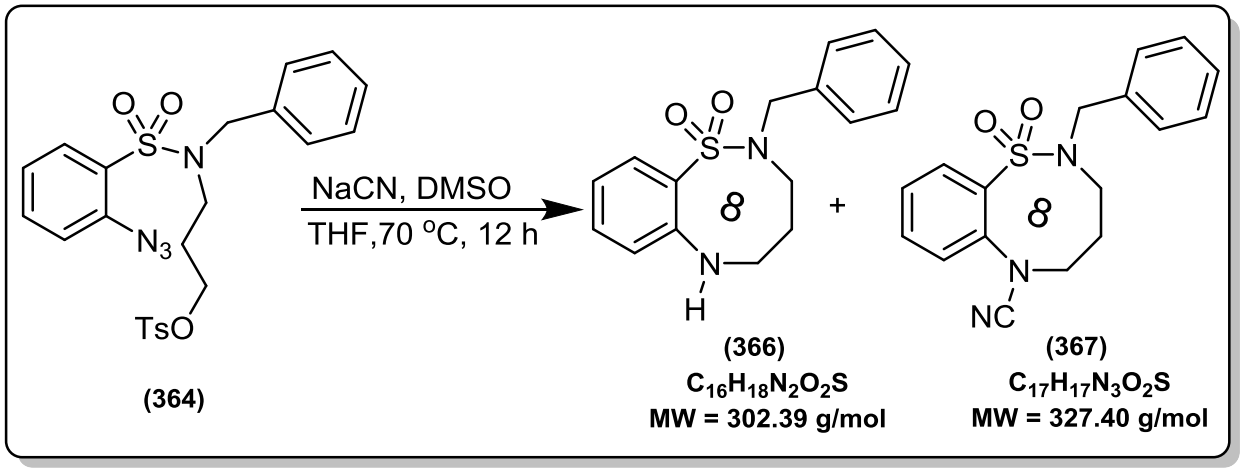
IR: υ_{max} (cm^{-1}): 759.4, 926.4, 978.8, 1020.6, 1085.1, 1146.1, 1187.7, 1266.9, 1322.5, 1376.6, 1463.6, 1576.0, 1595.1, 2852.2, 2920.7, 3409.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.07-1.18 (3H, m, C***H*****$_3$**), 2.06-2.09 (1H, m, $NCH_2C\boldsymbol{H_2}$), 2.24-2.35 (2H, m, $HNCH_2C\boldsymbol{H_2}$), 2.88 (2H, q, *J*=7.0 Hz, $HNCH_2C\boldsymbol{H_2}$), 3.36 (2H, t, *J*=4.6 Hz, $NC\boldsymbol{H_2}CH_2$), 3.76 (2H, t, *J*=6.2 Hz, $NC\boldsymbol{H_2}CH_3$), 4.79 (1H, bs, N***H***), 6.84 (1H, dd, J^1=8.0 Hz, J^2=7.4 Hz, Ar**H**), 7.00 (1H, d, *J*= 8.0 Hz, Ar**H**), 7.32 (1H, dd, J^1=8.0 Hz, J^2=7.4 Hz, Ar**H**), 7.71 (1H, d, *J*=8.0 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.13 (CH_3), 22.70 (CH_2), 26.08 (CH_2), 29.71 (CH_2), 43.88 (CH_2), 48.79 (CH_2), 120.01 (CH), 122.12 (CH), 128.93 (CH), 131.80 (qC), 133.25 (CH), 147.04 (qC) ppm.

HRMS (ESI$^+$): found 255.1165 $[M+H]^+$, $C_{12}H_{19}N_2O_2S$ requires 255.1162.

7.3.7. Attempted synthesis of 7-benzyl-4,5,6,7-tetrahydrobenzo [*h*]tetrazolo[5,1-*f*][1,2,7]thiadiazonine 8,8-dioxide.



To a stirred solution of the tosylate (350 mg, 0.7 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (69 mg, 1.4 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 °C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography gave two products:

2-Benzyl-3,4,5,6-tetrahydro-2*H*-benzo[*g*][1,2,6] thiadiazocine 1,1-dioxide (366).

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.3) yielded the product as a light yellow oil (142 mg, 80 %).

IR: υ_{max} (cm^{-1}): 724.5, 860.4, 905.1, 1025.1, 1122.0, 1150.1, 1239.4, 1326.4, 1463.1, 1487.6, 1595.1, 2934.4, 3368.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.48 (2H, br.t, *J*=3.6 Hz, $NCH_2C\boldsymbol{H_2}$), 3.26-3.31 (4H, m, $NC\boldsymbol{H_2}$ + $HNC\boldsymbol{H_2}$), 3.89 (2H, s, Ph-$C\boldsymbol{H_2}$), 5.07 (1H, br.s, N***H***), 6.97 (1H, t, *J*=7.6 Hz, Ar***H***), 7.07 (1H, d, *J*=7.9 Hz, Ar***H***), 7.16-7.23 (5H, m, 5 x Ar***H***), 7.35 (1H, dd, J^1=7.9 Hz, J^2=7.4 Hz, Ar***H***), 7.79 (1H, d, *J*=7.9 Hz, Ar***H***) ppm

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.07 (CH_2), 43.58 (CH_2), 48.99 (CH_2), 49.96 (CH_2), 121.91 (CH), 125.50 (CH), 127.93 (CH), 128.38 (2 x CH), 128.67 (2 x CH), 129.48 (CH), 132.44 (qC), 133.57 (CH), 135.58 (qC), 147.09 (qC) ppm.

HRMS (ESI^+): found 303.1157 $[M+H]^+$, $C_{16}H_{19}N_2O_2S$ requires 303.1162.

2-Benzyl-2,3,4,5-tetrahydro-6*H*-benzo[*g*][1,2,6] thiadiazocine-6-carbonitrile 1,1-dioxide (367).

(Eluent: petroleum ether/ethylacetate: 2/1, R_f = 0.2) yielded the product as a light yellow oil (38 mg, 17 %).

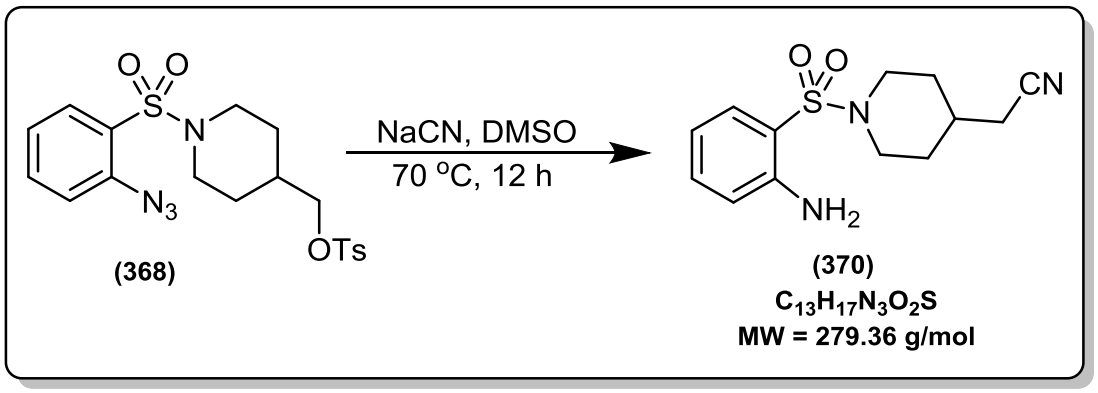
IR: υ_{max} (cm^{-1}): 793.4, 866.2, 924.1, 1075.8, 1153.6, 1332.7, 1473.7, 1494.9, 1585.0, 2216.5, 2929.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.93 (2H, app. p, *J*=5.7 Hz, $NCH_2C\boldsymbol{H_2}$), 3.60 (2H, t, *J*=5.6 Hz, NC-$NC\boldsymbol{H_2}$), 3.67 (2H, t, *J*=6.0 Hz, $NC\boldsymbol{H_2}CH_2$), 4.22 (2H, s, Ph-$C\boldsymbol{H_2}$), 7.22-7.34 (6H, m, 6 x Ar***H***), 7.39 (1H, ddd, J^1=8.2 Hz, J^2=7.9 Hz, J^3=1.3 Hz, Ar***H***), 7.49 (1H, dd, J^1=7.9 Hz, J^2=1.1 Hz, Ar***H***), 7.54 (1H, ddd, J^1=8.3 Hz, J^2=7.9 Hz, J^3=1.3 Hz, Ar***H***) ppm

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 23.45 (CH_2), 42.26 (CH_2), 49.04 (CH_2), 54.20 (CH_2), 114.73 (CN), 126.45 (CH), 128.29 (CH), 128.34 (3 x CH), 128.87 (2 x CH), 131.10 (CH), 133.89 (CH), 134.87 (qC), 136.73 (qC), 138.26 (qC) ppm.

HRMS (ESI^+): found 327.1040 $[M]^+$, $C_{17}H_{17}N_3O_2S$ requires 327.1041.

7.3.8. Attempted synthesis of 4,5,6,7-tetrahydro-5,8-ethanobenzo [*i*]tetrazolo[5,1-*g*][1,2,8]thiadiazecine 9,9-dioxide.



To a stirred solution of the tosylate (100 mg, 0.222 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (22 mg, 0.444 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 °C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.32) yielded the product as a yellow oil (38 mg, 57 %).

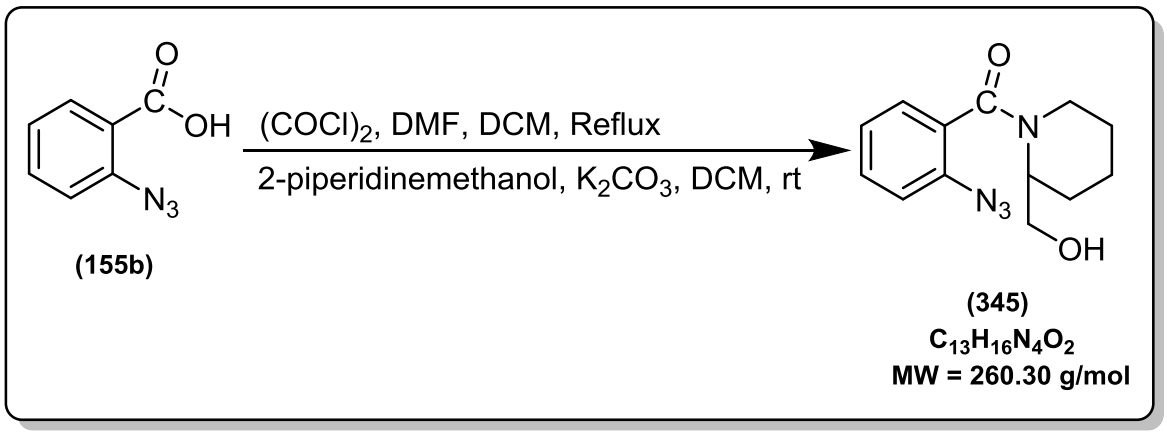
IR: υ_{max} (cm^{-1}): 840.0, 886.0, 933.1, 1047.4, 1090.8, 1246.7, 13224.8, 1450.9, 1483.7, 1564.6, 1617.6, 2247.3, 2852.7, 2923.1, 3378.0, 3476.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.35 (1H, qd, J^1=12.3 Hz, J^2=4.1 Hz, C***H***), 1.56-1.67 (2H, m, $NCH_2C\boldsymbol{H_2}$), 1.78 (2H, d, J=12.7 Hz, $NCH_2C\boldsymbol{H_2}$), 2.21 (2H, d, J=6.9 Hz, $C\boldsymbol{H_2}$-CN), 2.44 (2H, td, J^1=12.3 Hz, J^2=2.4 Hz, $NC\boldsymbol{H_2}CH_2$), 3.77 (2H, dd, J^1=10.1 Hz, J^2=2.1 Hz, $NC\boldsymbol{H_2}CH_2$), 4.95-4.97 (2H, m, $N\boldsymbol{H_2}$), 6.64-6.70 (1H, m, Ar***H***), 7.23 (1H, ddd, J^1=8.3 Hz, J^2=8.1 Hz, J^3=1.4 Hz, Ar***H***), 7.48 (1H, dd, J^1=8.3 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 23.77 (CH_2), 30.74 (2 x CH_2), 32.63 (CH), 45.62 (2 x CH_2), 117.28 (CH), 117.70 (CH), 117.82 (qC), 117.85 (qC), 130.26 (CH), 134.31 (CH), 146.24 (qC) ppm.

HRMS (ESI^+): found 279.1045 $[M]^+$, $C_{13}H_{17}N_3O_2S$ requires 279.1041.

7.3.9. Synthesis of (2-azidophenyl)(2-(hydroxymethyl)piperidin-1-yl)methanone.



2-Azidobenzoic acid[120,239] (1.075 g, 6.6 mmol, 2.2 eq) was heated at reflux in a 2M solution of $(COCl)_2$ in dichloromethane (7.5 mL, 15.0 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was allowed to reach room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude 2-azidobenzoyl chloride as a dark brown solid.

A solution of potassium carbonate (1.656 g, 12.0 mmol, 4.0 eq) in water (10 mL) was added in one portion to a stirring solution of 2-piperidinemethanol (345 mg, 3.0 mmol, 1.0 eq) in dichloromethane (10 mL). The 2-azidobenzoyl chloride was dissolved in dichloromethane (5 mL) and was added slowly to this solution. The reaction was allowed to stir at room temperature for 18 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography [petroleum ether/ethyl acetate: 5/1, R_f = 0.2] to yield the product as a brown oil (780 mg, 81 %).

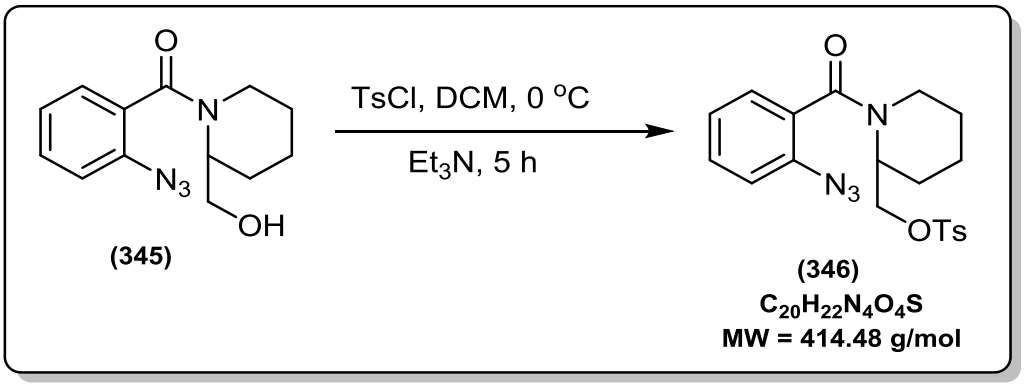
IR: υ_{max} (cm^{-1}): 872.7, 953.7, 1013.8, 1048.2, 1282.2, 1372.3, 1433.9, 1489.2, 1595.8, 1607.5, 1715.8, 2124.5, 2869.4, 2938.1, 3053.4, 3377.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.42-1.64 (5H, m, 2 x C***H*****$_2$** +C***H***H), 2.67-2.73 (1H, m, CH***H***), 3.13 (1H, d, *J*=13.2 Hz, HO-C***H***H), 3.61-3.72 (3H, m, HO-CH***H*** + NC***H*** + NC***H***H), 4.53 (1H, d, *J*=13.2 Hz, NCH***H***), 4.81 (1H, br.s, O***H***), 7.03-7.06 (1H, m, Ar***H***), 7.08-7.11 (1H, m, Ar***H***), 7.16-7.22 (1H, m, Ar***H***), 7.24-7.35 (1H, m, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 19.33 (CH_2), 24.68 (CH_2), 37.27 (CH_2), 43.29 (CH_2), 55.98 (CH), 60.36 (CH_2), 118.10 (CH), 125.09 (CH), 128.17 (CH), 128.83 (qC), 130.19 (CH), 135.93 (qC), 168.07 (C=O) ppm.

HRMS (ESI$^+$): found 261.1346 $[M+H]^+$, $C_{13}H_{17}N_4O_2$ requires 261.1335.

7.3.10. Synthesis of [1-(2-azidobenzoyl)piperidin-2-yl]methyl 4-methylbenzenesulfonate.



To a stirred solution the alcohol (300 mg, 1.16 mmol, 1.0 eq) and p-toluenesulfonyl chloride (331 mg, 1.74 mmol, 1.5 eq) in dichloromethane (10 mL) at 0 °C, triethylamine (586 mg, 5.8 mmol, 5.0 eq) was added dropwise. The mixture was stirred at room temperature over 5 h whilst being monitored by TLC. The reaction mixture was diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), and brine (2 x 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed in *vacuo*. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 3/1, R_f = 0.23) yielded the product as a light yellow oil (445 mg, 94 %).

IR: υ_{max} (cm^{-1}): 727.6, 908.3, 1076.5, 1147.4, 1124.7, 1247.6, 1293.5, 1445.8, 1486.9, 1597.0, 1720.8, 2120.5, 2867.2, 2942.7.

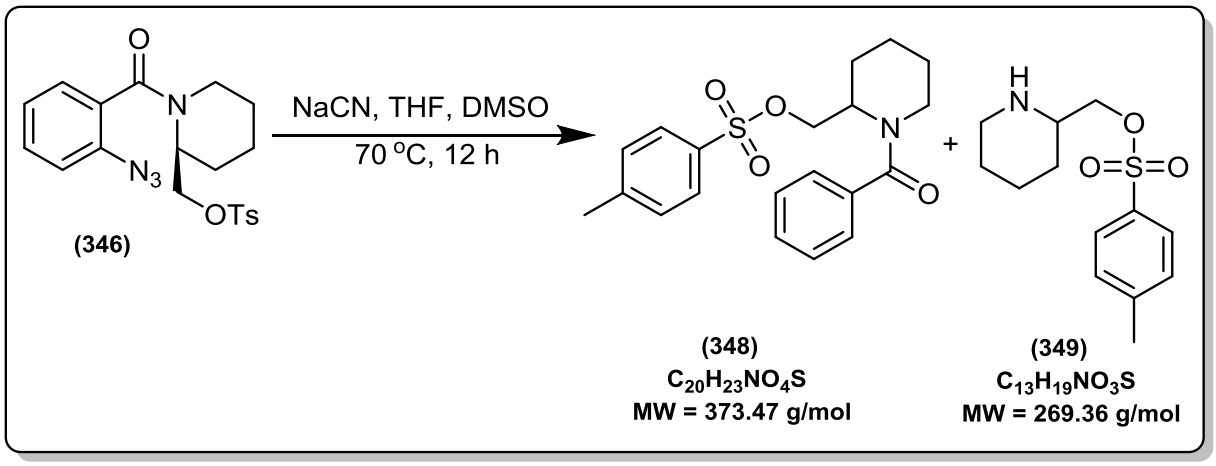
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.16-1.22 (1H, m, C***H***H), 1.40-1.49 (4H, m, 2 x C$\mathbf{H_2}$), 1.60-1.65 (1H, m, CH***H***), 2.26 (3H, br.s, C$\boldsymbol{H_3}$), 3.04 (1H, td, J^1=14.7 Hz, J^2=2.2 Hz, NC***H***H), 3.71 (1H, dd, J^1=14.2 Hz, J^2=4.0 Hz, NC***H***), 4.21 (1H, app. q, J=5.4 Hz, NCH***H***), 4.36-4.46

(2H, m, OC***H*****$_2$**), 7.06-7.13 (4H, m, 2 x Ar***H***), 7.43 (1H, ddd, J^1=7.9 Hz, J^2=7.7 Hz, J^3=1.4 Hz, Ar***H***), 7.61 (2H, d, *J*=8.2 Hz, 2 x Ar***H***), 7.83 (1H, dd, J^1=7.9 Hz, J^2=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.90 (CH_2), 21.46 (CH_3), 24.28 (CH_2), 25.19 (CH_2), 41.24 (CH_2), 51.07 (CH), 62.01 (CH_2), 119.79 (CH), 122.07 (qC), 124.54 (CH), 126.85 (2 x CH), 129.62 (2 x CH), 132.15 (CH), 133.37 (CH), 138.46 (qC), 140.14 (qC), 142.97 (qC), 164.72 (C=O) ppm.

HRMS (ESI$^+$): found 437.1234 $[M+Na]^+$, $C_{20}H_{22}N_4O_4SNa$ requires 437.1254.

7.3.11. Attempted synthesis of 11,12,13,14,14a,15-hexahydro-9*H*-benzo[*f*]-pyrido[1,2-*a*]tetrazolo[5,1-*d*][1,5]diazocin-9-one.



To a stirred solution of the tosylate (200 mg, 0.483 mmol, 1.0 eq) in DMSO (10 mL) was added sodium cyanide (47 mg, 0.966 mmol, 2.0 eq) in THF (5 mL). The resultant mixture was heated at 70 °C under a nitrogen atmosphere for 12 h whilst being monitored by TLC. The reaction was left to cool to room temperature. The reaction was diluted with water (10 mL) and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica chromatography gave two products:

(1-Benzoylpiperidin-2-yl)methyl 4-methylbenzenesulfonate (348):

[(eluent: Hexane/ethylacetate: 3/1, R_f = 0.24) yielded the product as a light yellow oil (95 mg, 31 %).

IR: υ_{max} (cm^{-1}): 814.5, 907.6, 991.3, 1093.1, 1113.8, 1148.4, 1160.6, 1272.6, 1327.6, 1450.5, 1600.0, 1719.5, 2854.7, 2925.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.18-1.64 (6H, m, 3 x C**H$_2$**), 2.28 (3H, s, C**H$_3$**), 3.05 (1H, td, J^1=13.0 Hz, J^2=1.7 Hz, N-C***H***), 3.73 (1H, dd, J^1=14.0 Hz, J^2=3.5 Hz, N-CH***H***), 4.22-4.29 (1H, m, N-C***H***H), 4.43-4.51 (2H, m, O-C**H$_2$**), 7.11 (2H, d, *J*=8.0 Hz, 2 x Ar**H**), 7.36 (2H, t, *J*=7.6 Hz, 2 x Ar***H***), 7.48 (1H, t, *J*=7.6 Hz, Ar**H**), 7.63 (2H, d, *J*=8.0 Hz, 2 x Ar**H**), 7.95 (2H, d, *J*=7.6 Hz, 2 x Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.96 (CH_2), 21.48 (CH_3), 24.42 (CH_2), 25.36 (CH_2), 41.30 (CH_2), 51.11 (CH), 61.92 (CH_2), 126.91 (2 x CH), 128.36 (2 x CH), 129.65 (2 x CH), 129.79 (2 x CH), 129.82 (qC), 133.07 (CH), 138.44 (qC), 142.99 (qC), 166.36 (C=O) ppm.

HRMS (ESI^+): found 396.1242 [M+Na]+, $C_{20}H_{23}NO_4SNa$ requires 396.1240.

Piperidin-2-ylmethyl 4-methyl benzenesulfonate (349).

(eluent: Hexane/ethylacetate: 2/1, R_f =0.2) yielded the product as a orange oil (45 mg, 35 %).

IR: υ_{max} (cm^{-1}): 725.0, 874.2, 987.9, 1092.5, 1153.5, 1186.1, 1303.9, 1325.2, 1446.2, 1597.5, 2942.1, 3517.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.18-1.53 (6H, m, 3 x C***H$_2$***), 2.17 (1H, bs, NCH***H***), 2.35 (3H, s, C***H$_3$***), 3.02 (1H, t, *J*=12.7 Hz, NC***H***H), 3.50 (1H, t, *J*=5.1 Hz, NC***H***), 3.70 (1H, bs, N***H***), 7.22 (2H, d, *J*=7.8 Hz, 2 x Ar**H**), 7.67 (2H, d, *J*=7.8 Hz, 2 x Ar**H**) ppm.

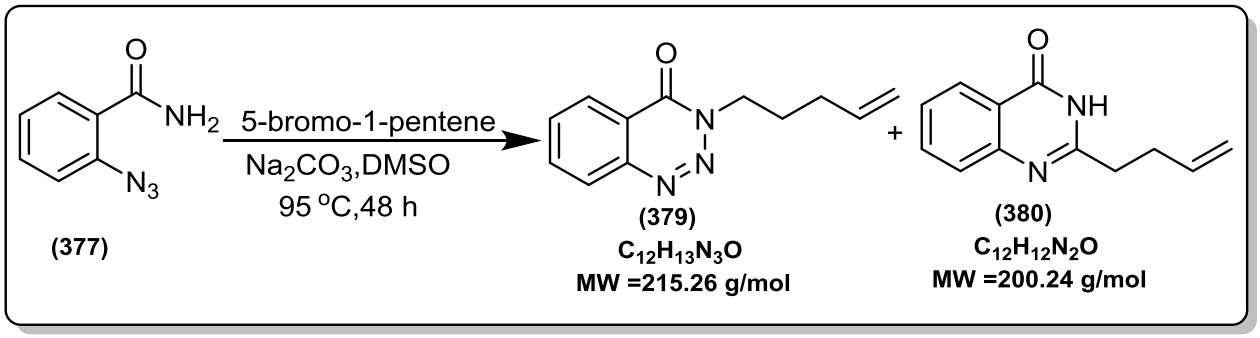
^{13}C NMR δ_c (100 MHz, $CDCl_3$): 19.15 (CH_2), 21.53 (CH_3), 24.19 (CH_2), 24.77 (CH_2), 41.41 (CH_2), 54.68 (CH), 60.66 (CH_2), 126.99 (2 x CH), 129.79 (2 x CH), 138.10 (qC), 143.28 (qC) ppm.

HRMS (ESI^+): found 270.1164 [M+H]+, $C_{13}H_{20}NO_3S$ requires 270.1158.

8. Chapter 8: Experimental for Chapter 4: Reactivity of 2-azidobenzamide.

8.1. Reactivity of 2-azidobenzamide.

8.1.1. Reactivity of 2-azidobenzamide with 5-bromo-1-pentene.



To a solution of 2-azidobenzamide[240] (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 5-bromo-1-pentene (368 mg, 2.46 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography to give two products:

3-(Pent-4-en-1-yl)benzo[*d*][1,2,3]triazin-4(3*H*)-one (379).

(Eluent: petroleum ether/ethyl acetate: 4/1, Rf = 0.2) yielded the product as a dark orange oil (100 mg, 38 %).

IR: υ_{max} (cm^{-1}): 559.1, 619.3, 645.5, 686.3, 775.1, 911.3, 968.9, 991.0, 1037.3, 1072.4, 1183.6, 1274.2, 1294.2, 1333.0, 1463.2, 1579.2, 1607.3, 1640.6, 1679.5, 2856.0, 2929.2, 3075.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.95 (2H, td, J^1=14.8 Hz, J^2= 3.6 Hz C**H**$_2$), 2.12 (2H, q, J= 7.1 Hz, C**H**$_2$), 4.41 (2H, t, J= 7.3 Hz, C**H**$_2$), 4.92 (1H, d, J= 10.2 Hz, CH**H**), 5.00 (1H, dd, J^1=17.1 Hz, J^2=0.8 Hz, C**H**H), 5.71-5.82 (H, m, C**H**), 7.72 (1H, dd, J^1=7.7 Hz, J^2=7.5 Hz, Ar**H**), 7.86 (1H, dd, J^1=7.7 Hz, J^2=7.3 Hz, Ar**H**), 8.07 (1H, d, J=7.7 Hz, Ar**H**), 8.27 (1H, d, J=7.7 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 27.93 (CH_2), 30.74 (CH_2), 49.40 (CH_2), 115.58 (CH_2), 119.82 (qC), 125.06 (CH), 128.22 (CH), 132.26 (CH), 134.72 (CH), 137.14 (CH), 144.32 (qC), 155.52 (C=O) ppm.

HRMS (ESI$^+$): found 215.1059 $[M]^+$, $C_{12}H_{13}N_3O$ requires 215.1059.

2-(But-3-en-1-yl)quinazolin-4(3*H*)-one (380).

(Eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.3) yielded the product as a light yellow solid (80 mg, 33 %, m.p.: 167-169 ^{o}C).

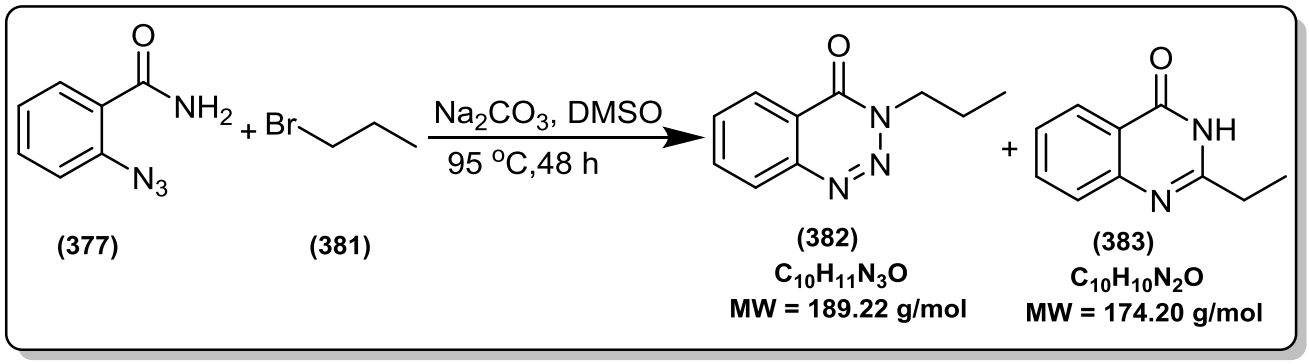
IR: υ_{max} (cm^{-1}): 766.6, 897.1, 994.0, 1105.3, 1139.6, 1194.7, 1253.1, 1288.4, 1341.5, 1421.1, 1445.0, 1469.1, 1563.6, 1608.9, 1673.1, 2916.5, 2975.5, 3030.0, 3168.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.59 (2H, q, *J*=7.3 Hz, C**H$_2$**), 2.84 (2H, t, *J*= 7.3 Hz, C**H$_2$**), 4.97 (1H, d, *J*=10.1 Hz, =C**H**H), 5.08 (1H, dd, J^1= 17.1 Hz, J^2=1.0 Hz, =CH**H**), 5.82-5.92 (1H, m, C**H**), 7.40 (1H, dd, J^1=7.8 Hz, J^2=7.2 Hz, Ar**H**), 7.63 (1H, d, *J*=8.0 Hz, Ar**H**), 7.70 (1H, dd, J^1=8.0 Hz, J^2=7.1 Hz, Ar**H**), 8.21 (1H, d, *J*=7.8 Hz, Ar**H**), 12.11 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 31.31 (CH_2), 35.19 (CH_2), 116.29 (CH_2), 120.53 (qC), 126.24 (CH), 126.44 (CH), 127.26 (CH), 134.82 (CH), 136.43 (CH), 149.45 (qC), 156.07 (qC), 164.39 (C=O) ppm.

HRMS (ESI$^+$): found 201.1023 $[M+H]^+$, $C_{12}H_{13}N_2O$ requires 201.1022

8.1.2. Reactivity of 2-azidobenzamide with 1-bromo propane.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 1-bromo propane (304 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^{o}C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography to give two products:

Synthesis of 3-propylbenzo[*d*][1,2,3]triazin-4(3*H*)-one (382).

(Eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.21) yielded the product as a light yellow solid (88 mg, 38 %, m.p.= 49 -51 ^{o}C).

IR: υ_{max} (cm^{-1}): 735.6, 891.3, 976.9, 1015.2, 1024.4, 1142.8, 1174.6, 1226.2, 1281.0, 1293.5, 1320.3, 1333.6, 1458.0, 1496.7, 1577.7, 1605.6, 1640.6, 2878.9, 2963.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 0.95 (3H, t, *J*=7.4 Hz, C**H**$_3$), 1.88 (2H, app. sextet, *J*= 7.4 Hz, C**H**$_2$), 4.37 (2H, t, *J*= 7.4 Hz, C**H**$_2$), 7.72 (1H, dd, J^1=7.9 Hz, J^2=7.3 Hz, Ar**H**), 7.87 (1H, dd, J^1=8.1 Hz, J^2=7.5 Hz, Ar**H**), 8.07 (1H, d, *J*=8.1 Hz, Ar**H**), 8.29 (1H, d, *J*=7.9 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 11.18 (CH_3), 22.29 (CH_2), 51.44 (CH_2), 119.85 (qC), 125.08 (CH), 128.20 (CH), 132.21 (CH), 134.68 (CH), 144.33 (qC), 155.54 (C=O) ppm.

HRMS (ESI$^+$): found 190.0973 $[M+H]^+$, $C_{10}H_{12}N_3O$ requires 190.0975.

Synthesis of 2-ethylquinazolin-4(3*H*)-one (383).

(Eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.28) yielded the product as a light yellow solid (50 mg, 23 %, m.p.=209-211 ^oC).

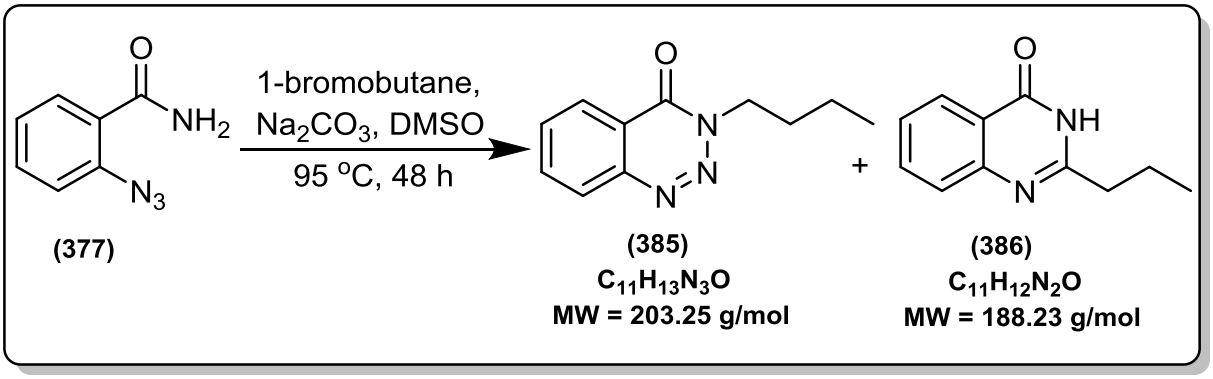
IR: υ_{max} (cm^{-1}): 771.3, 905.6, 1139.1, 1201.4, 1251.2, 1341.3, 1372.8, 1467.0, 1504.3, 1607.9, 1619.1, 1674.3, 2852.5, 2922.0, 3043.8, 3163.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.17-1.38 (2H, m, **CH_3**), 2.78 (2H, d, *J*= 6.9 Hz, C**H_2**), 7.18 (1H, bs, Ar**H**), 7.39 (1H, m, Ar**H**), 7.64-7.68 (2H, m, 2 x Ar**H**), 8.22 (1H, d, *J*=6.8 Hz, Ar**H**), 12.17 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 11.57 (CH_3), 29.71 (CH_2), 120.50 (qC), 126.23 (CH), 126.33 (CH), 127.22 (CH), 134.78 (CH), 149.54 (qC), 156.78 (qC), 164.57 (C=O) ppm.

HRMS (ESI^+): found 175.0869 $[M+H]^+$, $C_{10}H_{11}N_2O$ requires 175.0866.

8.1.3. Reactivity of 2-azidobenzamide with 1-bromobutane.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 1-bromobutane (338 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^{o}C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and

the solvent was removed under vacuum. The residue was purified by using column chromatography to give two products:

Synthesis of 3-butylbenzo[*d*][1,2,3]triazin-4(3*H*)-one (385).

(Eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.2) yielded the product as a light yellow oil (92 mg, 37 %).

IR: υ_{max} (cm^{-1}): 775.8, 889.4, 966.6, 1032.1, 1163.5, 1293.9, 1319.9, 1379.7, 1428.8, 1463.3, 1607.1, 1678.4, 2872.9, 2959.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 0.91 (3H, t, *J*=7.4 Hz, C**H**$_3$), 1.37 (2H, app. sextet, *J*= 7.6 Hz, C**H**$_2$), 1.86 (2H, app. pentet, *J*= 7.5 Hz, C**H**$_2$), 4.40 (2H, t, *J*= 7.1 Hz, C**H**$_2$), 7.71 (1H, dd, J^1=7.9 Hz, J^2=7.5 Hz, **H**Ar), 7.86 (1H, dd, J^1=7.9 Hz, J^2=7.5 Hz, **H**Ar), 8.07 (1H, d, *J*=8.1 Hz, **H**Ar), 8.28 (1H, d, *J*=8.1 Hz, **H**Ar) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.66 (CH_3), 19.89 (CH_2), 30.94 (CH_2), 49.67 (CH_2), 119.83 (qC), 125.05 (CH), 128.18 (CH), 132.20 (CH), 134.66 (CH), 144.33 (qC), 155.50 (C=O) ppm.

HRMS (ESI^+): found 204.1127 $[M+H]^+$, $C_{11}H_{14}N_3O$ requires 204.1131.

Synshesis of 2-propylquinazolin-4(3*H*)-one (386).

(Eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.22) yielded the product as a light yellow (estimated 20 %).

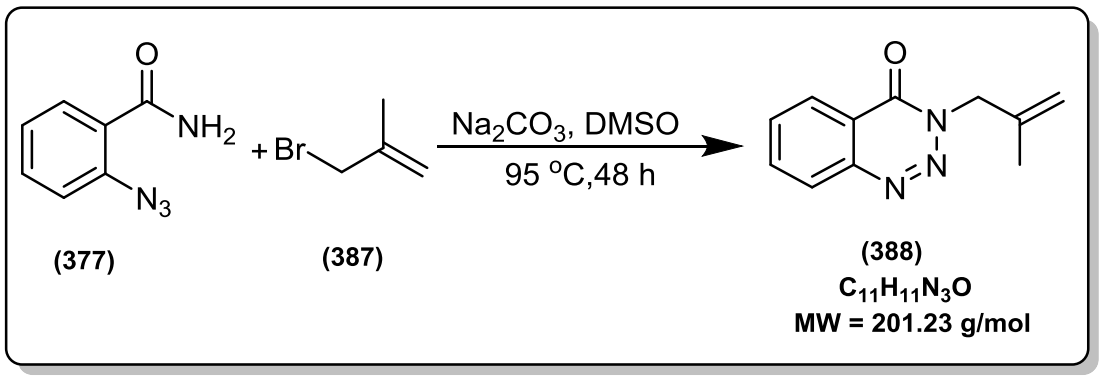
IR: υ_{max} (cm^{-1}): 752.7, 867.9, 908.0, 1082.4, 1161.3, 1265.4, 1293.3, 1394.8, 1449.9, 1478.8, 1565.3, 1615.4, 1650.0, 2962.6, 3173.6.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 0.98 (3H, t, *J*=7.5 Hz, C**H**$_3$), 1.69 (2H, app. sextet, *J*= 7.4 Hz, C**H**$_2$), 2.68 (2H, t, *J*= 7.8 Hz, C**H**$_2$), 7.37 (1H, dd, J^1=8.0 Hz, J^2=7.0 Hz, **H**Ar), 7.61 (1H, d, *J*=8.0 Hz, **H**Ar), 7.68 (1H, dd, J^1=8.0 Hz, J^2=7.0 Hz, **H**Ar), 8.17 (1H, d, *J*=8.0 Hz, **H**Ar), 11.12 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.77 (CH_3), 18.99 (CH_2), 40.47 (CH_2), 121.46 (qC), 122.46 (CH), 125.18 (CH), 127.35 (CH), 132.96 (CH), 149.47 (qC), 157.17 (qC), 164.25 (C=O) ppm.

HRMS (ESI^+): found 189.1023 $[M+H]^+$, $C_{11}H_{13}N_2O$ requires 189.1022.

8.1.4. Reactivity of 2-azidobenzamide with 3-bromo-2-methylpropene.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 3-bromo-2-methylpropene (333 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.21) to yield the product as a light orange solid (90 mg, 36 %, m.p.= 69-71 °C).

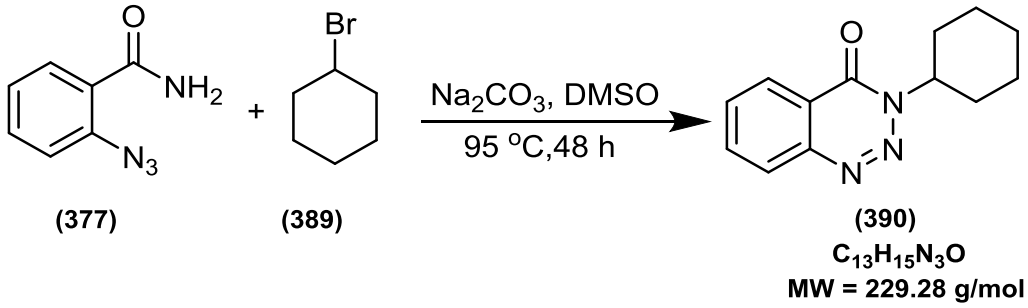
IR: υ_{max} (cm^{-1}): 777.9, 917.5, 1009.9, 1089.1, 1153.1, 1223.7, 1275.6, 1296.6, 1332.5, 1463.2, 1579.9, 1608.9, 1683.8, 2929.6, 2972.6, 3083.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.84 (3H, sb, C**H**$_3$), 4.85 (1H, s, =C**H**H), 5.00 (H, s, =CH**H**), 5.03 (2H, s, C**H**$_2$), 7.83 (1H, ddd, J^1=8.1 Hz, J^2=8.0 Hz, J^3=1.1 Hz, **H**Ar), 7.97 (1H, ddd, J^1=8.1 Hz, J^2=8.0 Hz, J^3=1.1 Hz, **H**Ar), 8.18 (1H, d, J=8.1 Hz, **H**Ar), 8.38 (1H, dd, J^1=8.1 Hz, J^2=1.0 Hz, **H**Ar) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.45 (CH_3), 54.77 (CH_2), 113.54 (CH_2), 119.88 (qC), 125.22 (CH), 128.33 (CH), 132.38 (CH), 134.84 (CH), 139.51 (qC), 144.29 (qC), 155.43 (C=O) ppm.

HRMS (ESI^+): found 202.0975 $[M+H]^+$, $C_{11}H_{12}N_3O$ requires 202.0975.

8.1.5. Reactivity of 2-azidobenzamide with bromocyclohexane.



(377) **(389)** **(390)**
$C_{13}H_{15}N_3O$
MW = 229.28 g/mol

Scheme 8.6

To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), bromocyclohexane (403 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.23) to yield the product as a light yellow solid (85 mg, 30 %, m.p.= 137-139 °C).

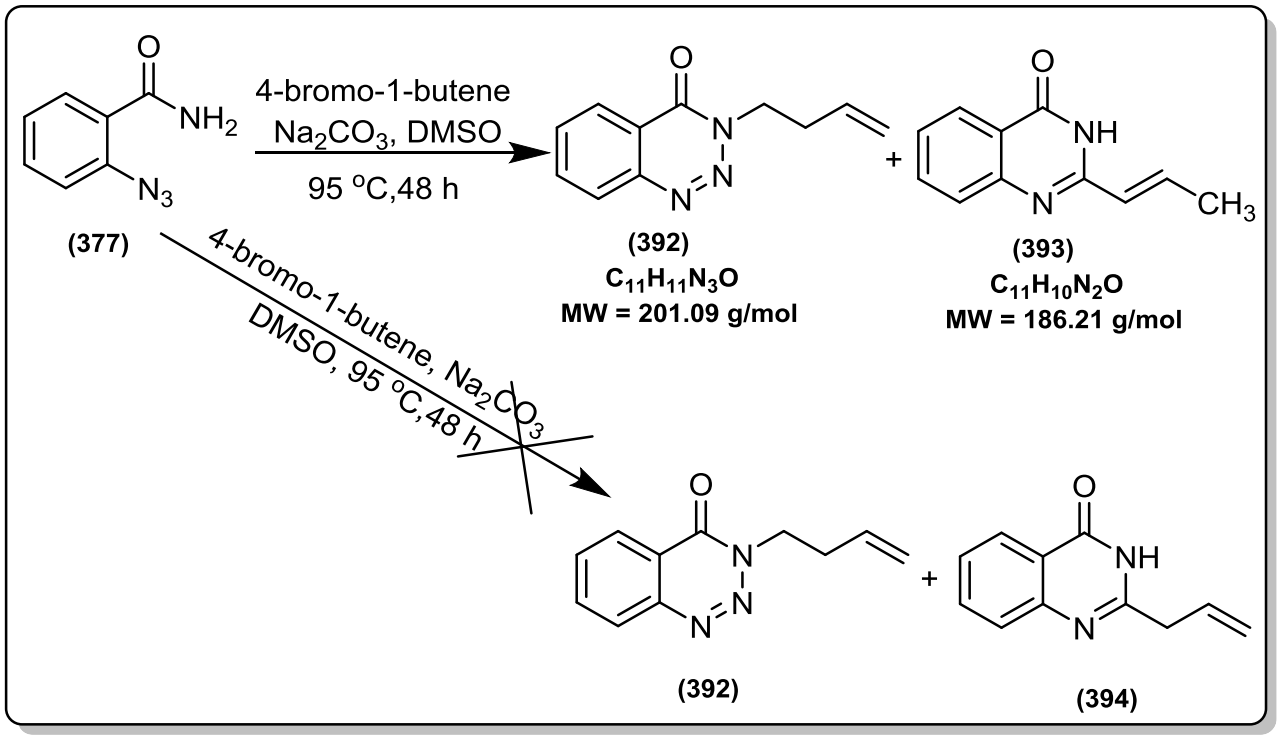
IR: υ_{max} (cm^{-1}): 773.8, 808.5, 905.0, 1064.4, 1164.4, 1160.6, 1180.8, 1220.8, 1267.2, 1292.3, 1331.2, 1375.5, 1460.4, 1606.6, 1681.1, 2850.9, 2928.3, 3073.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.17-1.30 (1H, m, CH**H**.), 1.39-1.50 (2H, m, C**H_2**), 1.68-2.72 (1H, m, C**H**H.), 1.86-2.01 (6H, m, 3 x C**H_2**), 4.96 (1H, p, *J*=7.6 Hz, C**H**), 7.70 (1H, dd, J^1=8.0 Hz, J^2=7.3 Hz, **H**Ar), 7.85 (1H, ddd, J^1=8.1 Hz, J^2=8.0 Hz, J^3=1.1 Hz, **H**Ar), 8.06 (1H, d, *J*=8.0 Hz, **H**Ar), 8.28 (1H, d, *J*=8.1 Hz, **H**Ar).

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 25.31 (CH_2), 25.80 (2 x CH_2), 56.64 (2 x CH_2), 119.60 (qC), 123.01 (qC), 125.27 (CH), 128.02 (CH), 132.00 (CH), 134.62 (CH), 143.88 (qC), 155.12 (C=O) ppm.

HRMS (ESI^+): found 230.1285 $[M+H]^+$, $C_{13}H_{16}N_3O$ requires 230.1288.

8.1.6. Reactivity of 2-azidobenzamide with 4-bromo-1-butene.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 4-bromo-1-butene (333 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^oC for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography to give two products:

Synthesis of 3-(but-3-en-1-yl)benzo[*d*][1,2,3] triazin-4(3*H*)-one (392).

(Eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.21) yielded the product as a yellow oil (85 mg, 35 %).

IR: υ_{max} (cm^{-1}): 777.1, 921.5, 995.5, 1042.6, 1105.2, 1164.7, 1279.5, 1295.5, 1346.1, 1463.4, 1607.6, 1641.7, 1681.0, 2840.2, 2954.0, 3074.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.61 (2H, q, *J*=7.0 Hz, C**H**$_2$), 4.47 (2H, t, *J*= 7.2 Hz, C**H**$_2$), 4.99 (2H, td, J^1= 18.3 Hz, J^2=2.7 Hz, =C**H**$_2$), 5.71-5.84 (1H, m, =C**H**), 7.72 (1H, dd, J^1=7.7 Hz, J^2=7.4 Hz, **H**Ar), 7.86 (1H, ddd, J^1=8.1 Hz, J^2=8.0 Hz, J^3=0.9 Hz, **H**Ar), 8.06 (1H, d, *J*=8.1 Hz, **H**Ar), 8.27 (1H, d, *J*=7.7 Hz, **H**Ar) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 33.15 (CH_2), 49.03 (CH_2), 117.78 (CH_2), 119.77 (qC), 125.07 (CH), 128.24 (CH), 132.27 (CH), 133.97 (CH), 134.73 (CH), 144.27 (qC), 155.50 (C=O) ppm.

HRMS (ESI^+): found 202.0970 $[M+H]^+$, $C_{11}H_{12}N_3O$ requires 202.0975.

Synthesis of 2-allylquinazolin-4(3*H*)-one (393).

(Eluent: petroleum ether/ethyl acetate: 1/1, R_f = 0.29) yielded the product as a yellow solid (65 mg, 29 %, m.p.= 148-150 ^{o}C).

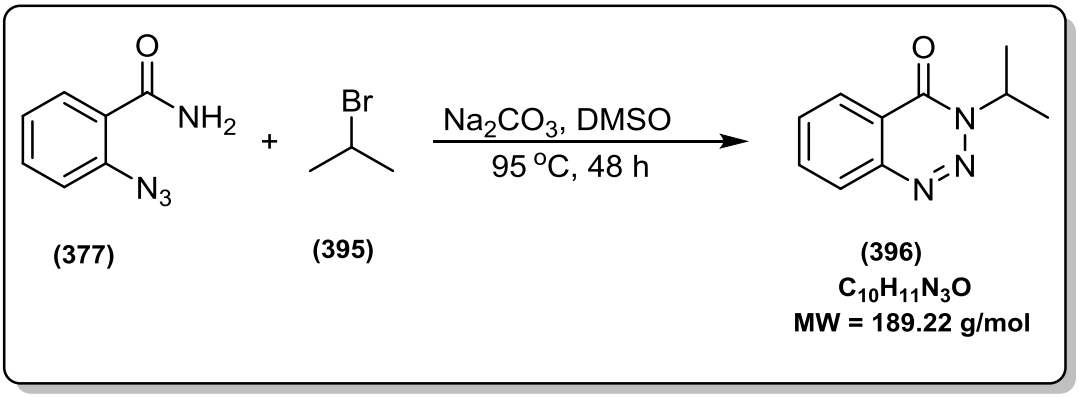
IR: υ_{max} (cm^{-1}): 682.5, 704.9, 763.7, 813.9, 908.6, 1007.1, 1144.2, 1252.4, 1295.5, 1342.8, 1468.3, 1562.1, 1606.9, 1658.7, 2924.4, 3062.9, 3182.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.08 (3H, dd, J^1=6.8 Hz, J^2=1.1 Hz, C**H**$_3$), 6.40 (1H, dd, J^1=15.9 Hz, J^2=1.3 Hz, =C**H**), 7.19-7.26 (1H, m, =C**H**), 7.47 (1H, dd, J^1=7.6 Hz, J^2=7.3 Hz, Ar**H**), 7.72 (1H, d, *J*=7.8 Hz, Ar**H**), 7.78 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 8.30 (1H, d, *J*=7.6 Hz, Ar**H**), 11.98 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 18.77 (CH_3), 120.75 (qC), 125.32 (CH), 126.28 (CH), 126.36 (CH), 127.51 (CH), 134.83 (CH), 138.47 (CH), 149.67 (qC), 150.89 (qC), 164.12 (C=O) ppm.

HRMS (ESI^+): found 187.0860 $[M+H]^+$, $C_{11}H_{11}N_3O$ requires 187.0793.

8.1.7. Reactivity of 2-azidobenzamide with 2-bromopropane.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 2-bromopropane (301 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^{o}C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.23) to yield the product as a light yellow solid (80 mg, 34 %, m.p.=47-49 ^{o}C).

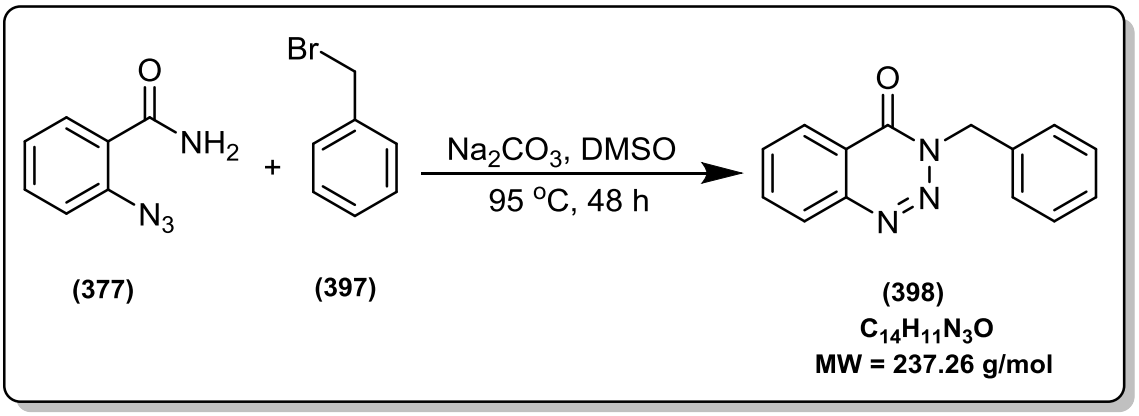
IR: υ_{max} (cm^{-1}): 776.9, 850.2, 900.5, 965.8, 1016.2, 1131.3, 1195.1, 1266.3, 1290.1, 1338.4, 1386.1, 1461.6, 1494.2, 1608.3, 1676.5, 2874.9, 2976.1.

^{1}H NMR: δ_H (400 MHz, CDCl$_3$): 1.60 (6H, d, *J*=6.8 Hz, 2 x C**H$_3$**), 5.45 (1H, sp, *J*= 6.7 Hz, C**H**), 7.79 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, **H**Ar), 7.94 (1H, dd, J^1=7.8 Hz, J^2=7.5 Hz, **H**Ar), 8.15 (1H, d, *J*=8.1 Hz, **H**Ar), 8.36 (1H, d, *J*=8.1 Hz, **H**Ar) ppm.

^{13}C NMR δ_c (100 MHz, CDCl$_3$): 21.61 (2 x CH_3), 49.53 (CH), 119.61 (qC), 125.20 (CH), 128.05 (CH), 132.07 (CH), 134.66 (CH), 144.00 (qC), 155.09 (C=O) ppm.

HRMS (ESI$^+$): found 190.0970 $[M+H]^+$, $C_{10}H_{12}N_3O$ requires 190.0975.

8.1.8. Reactivity of 2-azidobenzamide with benzyl bromide.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), benzyl bromide (422 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.2) to yield the product as a yellow solid (95 mg, 33 %, m.p.= 110-112 °C).

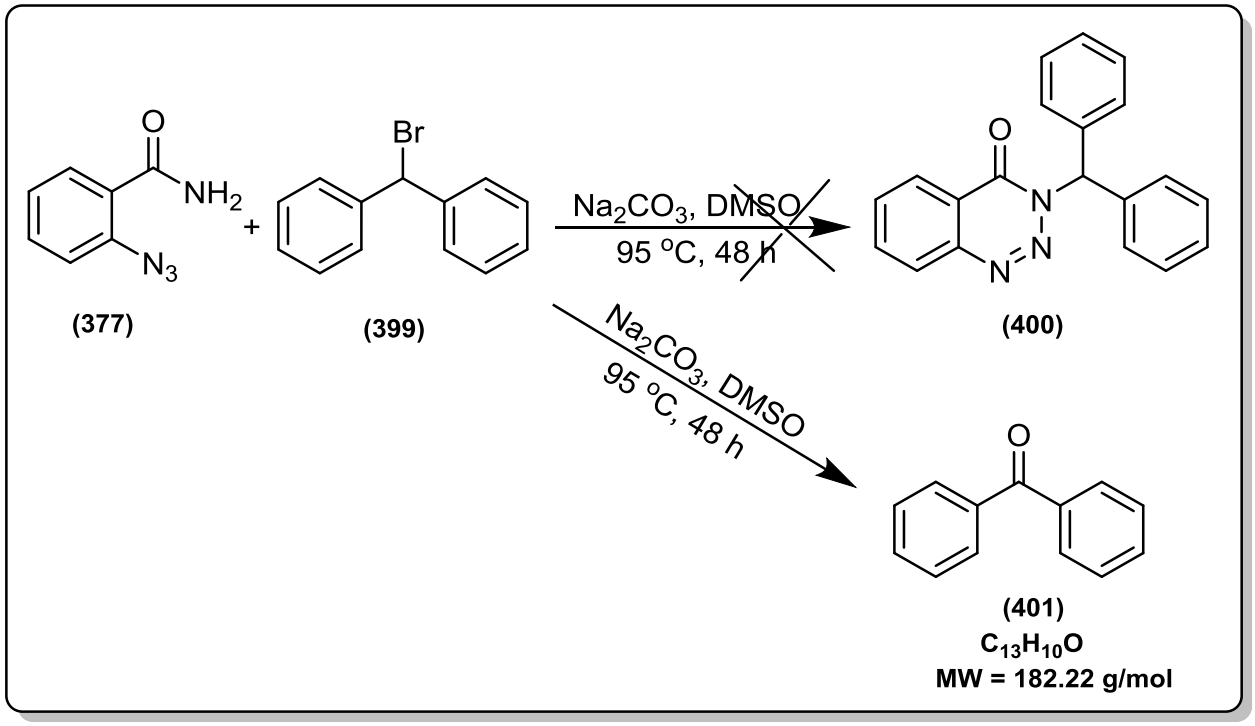
IR: υ_{max} (cm^{-1}): 777.7, 910.3, 976.6, 1002.8, 1048.8, 1086.2, 1178.6, 1204.7, 1295.1, 1349.4, 1454.0, 1492.3, 1580.8, 1605.4, 1681.8, 3032.5, 3062.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.65 (2H, s, C**H**$_2$), 7.29-7.38 (3H, m, 3 x **H**Ar), 7.55 (2H, d, *J*=6.9 Hz, 2 x **H**Ar), 7.79 (1H, dd, J^1=7.7 Hz, J^2=7.3 Hz, **H**Ar), 7.94 (1H, dd, J^1=8.0 Hz, J^2=7.3 Hz, **H**Ar), 8.16 (1H, d, *J*=8.0 Hz, **H**Ar), 8.35 (1H, d, *J*=7.7 Hz, **H**Ar) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 53.39 (CH_2), 120.10 (qC), 125.18 (qC), 128.23 (CH), 128.33 (CH), 128.73 (2 x CH), 128.87 (2 x CH), 132.36 (CH), 134.82 (CH), 135.76 (qC), 144.34 (qC), 155.39 (C=O) ppm.

HRMS (ESI^+): found 238.0977 $[M+H]^+$, $C_{14}H_{12}N_3O$ requires 238.0975.

8.1.9. Reactivity of 2-azidobenzamide with bromodiphenylmethane.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), bromodiphenylmethane (610 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^{o}C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.23) to yield the product as a white solid (76 mg, 84 %, m.p.=49-51 ^{o}C, lit. m.p.=48-50 ^{o}C[241]).

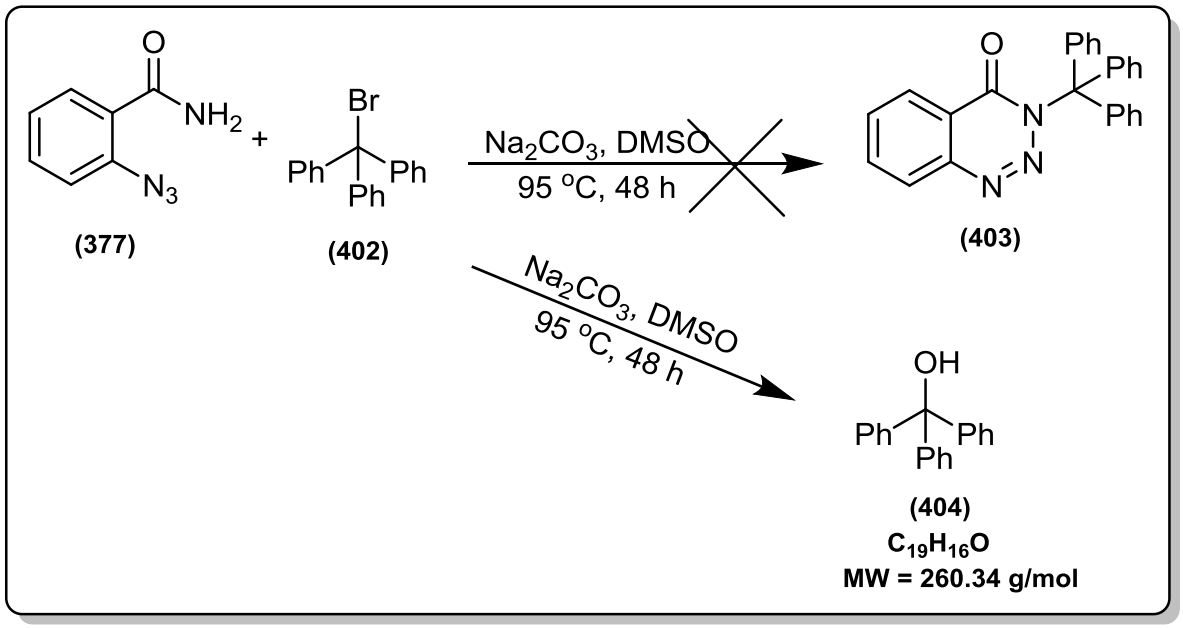
IR: υ_{max} (cm^{-1}): 637.7, 648.0, 696.1, 726.7, 905.1, 1028.1, 1176.4, 1276.5, 1446.9, 1598.5, 1655.5, 3059.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.50 (4H, dd, J^1= 7.5 Hz, J^2=7.4, 4 x Ar***H***), 7.61 (2H, t, J=7.5 Hz, 2 x Ar***H***), 7.83 (4H, dd, J^1=7.5 Hz, J^2=1.3 Hz, 4 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 128.30 (4 x CH), 130.08 (4 x CH), 132.45 (2 x CH), 137.60 (2 x qC), 196.79 (C=O) ppm.

HRMS (ESI$^+$): found 183.0803 $[M+H]^+$, $C_{13}H_{11}O$ requires 183.0804.

8.1.10. Reactivity of 2-azidobenzamide with triphenylmethyl bromide.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), triphenylmethyl bromide (797 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 ^oC for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.24) to yield the product as a white solid (561 mg, 88 %, m.p.=163-164 ^oC, lit. m.p.=48-50 ^oC[242]).

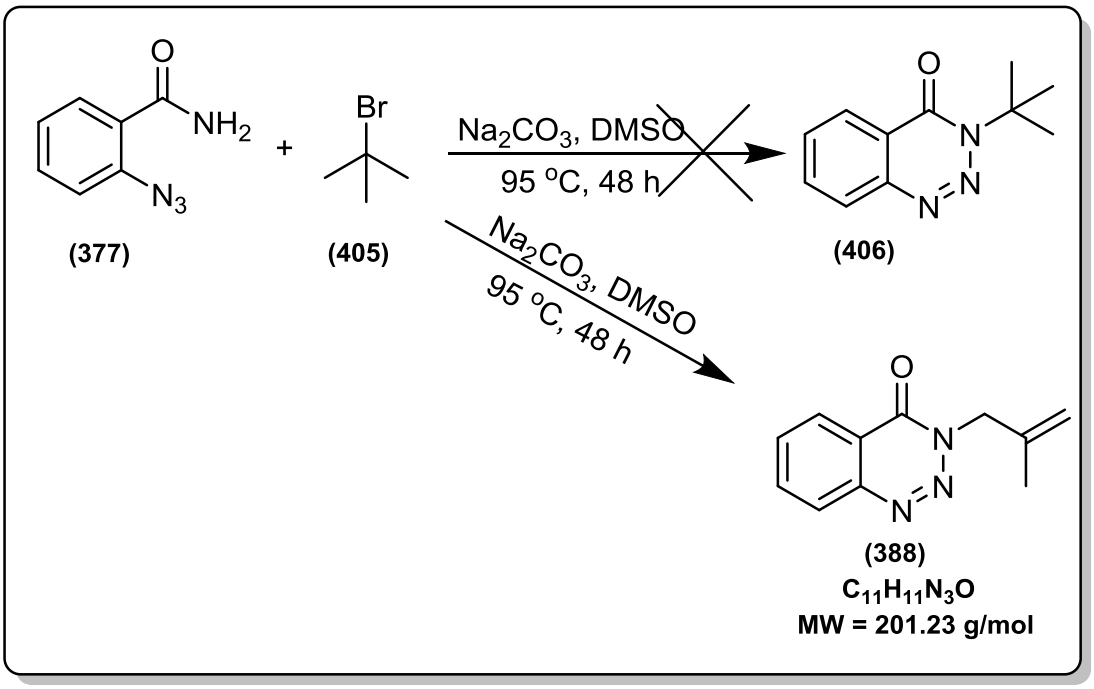
IR: υ_{max} (cm^{-1}): 637.3, 695.5, 756.2, 889.7, 910.2, 1008.9, 1156.3, 1328.1, 1444.2, 1596.7, 3060.0, 3462.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.73 (1H, s, O***H***), 7.15-7.24 (15 H, m, 15 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 82.06 (C-OH), 127.29 (3 x CH), 127.96 (12 x CH), 146.88 (3 x qC) ppm.

HRMS (ESI$^+$): found 242.1095 $[M-H_2O]^+$, $C_{19}H_{14}$ requires 242.1096.

8.1.11. Reactivity of 2-azidobenzamide with 2-bromo-2-methylpropane.



To a solution of 2-azidobenzamide (200 mg, 1.23 mmol, 1.0 eq) and sodium carbonate (392 mg, 3.70 mmol, 3.0 eq) in extra dry DMSO (10 mL), 2-bromo-2-methylpropane (338 mg, 2.47 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 4/1, R_f = 0.21) to yield the product as a light yellow oil (50 mg, 20 %).

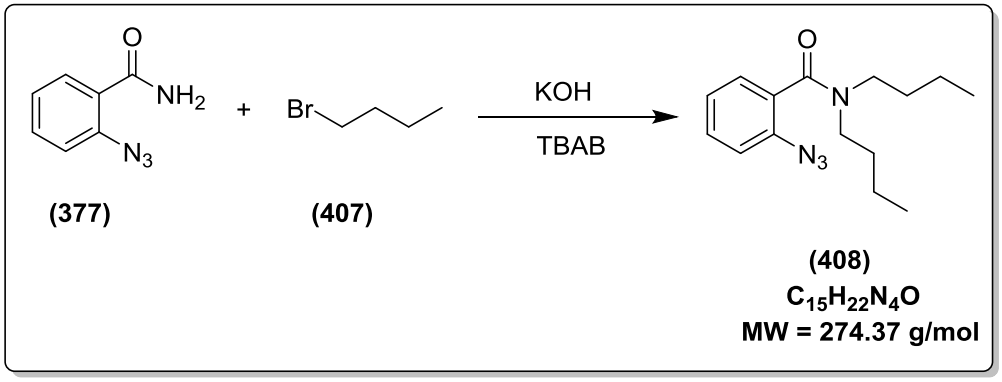
IR: υ_{max} (cm^{-1}): 776.5, 893.8, 917.9, 970.4, 1086.3, 1180.6, 1293.9, 1463.0, 1493.9, 1580.7, 1608.3, 1686.5, 2920.8, 3082.0.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 2.26 (3H, s, C***H***$_3$), 4.92 (1H, s, C=CH***H***), 4.94 (1H, s, C=C***H***H), 5.41 (2H, s, NC***H***$_2$), 7.74 (1H, dd, J^1=7.0 Hz, J^2=6.7 Hz, Ar***H***), 7.86-7.91 (1H, m, Ar***H***), 8.10 (1H, d, J=8.0 Hz, Ar***H***), 8.30 (1H, dd, J^1=8.0 Hz, J^2=2.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 20.45 (CH_3), 52.92 (CH_2), 113.54 (=CH_2), 119.88 (qC), 125.22 (CH), 128.38 (CH), 132.39 (CH), 134.85 (CH), 139.51 (qC), 144.23 (qC), 155.11 (C=O) ppm.

HRMS (ESI$^+$): found 202.0982 $[M+H]^+$, $C_{11}H_{12}N_3O$ requires 202.0975.

8.1.12. Reactivity of 2-azidobenzamide with 1-bromobutane.



2-Azidobenzamide (98 mg, 0.60 mmol, 1.0 eq), commercial KOH (50 mg, 0.90 mmol, 1.5 eq) and TBAB (58 mg, 0.18 mmol, 0.3 eq) were mixed and stirred for 15 minutes at room temperature and then 1-bromobutane (102 mg, 81 µL, 0.75 mmol, 1.25 eq) was added. The mixture was heated at 80 ^oC in an oil bath for 15 minutes. The crude mixture was diluted with water (10 mL), and then was extracted with dichloromethane (3 x 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed in *vacuo*. Purification by silica chromatography (eluent: petroleum ether/*ethylacetate*: 2/1, R_f = 0.25) yielded the product as a yellow oil (115 mg, 70 %).

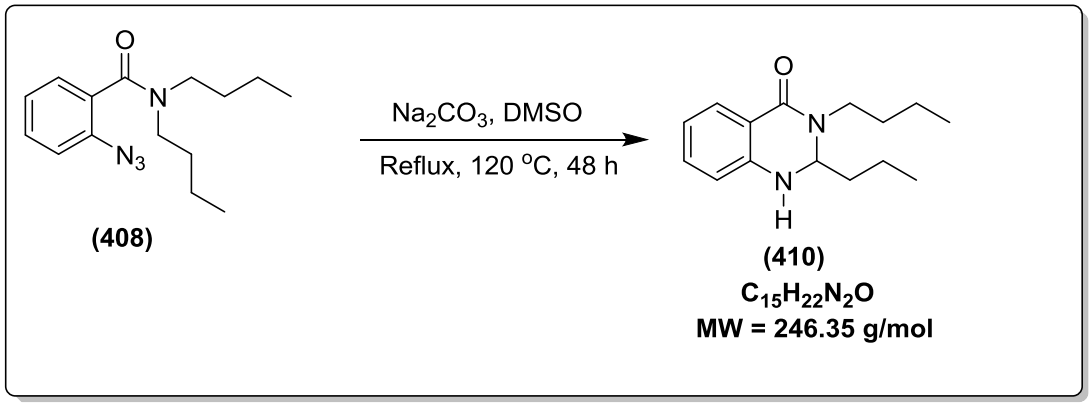
IR: υ_{max} (cm^{-1}): 751.8, 940.2, 1081.2, 1117.5, 1200.7, 1288.8, 1424.6, 1443.7, 1577.3, 1598.2, 1632.8, 2091.1, 2872.6, 2931.6, 2957.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 0.68 (3H, t, *J*=7.3 Hz, C***H***$_3$), 0.90 (3H, t, *J*=7.3 Hz, C**H**$_3$), 1.04 (2H, app. sextet, *J*=7.3 Hz, C***H***$_2$), 1.29-1.38 (4H, m, 2 x C***H***$_2$), 1.57 (2H, app. pentet, *J*=7.6 Hz, C***H***$_2$), 2.96-2.98 (2H, m, C***H***$_2$), 3.29 (1H, br.s, CH***H***), 3.54 (1H, br.s, C***H***H), 7.06-7.10 (2H, m, 2 x Ar***H***), 7.14 (1H, dd, J^1=7.5 Hz, J^2=1.4 Hz, Ar***H***), 7.31 (1H, ddd, J^1=8.2 Hz, J^2=8.0 Hz, J^3=1.4 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.56 (CH_3), 13.93 (CH_3), 19.70 (CH_2), 20.25 (CH_2), 29.51 (CH_2), 30.55 (CH_2), 44.22 (CH_2), 48.18 (CH_2), 118.41 (CH), 124.93 (CH), 127.87 (CH), 129.44 (qC), 129.95 (CH), 136.17 (qC), 168.19 (C=O) ppm.

HRMS (ESI$^+$): found 275.1860 $[M+H]^+$, $C_{15}H_{23}N_4O$ requires 275.1866.

8.1.13. Reactivity of 2-azido-*N*,*N*-dibutylbenzamide.



To a solution of 2-azido-*N*,*N*-dibutylbenzamide (98 mg, 0.358 mmol, 1.0 eq) and sodium carbonate (114 mg, 1.07 mmol, 3.0 eq) in extra dry DMSO (8 mL), 2-bromopropane (88 mg, 67 µL, 0.716 mmol, 2.0 eq) was added. The whole was heated at 95 °C for 48 hours under a nitrogen atmosphere and after completion of the reaction, monitored by TLC which showed no product. The reaction mixture was heated at 120 °C for 48 hours and after completion of the reaction, monitored by TLC, the resulting mixture was diluted with dichloromethane (30 mL) and washed with 0.1M NaCl and water many times to remove the DMSO. The mixture was dried with anhydrous magnesium sulfate, filtered under gravity and the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.21) to yield the product as a yellow oil (55 mg, 63 %).

IR: υ_{max} (cm^{-1}): 750.2, 908.5, 1027.9, 1153.0, 1169.0, 1321.9, 1463.6, 1509.3, 1579.7, 1610.1, 2871.6, 2929.9, 1956.7, 3284.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 0.84 (6H, app. pentet, *J*=7.2 Hz, 2 x C***H*****$_3$**), 1.15-1.24 (1H, m, C**H**H), 1.29-1.36 (3H, m, C***H*****$_2$** + C**H**H), 1.50-1.59 (3H, m, C***H*****$_2$** + C**H**H), 1.74-1.84 (1H, m, C***H***H), 2.72-2.79 (1H, m, C**H**), 4.00-4.07 (1H, m, N***H***), 4.48-4.50 (2H, m, C***H*****$_2$**), 6.55 (1H, d,

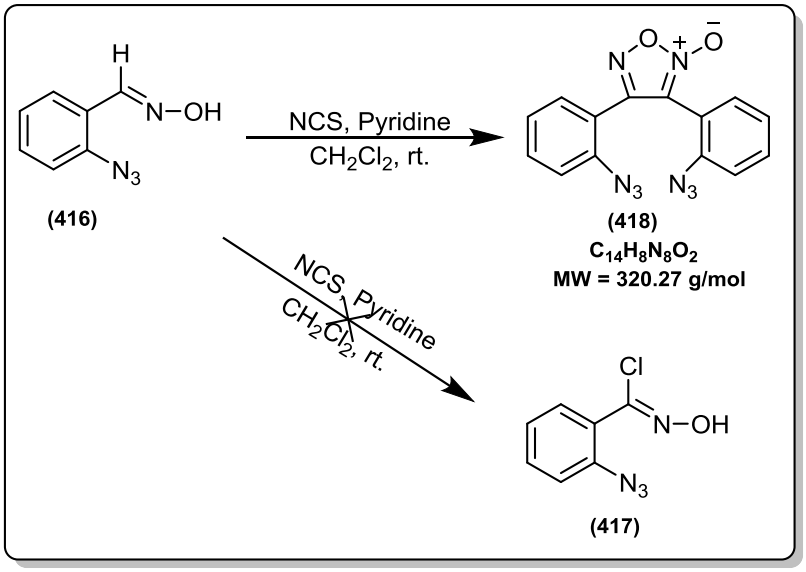
J=8.0 Hz, Ar***H***), 6.75 (1H, ddd, J^1=7.8 Hz, J^2=7.6 Hz, J^3=1.2 Hz, Ar***H***), 7.16-7.20 (1H, m, Ar**H**), 7.81 (1H, dd, J^1=7.8 Hz, J^2=1.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.68 (CH_3), 13.89 (CH_3), 18.64 (CH_2), 20.15 (CH_2), 30.48 (CH_2), 35.48 (CH_2), 44.88 (CH_2), 69.25 (CH), 114.81 (CH), 117.14 (qC), 118.41 (CH), 128.41 (CH), 133.06 (CH), 145.06 (qC), 162.34 (C=O) ppm.

HRMS (ESI$^+$): found 247.1802 $[M+H]^+$, $C_{13}H_{16}N_3O$ requires 247.1805.

8.2. Reactivity of o-Azidobenzaldoxime and 2-azidobenzaldehyde.

8.2.1. Synthesis of 3,4-bis(2-azidophenyl)-1,2,5-oxadiazole 2-oxide.



To a solution of N-chlorosuccinimide (403 mg, 3.03 mmol, 1.01 eq) in anhydrous DCM (15 mL) and pyridine (0.1 mL) was added o-azidobenzaldoxime (486 mg, 3 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 48 hours. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (petroleum ether/ethylacetate: 5/1, R_f=0.24) to yield the product (750 mg, 78 % yield) as a deep brown oil.

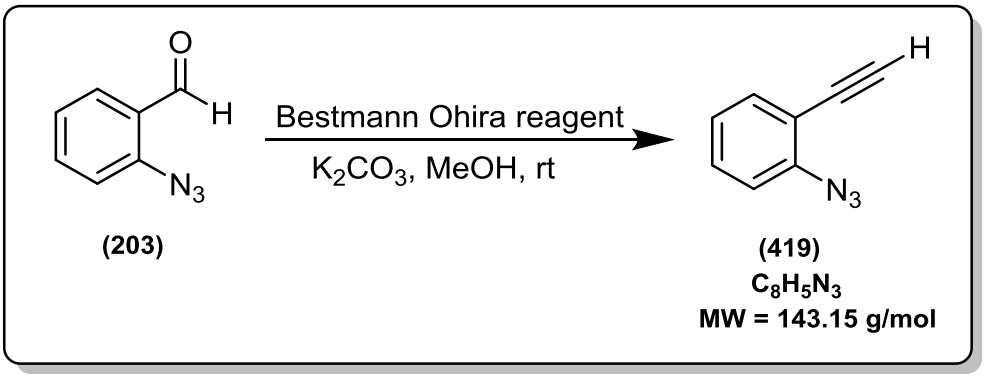
IR: υ_{max} (cm^{-1}): 748.2, 830.9, 961.7, 1080.7, 1130.6, 1291.6, 1417.7, 1499.1, 1575.5, 1592.8, 2091.3, 2980.3, 3063.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.06 (1H, d, *J*=8.1 Hz, Ar**H**), 7.09-7.14 (2H, m, 2 x Ar**H**), 7.18 (1H, d, *J*=7.7 Hz, Ar**H**), 7.27 (1H, dd, J^1=7.7 Hz, J^2=1.1 Hz, Ar**H**), 7.38-7.50 (3H, m, 3 x Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 113.61 (qC), 115.23 (qC), 118.79 (qC), 118.83 (qC), 118.90 (CH), 118.96 (CH), 125.21 (CH), 125.27 (CH), 130.88 (CH), 130.99 (CH), 132.12 (CH), 132.30 (CH), 138.54 (qC), 139.28 (qC) ppm.

HRMS (ESI^+): found 265.0717 $[M-2N_2+H]^+$, $C_{14}H_9N_4O$ requires 265.0720.

8.2.2. Synthesis of 1-azido-2-ethynylbenzene.



The aldehyde (638 mg, 4.34 mmol, 1.0 eq) was dissolved in dry methanol (5 mL); potassium carbonate (1.197 mg, 8.68 mmol, 2.0 eq) and the Bestmann-Ohira reagent (1.17 mL, 1.0 mg, 5.21 mmol, 1.2 eq) were added and the whole was stirred for 24 hours under nitrogen. The reaction was quenched with saturated aqueous ammonium chloride (25 mL), the organic phase was separated and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yield an orange solid. Purification by silica chromatography (petroleum ether/ethyl acetate: 1/50, R_f = 0.2) yielded the product as a brown oil (559 mg, 90 %).

IR: υ_{max} (cm^{-1}): 751.1, 823.2, 943.0, 1089.3, 1163.2, 1273.4, 1295.0, 1439.7, 1483.9, 1571.7, 1594.8, 2102.8, 2925.3, 3290.5.

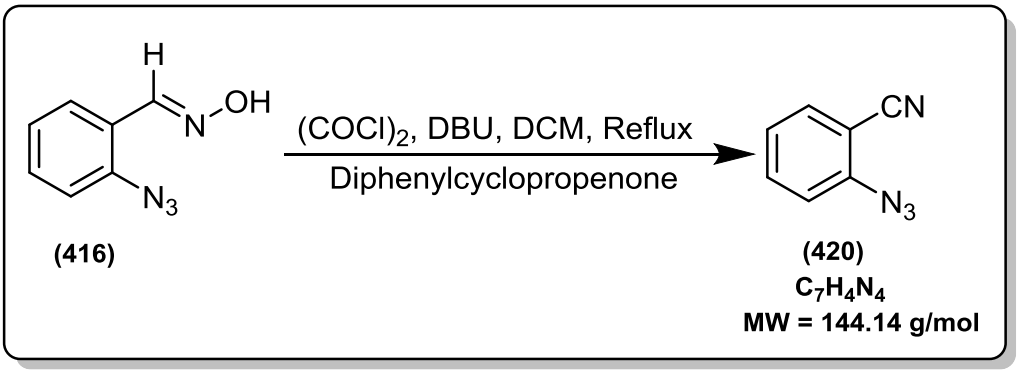
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 3.30 (1H, s, C**H**), 6.99-7.06 (2H, m, 2 x Ar**H**), 7.29 (1H, dd, J^1=7.5 Hz, J^2=7.4 Hz, Ar**H**), 7.39 (1H, d, J=7.5 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 79.33 (CH), 82.88 (qC), 114.05 (CH), 118.50 (qC), 124.62 (CH), 130.13 (CH), 134.28 (CH), 141.71 (qC) ppm.

HRMS (ESI$^+$): found 286.0958 $[2M]^+$, $C_{16}H_{10}N_6$ requires 286.0967.

The data is identical to that reported in the literature.[223]

8.2.3. Synthesis of 2-azidobenzonitrile.



To a stirred mixture of diphenylcyclopropenone (62 mg, 0.3 mmol, 5 mol%) and aldoxime (972 mg, 6.0 mmol, 1.0 eq) in DCM (10 mL) was added a solution of $(COCl)_2$ (756 mg, 6.0 mmol, 1.0 eq) in DCM (1.0 mL) by using a syringe pump over 1h and then was added by slow addition DBU (2.736 mg, 18.0 mmol, 3.0 eq) in DCM (3 mL). The mixture was heated at reflux whilst being monitored by TLC. The reaction mixture was diluted with DCM and washed by water (3 x 40 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered, concentrated under reduced pressure and purified by silica column chromatography [petroleum ether/ethyl acetate: 10/1, R_f = 0.24] to yield the product as a yellow solid (750 mg, 87 %, m.p. = 54 - 55 ^{o}C, lit. m.p. = 52 - 53 ^{o}C)[213].

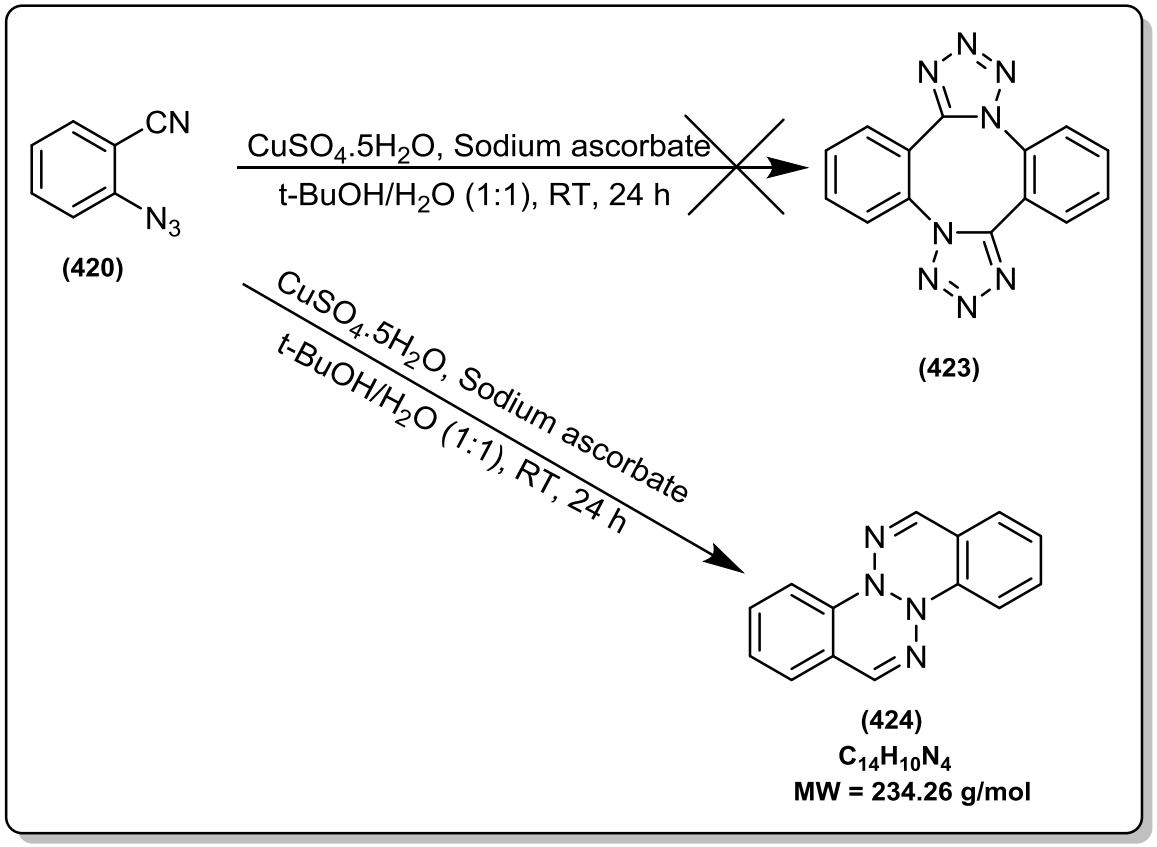
IR: υ_{max} (cm^{-1}): 755.4, 823.6, 950.4, 1035.7, 1147.5, 1166.9, 1250.5, 1277.1, 1293.4, 1306.2, 1445.8, 1485.7, 1575.9, 1594.2, 2109.8, 2227.9, 3068.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.24 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.29 (1H, d, J= 8.8 Hz, Ar**H**), 7.62-7.66 (2H, m, 2 x Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 104.22 (CN), 115.59 (qC), 118.80 (CH), 125.00 (CH), 133.95 (CH), 134.03 (CH), 143.44 (qC) ppm.

HRMS (ESI^+): found 233.0790 $[2M-2N_2+H]^+$, $C_{14}H_9N_4$ requires 233.0822.

8.2.4. Synthesis of benzo[*e*]benzo[5,6][1,2,3]triazino[2,1-*a*][1,2,3]triazine.



A solution of sodium ascorbate (17.2 mg, 0.069 mmol, 0.1 eq) and $CuSO_4.5H_2O$ (2.73 mg, 0.0123 mmol, 0.02 eq) in water (2 mL) was added to a solution of 2-azidobenzonitrile (100 mg, 0.69 mmol, 1.0 eq) in t-BuOH (2 mL). The whole was stirred at ambient temperature under a nitrogen atmosphere for 48 hours. The reaction mixture was diluted with water (10 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. The crude product was purified by silica column chromatography [petroleum ether/ethyl acetate: 2/1]. The product was tentatively assigned as light yellow oil (17 mg, 10 %) .

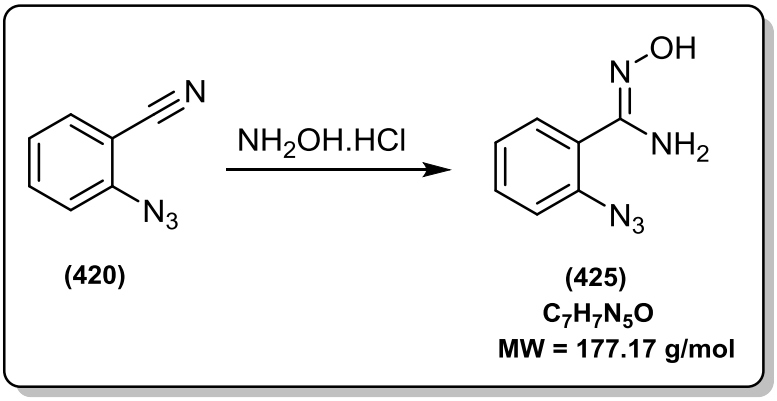
IR: υ_{max} (cm^{-1}): 766.5, 980.5, 1093.3, 1190.2, 1338.4, 1448.7, 1494.4, 1575.3, 1616.7, 1650.9, 2855.6, 2923.6, 3024.4, 3057.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 6.29 (1H, m, Ar**H**), 6.62 (1H, d, *J*= 8.5.0 Hz, Ar**H**), 6.69 (1H, d, *J*=7.5 Hz, Ar**H**), 7.02 (1H, m, Ar**H**), 7.22-7.41 (3H, m, 3 x Ar**H**), 7.53-7.55 (2H, m, 2 x Ar**H**), 7.67 (1H, d, *J*=7.5 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 125.43 (CH), 126.71 (CH), 128.30 (CH), 128.36 (CH), 128.86 (qC), 128.88 (qC), 128.98 (CH), 129.09 (CH), 130.42 (CH), 130.52 (CH), 134.81 (qC), 135.46 (qC), 143.39 (CH), 143.56 (CH) ppm.

HRMS (ESI^+): found 234.1045 $[M]^+$, $C_{14}H_{10}N_4$ requires 234.0905.

8.2.5. Synthesis of 2-azido-*N*'-hydroxybenzimidamide.



Sodium carbonate (599 mg, 5.65 mmol, 1.1 eq) in small portions was added to hydroxylamine hydrochloride (393 mg, 5.65 mmol, 1.1 eq) in water (30 mL). To the solution 2-azidobenzonitrile (740 mg, 5.14 mmol, 1.0 eq) in ethanol (30 mL) was added. The whole was heated at reflux temperature for 24 hours. The reaction mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 1/1, R_f = 0.18) yielded the product as an orange solid (610 mg, 67 %, m.p.=110-112 ^{o}C).

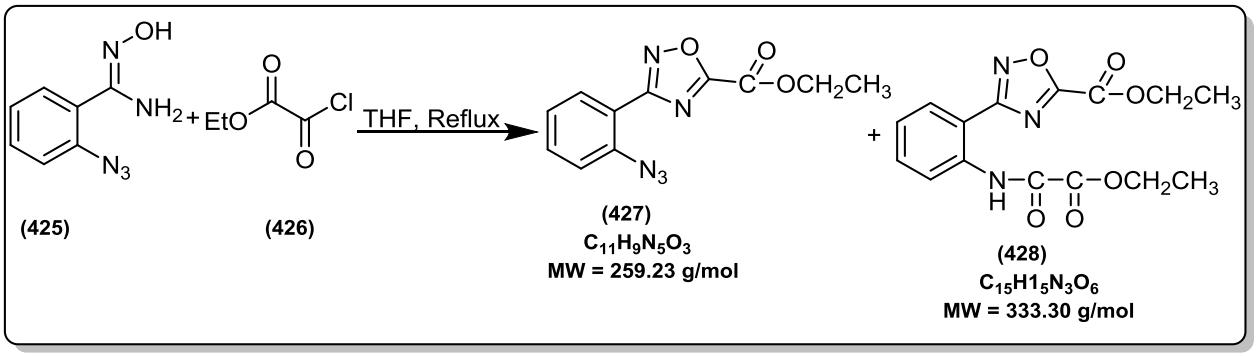
IR: υ_{max} (cm^{-1}): 757.6, 834.3, 934.1, 1028.3, 1082.0, 1164.7, 1290.7, 1379.1, 1446.4, 1497.7, 1575.5, 1637.3, 2121.5, 2807.9, 3062.9, 3151.7, 3371.0, 3483.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.97 (1H, s, NH**H**), 5.22 (1H, s, NH**H**), 7.19 (1H, dd, J^1= 7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.36-7.46 (2H, m, 2 x Ar**H**), 7.63 (1H, ddd, J^1=7.2 Hz, J^2=7.0 Hz, J^3=1.4 Hz, Ar**H**), 9.40 (1H, br.s, O**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 118.81 (CH), 123.96 (qC), 125.65 (CH), 128.65 (CH), 130.44 (CH), 137.62 (qC), 151.23 (C=N) ppm.

HRMS (ESI^+): found 178.0719 $[M+H]^+$, $C_7H_8N_5O$ requires 178.0723.

8.2.6. Synthesis of ethyl 3-(2-azidophenyl)-1,2,4-oxadiazole-5-carboxylate.



To a solution of ethyl 2-chloro-2-oxoacetate (202 mg, 1.49 mmol, 1.2 eq) in THF (10 mL), (*Z*)-2-azido-*N*'-hydroxybenzimidamide (220 mg, 1.24 mmol, 1.0 eq) was added. The mixture was heated at reflux temperature for 24 hours, whilst being monitored by TLC. The solvent was distilled off under vacuum and the residue was purified by silica chromatography to give two products:

Ethyl 3-(2-azidophenyl)-1,2,4-oxadiazole-5-carboxylate (427).

[(eluent: petroleum ether/ethyl acetate: 3/1, R_f = 0.25) yielded the product as a yellow oil (300 mg, 93 %)].

IR: υ_{max} (cm^{-1}): 748.2, 816.3, 909.3, 1018.9, 1165.0, 1186.7, 1262.3, 1372.7, 1429.4, 1478.7, 1588.1, 1748.0, 2097.1, 2987.0, 3065.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, *J*=7.1 Hz, C**H$_3$**), 4.58 (2H, q, *J*=7.1 Hz, C**H$_2$**), 7.29 (1H, ddd, J^1=7.8 Hz, J^2=7.6 Hz, J^3=1.2 Hz, Ar**H**), 7.35 (1H, d, *J*= 8.1 Hz, Ar**H**), 7.59

(1H, ddd, J^1= 8.1 Hz, J^2=7.9 Hz, J^3=1.5 Hz, Ar**H**), 8.04 (1H, dd, J^1= 7.8 Hz, J^2=1.2 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.05 (CH_3), 64.03 (CH_2), 117.23 (qC), 119.96 (CH), 124.96 (CH), 131.80 (CH), 132.71 (CH), 139.19 (qC), 154.11 (C=N), 166.06 (C=N), 167.52 (C=O) ppm.

HRMS (ESI$^+$): found 282.0600 $[M+Na]^+$, $C_{11}H_9N_5O_3Na$ requires 282.0598.

Ethyl 3-(2-(2-ethoxy-2-oxoacetamido)phenyl)-1,2,4-oxadiazole-5-carboxylate (428).

(Eluent: petroleum ether/ethyl acetate: 3/1, R_f = 0.16) yielded the product as a yellow oil (20 mg, 5 %).

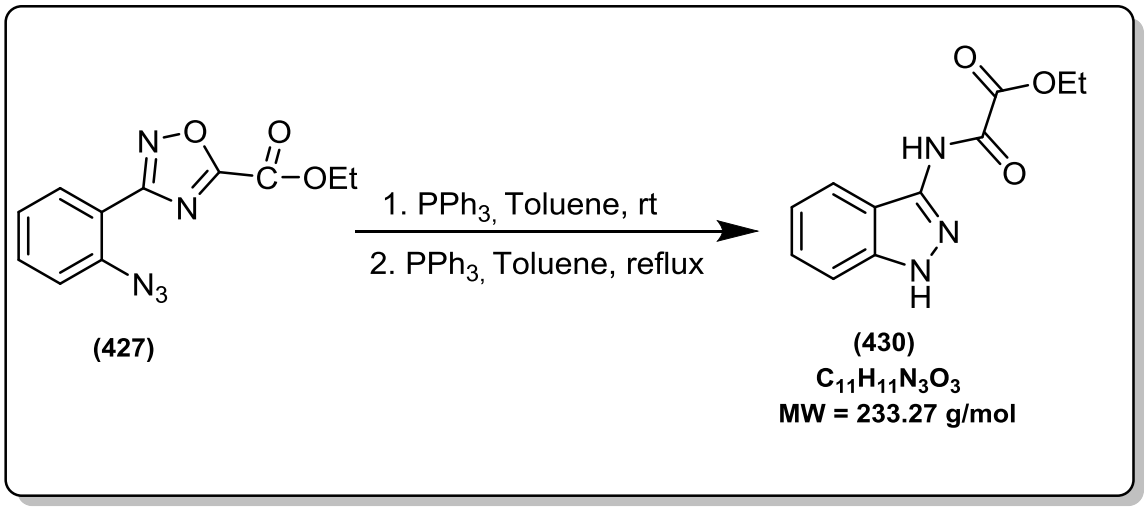
IR: υ_{max} (cm^{-1}): 753.6, 846.8, 938.1, 1018.9, 1177.0, 1204.1, 1278.9, 1369.5, 1433.6, 1504.0, 1546.8, 1583.0, 1597.0, 1610.7, 1711.5, 1753.7, 2993.0, 3253.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.38 (3H, t, *J*=7.1 Hz, C**H$_3$**), 1.43 (3H, t, *J*=7.1 Hz, C**H$_3$**), 4.39 (2H, q, *J*=7.1 Hz, C**H$_2$**), 4.52 (2H, q, *J*=7.1 Hz, C**H$_2$**), 7.24 (1H, dd, J^1=8.0 Hz, J^2=7.5 Hz, Ar**H**), 7.53 (1H, dd, J^1= 8.2 Hz, J^2=7.5 Hz, Ar**H**), 8.23 (1H, dd, J^1= 8.0 Hz, J^2=0.9 Hz, Ar**H**), 8.68 (1H, d, *J*= 8.2 Hz, Ar**H**), 11.51 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.00 (CH_3), 14.04 (CH_3), 63.73 (CH_2), 64.27 (CH_2), 114.00 (qC), 121.18 (CH), 125.02 (CH), 130.09 (CH), 133.18 (CH), 136.34 (qC), 153.74 (C=O), 154.80 (C=N), 160.38 (C=O), 165.91 (qC), 168.33 (C=O) ppm.

HRMS (ESI$^+$): found 356.0844 $[M+Na]^+$, $C_{15}H_{15}N_3O_6Na$ requires 356.0853.

8.2.7. Reactivity of ethyl 3-(2-azidophenyl)-1,2,4-oxadiazole-5-carboxylate.



To a solution of ethyl 3-(2-azidophenyl)-1,2,4-oxadiazole-5-carboxylate (180 mg, 0.695 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added triphenylphosphine (218 mg, 0.834 mmol, 1.2 eq). The whole was stirred for 6 hours at ambient temperature under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the mixture was heated at reflux temperature for 24 hours under a nitrogen atmosphere. The solvent was removed under vacuum and the residue was purified by using silica column chromatography [petroleum ether/ethyl acetate: 1/1, R_f = 0.2] to yield the product as a light yellow solid (100 mg, 61 %, m.p=214-216 ^{o}C).

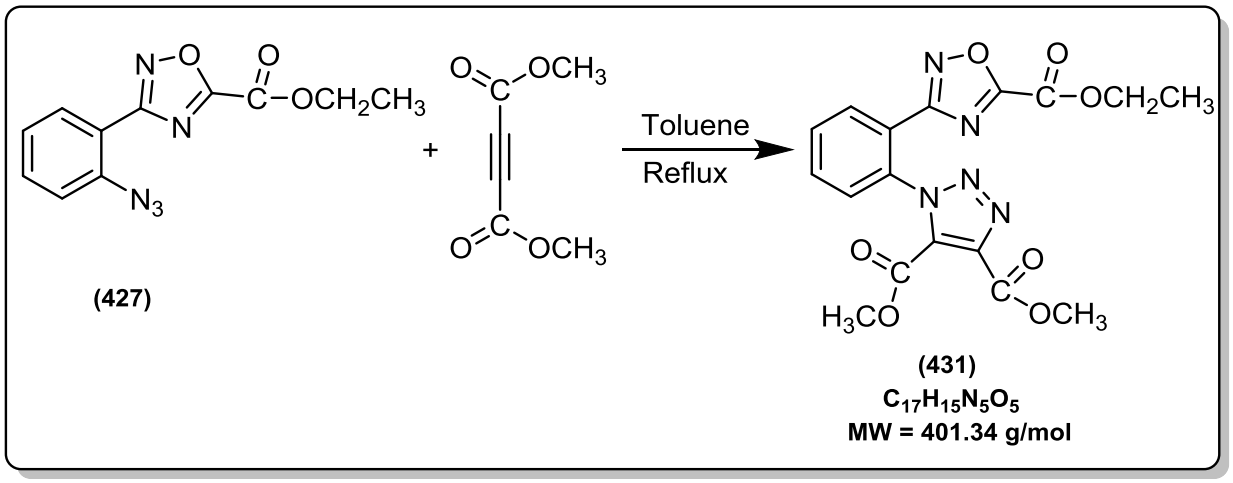
IR: υ_{max} (cm^{-1}): 797.1, 832.5, 944.5, 1024.7, 1116.8, 1156.3, 1203.3, 1253.9, 1294.3, 1368.7, 1470.8, 1503.0, 1581.5, 1619.4, 1651.3, 1701.8, 1732.1, 2978.9, 3001.1, 3044.7, 3158.5, 3376.7.

^{1}H NMR: δ_H (400 MHz, DMSO): 1.34 (3H, t, *J*=7.0 Hz, $OCH_2\mathbf{CH_3}$), 4.33 (2H, q, *J*=7.0 Hz, $OC\mathbf{H_2}CH_3$), 7.10 (1H, m, Ar**H**), 7.37 (1H, dd, J^1=8.0 Hz, J^2= 7.5 Hz, Ar**H**), 7.50 (1H, d, J=8.0 Hz, Ar**H**), 7.69 (1H, d, *J*= 7.0 Hz, Ar**H**), 11.19 (1H, s, N**H**), 12.94 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 14.30 (CH_3), 62.82 (CH_2), 110.81 (CH), 116.91 (qC), 120.48 (CH), 121.72 (CH), 127.01 (CH), 138.64 (qC), 141.40 (qC), 156.89 (C=O), 160.97 (C=O) ppm.

HRMS (ESI^+): found 233.0799 $[M]^+$, $C_{11}H_{11}N_3O_3$ requires 233.0800.

8.2.8. Synthesis of dimethyl 1-{2-[5-(ethoxycarbonyl)-1,2,4-oxadiazol-3-yl]phenyl}-1*H*-1,2,3-triazole-4,5-dicarboxylate.



To a solution of ethyl 3-(2-azidophenyl)-1,2,4-oxadiazole-5-carboxylate (150 mg, 0.58 mmol, 1.0 eq) in dry toluene (10 mL) was added dimethylacetylene dicarboxylate (791 mg, 0.637 mmol, 1.1 eq). The mixture was heated at reflux under nitrogen for 24 hours whilst being monitored by TLC. The solvent was distilled of under vacuum and the mixture was purified by using silica chromatography [petroleum ether/ethyl acetate: 1/1, R_f = 0.22] to give the product as a brown solid (175 mg, 75 %, m.p.=117-119 ^oC).

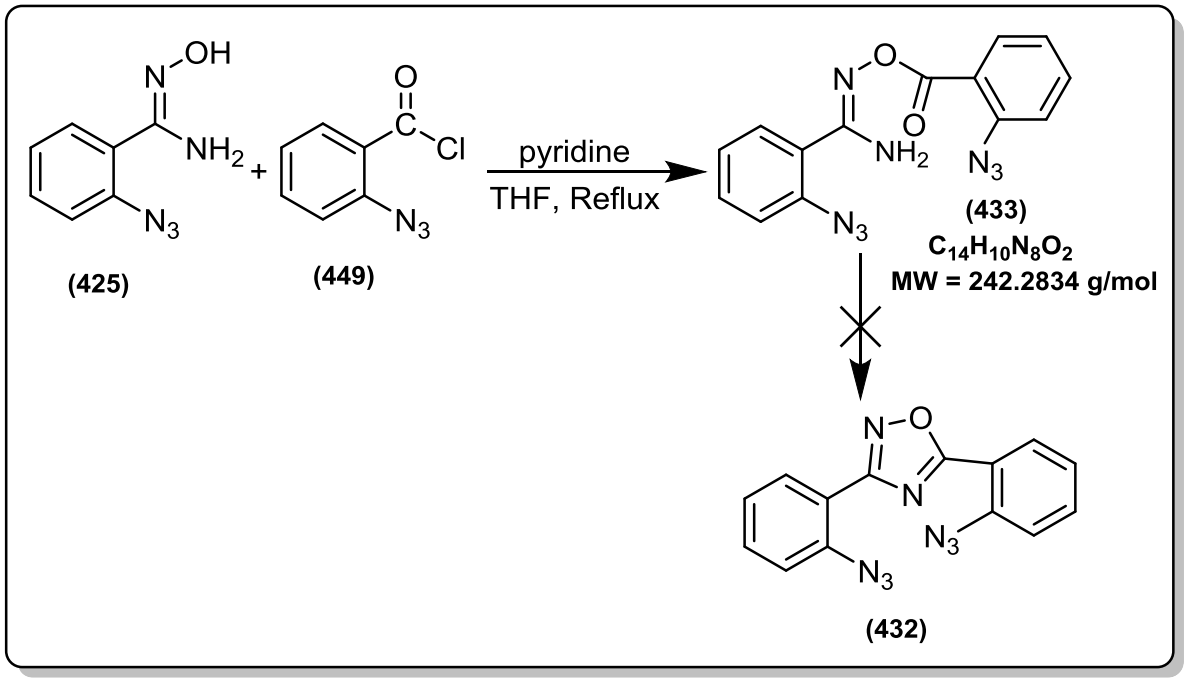
IR: υ_{max} (cm^{-1}): 776.2, 826.0, 913.4, 1018.8, 1100.7, 1191.9, 1288.9, 1360.2, 1448.0, 1491.5, 1524.9, 1565.8, 1590.7, 1608.7, 1731.8, 2955.4, 2985.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.43 (3H, t, *J*=7.1 Hz, $OCH_2\mathbf{CH_3}$), 3.76 (3H, s, $OC\mathbf{H_3}$), 4.02 (3H, s, $OC\mathbf{H_3}$), 4.50 (2H, q, *J*=7.1 Hz, $OC\mathbf{H_2}CH_3$), 7.57 (1H, dd, J^1=7.7 Hz, J^2= 1.9 Hz, Ar**H**), 7.73-7.80 (2H, m, **2** x Ar**H**), 8.36 (1H, dd, J^1= 7.1 Hz, J^2=1.6 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 13.90 (CH_3), 52.78 (CH_3), 53.39 (CH_3), 64.01 (CH_2), 123.73 (qC), 128.80 (CH), 130.72 (CH), 131.61 (CH), 132.29 (CH), 132.93 (qC), 134.00 (qC), 139.31 (qC), 153.62 (qC), 158.16 (qC), 160.30 (qC), 166.37 (qC), 166.43 (qC) ppm.

HRMS (ESI^+): found 402.0975 $[M+H]^+$, $C_{17}H_{16}N_5O7$ requires 402.1044.

8.2.9. Attempted Synthesis of 3,5-bis(2-azidophenyl)-1,2,4-oxadiazole.



To a solution of the acid chloride (150 mg, 0.84 mmol, 1.0 eq) in THF (10 mL), was added (*Z*)-2-azido-*N*'-hydroxybenzimidamide (168 mg, 0.93 mmol, 1.1 eq) followed by additon of pyridine (150 µL, 1.86 mmol, 1.1 eq). The mixture was heated at reflux for 24 hours, whilst being monitored by TLC. The solvent was distilled off under vacuum and the residue was purified by using silica chromatography [petroleum ether/ethyl acetate: 1/2, R_f = 0.20] to give the product (**433**) as a brown oil (120 mg, 44 %).

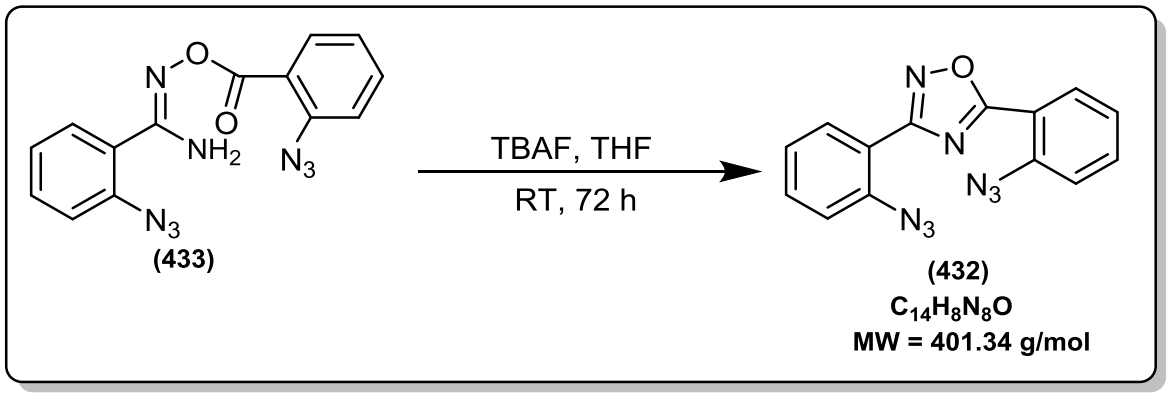
IR: υ_{max} (cm^{-1}): 748.2, 909.6, 1043.1, 1116.5, 1241.8, 1446.2, 1482.9, 1576.9, 1596.4, 1620.4, 1721.8, 2118.3, 2979.2, 3072.1, 3341.7, 3465.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.90 (2H, bs, N***H***$_2$), 7.15-7.22 (2H, m, 2 x Ar***H***), 7.25 (2H, dd, J^1=8.0 Hz, J^2=6.7 Hz, 2 x Ar***H***), 7.47 (1H, dd, J^1=7.7 Hz, J^2=7.5 Hz, Ar***H***), 7.57 (1H, dd, J^1=7.7 Hz, J^2= 7.5 Hz, Ar***H***), 7.77 (1H, d, *J*=7.5 Hz, Ar***H***), 8.00 (1H, d, *J*= 7.5 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 118.71 (CH), 119.25 (CH), 121.85 (qC), 122.11 (qC), 124.91 (CH), 125.04 (CH), 131.21 (CH), 131.89 (CH), 132.77 (CH), 133.45 (CH), 138.10 (qC), 139.27 (qC), 156.49 (C=N), 163.26 (C=O) ppm.

HRMS (ESI^+): found 323.0990 $[M+H]^+$, $C_{14}H_{11}N_8O_2$ requires 323.0999.

8.2.10. Synthesis of 3,5-bis(2-azidophenyl)-1,2,4-oxadiazole.



To a solution of ((benzoyloxy)amino)(phenyl)methanamine (80 mg, 0.248 mmol, 1.0 eq) in THF (10 mL), tetrabutylammonium fluoride (1 M in THF, 248 µL, 0.248 mmol, 1.0 eq) was added dropwise. The mixture was stirred at room temperature for 72 h whilst being monitored by TLC. The reaction mixture was diluted with water, the organic layer was separated and the aqueous layer was extracted with ethylacetate (3 x 10 mL). The combined organic layers were washed with water and brine. The organic layer was dried with anhydrous ($MgSO_4$), filtered and the solvent removed in *vacuo*. Purification by silica chromatography (eluent: petroleum ether/ethylacetate: 3/2, R_f = 0.2) yielded the product as a light yellow oil (68 mg, 90 %).

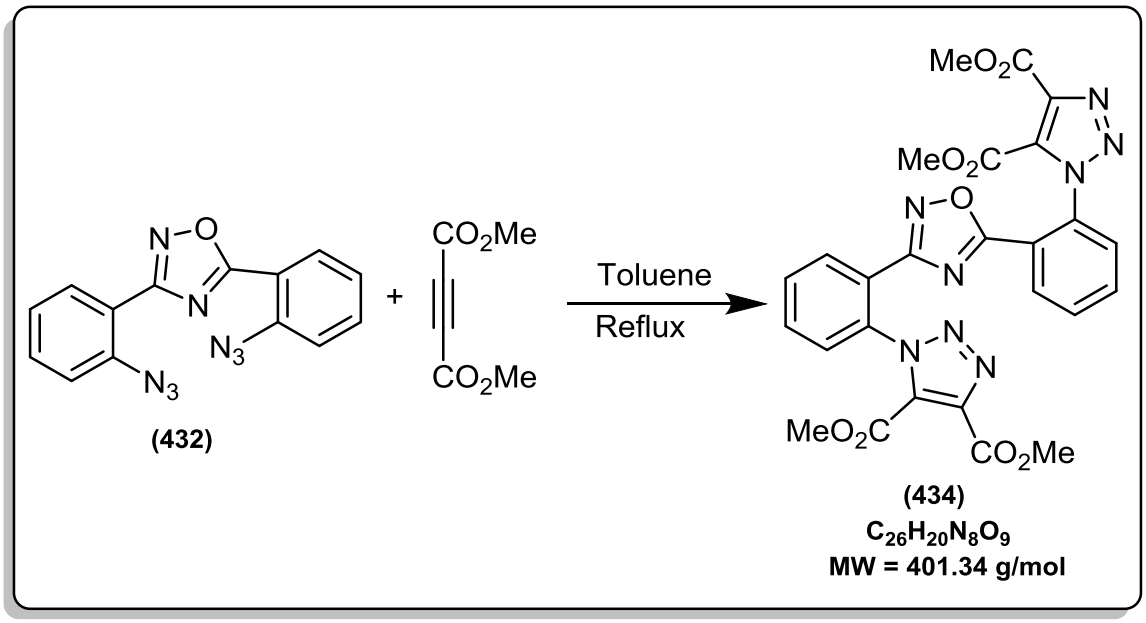
IR: υ_{max} (cm^{-1}): 710.0, 886.9, 1141.6, 1290.0, 1352.0, 1467.5, 1487.1, 1578.2, 1591.7, 2082.9, 3091.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.19-7.24 (2H, m, 2 x Ar***H***), 7.27 (2H, m, 2 x Ar***H***), 7.48 (1H, ddd, J^1=8.4 Hz, J^2=8.3 Hz, J^3=1.3 Hz, Ar***H***), 7.55 (1H, ddd, J^1=8.4 Hz, J^2= 8.3 Hz, J^3=1.2 Hz, Ar***H***), 7.99 (1H, dd, J^1=7.8 Hz, J^2=1.2 Hz, Ar***H***), 8.06 (1H, dd, J^1= 7.8 Hz, J^2=1.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 115.78 (qC), 118.54 (qC), 119.36 (CH), 119.82 (CH), 124.95 (CH), 125.03 (CH), 131.75 (CH), 131.78 (CH), 132.12 (CH), 133.69 (CH), 138.98 (qC), 139.72 (qC), 166.83 (C=N), 173.38 (C=N) ppm.

HRMS (ESI^+): found 305.0894 $[M+H]^+$, $C_{14}H_9N_8O$ requires 305.0894.

8.2.11. Synthesis of tetramethyl 1,1'-[(1,2,4-oxadiazole-3,5-diyl)bis(2,1-phenylene)]bis(1*H*-1,2,3-triazole-4,5-dicarboxylate).



(432)

(434)
$C_{26}H_{20}N_8O_9$
MW = 401.34 g/mol

To a solution of 3,5-bis(2-azidophenyl)-1,2,4-oxadiazole (65 mg, 0.21 mmol, 1.0 eq) in dry toluene (10 mL) was added dimethylacetylene dicarboxylate (66 mg, 0.47 mmol, 2.2 eq). The mixture was heated at reflux under nitrogen for 24 hours and whilst being monitored by TLC. The solvent was distilled under vacuum and the mixture was purified by using silica chromatography [petroleum ether/ethyl acetate: 5/3, R_f = 0.22] to give the product as a yellow oil (125 mg, 95 %).

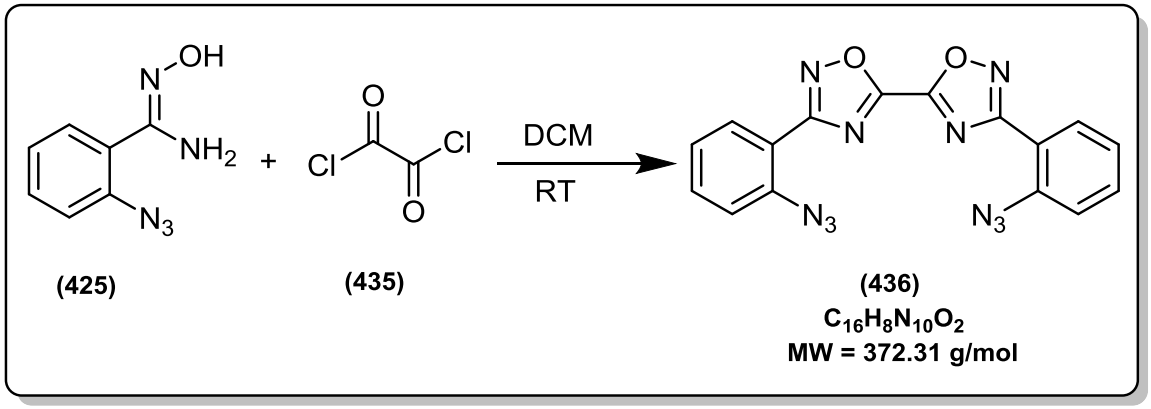
IR: υ_{max} (cm^{-1}): 724.0, 825.7, 907.9, 1004.0, 1079.7, 1204.3, 1290.4, 1349.0, 1491.5, 1562.1, 1592.8, 1608.7, 1731.5, 2955.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 3.64 (6H, bs, 2 x CH_3), 3.94 (3H, s, CH_3), 3.98 (3H, s, CH_3), 7.42 (1H, d, J^1=7.8 Hz, Ar***H***), 7.53 (1H, d, *J*=7.2 Hz, Ar***H***), 7.62 (1H, d, J^1=7.8 Hz, Ar***H***), 7.68-7.75 (2H, m, 2 x Ar***H***), 7.87 (1H, d, *J*=7.8 Hz, Ar***H***), 8.12 (1H, d, J^1= 7.2 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 52.79 (CH_3), 52.95 (CH_3), 53.38 (CH_3), 53.45 (CH_3), 121.14 (qC), 123.99 (qC), 128.60 (CH), 129.07 (CH), 130.40 (CH), 130.64 (CH), 131.56 (CH), 131.78 (CH), 131.85 (CH), 132.74 (qC), 133.04 (qC), 133.58 (CH), 133.71 (qC), 134.11 (qC), 139.22 (qC), 139.57 (qC), 157.88 (C=O), 158.06 (C=O), 160.38 (C=O), 160.44 (C=O), 165.65 (C=N), 171.56 (C=N) ppm.

HRMS (ESI$^+$): found 589.1422 $[M+H]^+$, $C_{26}H_{21}N_8O_9$ requires 589.1426.

8.2.12. Synthesis of 3,3'-bis(2-azidophenyl)-5,5'-bi(1,2,4-oxadiazole).



To a solution of oxalyl chloride (86 mg, 0.678 mmol, 1.2 eq) in DCM (10 mL), was added (Z)-2-azido-N'-hydroxybenzimidamide (100 mg, 0.565 mmol, 1.0 eq) followed by the addition of pyridine (100 µL). The mixture was stirred at room temperature for 24 hours, whilst being monitored by TLC. The solvent was distilled off under vacuum and the residue was purified by silica chromatography [eluent: petroleum ether/ethyl acetate: 5/1, R_f = 0.2] yielded the desired product (**426**) as a partially pure sample (light yellow oil, 168 mg, 80 %).

IR: υ_{max} (cm^{-1}): 752.7, 1107.6, 1166.9, 1293.8, 1446.3, 1471.0, 1510.0, 1576.9, 1594.8, 2111.7.

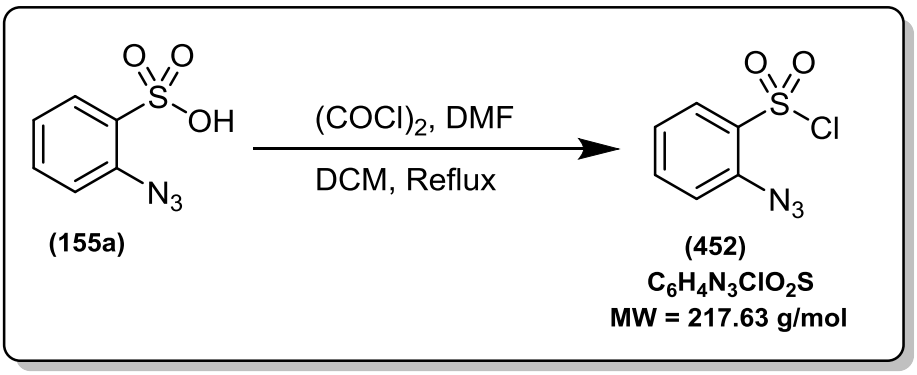
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.14 (2H, dd, J^1=7.9 Hz, J^2= 7.7 Hz, 2 x Ar***H***), 7.17-7.20 (2H, m, 2 x Ar***H***), 7.53 (2H, ddd, J^1=7.7 Hz, J^2= 7.5 Hz, J^3=1.5 Hz, 2 x Ar***H***), 7.93 (2H, dd, J^1=7.7 Hz, J^2=1.5 Hz, 2 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 118.81 (2 x CH), 125.02 (2 x CH), 133.91 (2 x CH), 134.08 (2 x CH), 138.93 (2 x qC), 143.37 (2 x qC), 164.28 (2 x qC (C-C)), 165.76 (2 x qC (C=N)) ppm.

HRMS (ESI$^+$): found 395.0727 $[M+Na]^+$, $C_{16}H_8N_{10}O_2Na$ requires 395.0724.

8. Experimental: 3. Reactivity of 2-azidobenzenesulfonic acid and 2-azidobenzoic acid.

8.3.1. Synthesis of o-azido benzene sulfonyl chloride



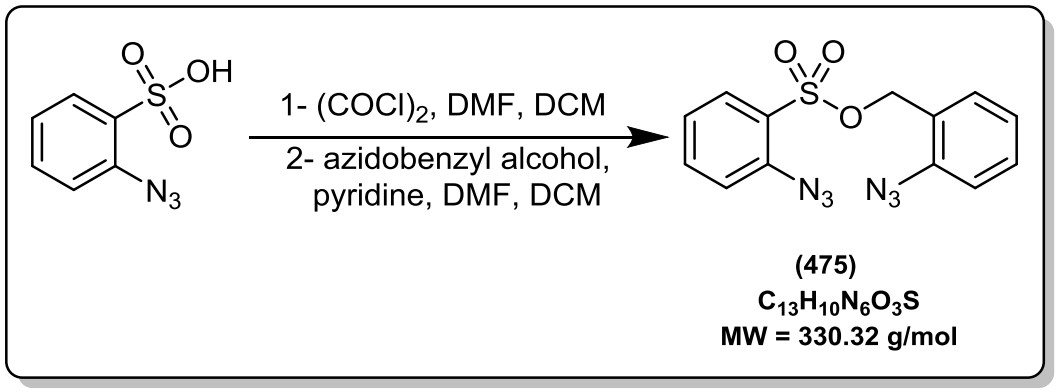
2-Azidobenzene sulfonic acid (2.0 g, 10.054 mmol, 2.2 eq) was heated to reflux in a 2M solution of $(COCl)_2$ in dichloromethane (11.85 mL, 22.85 mmol, 5 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride in as an orange solid (1.91 g, 87 %).[186,231]

IR: υ_{max} (cm^{-1}): 728.4, 763.4, 1057.3, 1124.3, 1148.2, 1170.3, 1270.0, 1287.3, 1367.3, 1470.6, 1581.0, 2101.9, 2940.7, 3098.3.

^{1}H NMR: δ_H (400 MHz, DMSO): 7.13 (1H, dd, J^1=7.6 Hz, J^2=7.4 Hz, Ar**H**), 7.21 (1H, d, J= 7.7 Hz, Ar**H**), 7.39 (1H, ddd, J^1=7.6 Hz, J^2=7.5 Hz, J^3=1.4 Hz, Ar**H**), 7.76 (1H, dd, J^1=7.7 Hz, J^2=1.4 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 120.95 (CH), 124.68 (CH), 129.01 (CH), 130.84 (CH), 136.47 (qC), 138.93 (qC) ppm.

8.3.2. Synthesis of 2-azidobenzyl 2-azidobenzenesulfonate.



To 2-azidobenzene sulfonic acid (1.194 g, 6.0 mmol, 2.0 eq) was added a 2M solution of oxalyl chloride in dichloromethane (7.5 mL, 15.0 mmol, 5.0 eq) followed by the addition of DMF (100 µL). The whole was heated to reflux for 15 hours under nitrogen. The excess oxalyl chloride was removed in vacuo and the residue was washed with dichloromethane (3 x 10 mL) to give the crude sulfonyl chloride as an orange solid.

Pyridine (241 µL, 237 mg, 3.0 mmol, 1.0 eq) was added dropwise to a stirring solution of 2-azidobenzyl alcohol (447 mg, 3.0 mmol, 1.0 eq) in DCM (10 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added dropwise to this solution followed by addition a drop of DMF. The mixture was heated to reflux under a nitrogen atmosphere for 48 hours whilst being monitored by TLC. The solvent was removed under vacuum and the mixture was purified by using column chromatography (eluent: methanol/ethyl acetate: 1/2, R_f = 0.4) yielded the product as a deep brown solid (750 mg, 76 %, m.p.=168-170 ^oC).

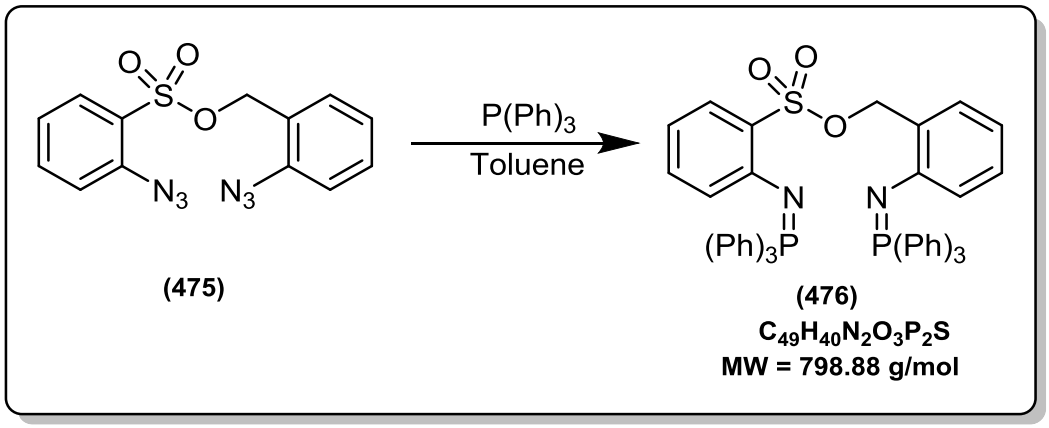
IR: υ_{max} (cm^{-1}): 762.3, 876.3, 978.8, 1025.1, 1088.6, 1105.0, 1195.2, 1280.7, 1438.6, 1472.4, 1493.7, 1575.7, 2125.7.

^{1}H NMR: δ_H (400 MHz, DMSO): 4.72 (2H, s, C***H*****$_2$**), 7.12-7.21 (2H, m, 2 x Ar***H***), 7.24 (1H, dd, J^1= 8.0 Hz, J^2=1.0 Hz, Ar***H***), 7.29 (1H, dd, J^1=8.0 Hz, J^2=1.0 Hz, Ar***H***), 7.37-7.43 (3H, m, 3 x Ar***H***), 7.77 (1H, dd, J^1=7.7 Hz, J^2=1.6 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 63.28 (CH_2), 118.75 (CH), 120.65 (CH), 124.66 (CH), 125.29 (CH), 128.99 (CH), 129.30 (qC), 129.41 (CH), 129.62 (CH), 130.91 (CH), 136.48 (qC), 137.24 (qC), 138.76 (qC) ppm.

HRMS (ESI$^+$): found 353.0427 $[M+Na]^+$, $C_{13}H_{10}N_6O_3SNa$ requires 353.0427.

8.3.3. Synthesis of 2-[(triphenyl-λ^5-phosphanylidene)amino]benzyl 2-[(triphenyl-λ^5-phosphanylidene)amino]benzenesulfonate.



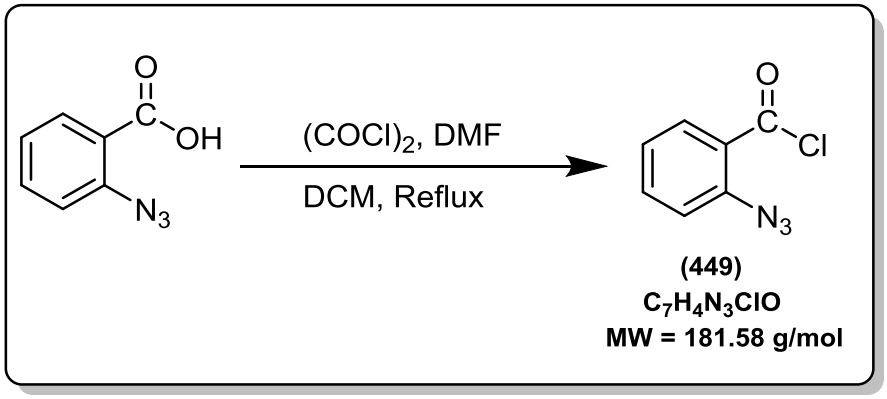
To a solution of 2-azidobenzyl 2-azidobenzenesulfonate (330 mg, 1.0 mmol, 1.0 eq) in anhydrous toluene (10 mL), triphenylphosphine (524 mg, 2.0 mmol, 2.0 eq) was added. The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using silica column chromatography with [methanol /ethyl acetate = 1/3, R_f= 0.23 as eluent] to give a brown solid as the product (570 mg, 71 %, m.p.=101-103 ^oC).

IR: υ_{max} (cm^{-1}): 540.7, 691.8, 905.3, 1013.9, 1111.0, 1180.7, 1336.5, 1450.4, 1479.1, 1586.5, 3055.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.15 (2H, bs, C**H**$_2$), 6.32-6.43 (4H, m, 4 x Ar**H**), 6.61-6.92 (5H, m, 5 x Ar**H**), 7.33-7.10 (21H, m, 21 x Ar**H**), 8.01-8.10 (8H, m, 8 x Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 26.73 (CH_2) 119.27 (qC), 121.27 (CH), 128.53 (4 x CH), 128.60 (4 x CH), 128.65 (3 x CH), 128.80 (4 x CH), 128.92 (3 x CH), 129.33 (qC), 129.47 (CH), 129.99 (CH), 130.11 (CH), 130.33 (2 x qC), 130.81 (qC) 132.04 (3 x CH), 132.32 (CH), 132.42 (CH), 133.07 (qC), 133.66 (3 x CH), 133.85 (3 x CH), 134.02 (CH), 134.11 (3 x CH), 134.86 (CH), 137.12 (2 x qC), 137.22 (qC), 150.90 (qC) ppm.

8.3.4. Synthesis of 2-azidobenzoyl chloride[243]



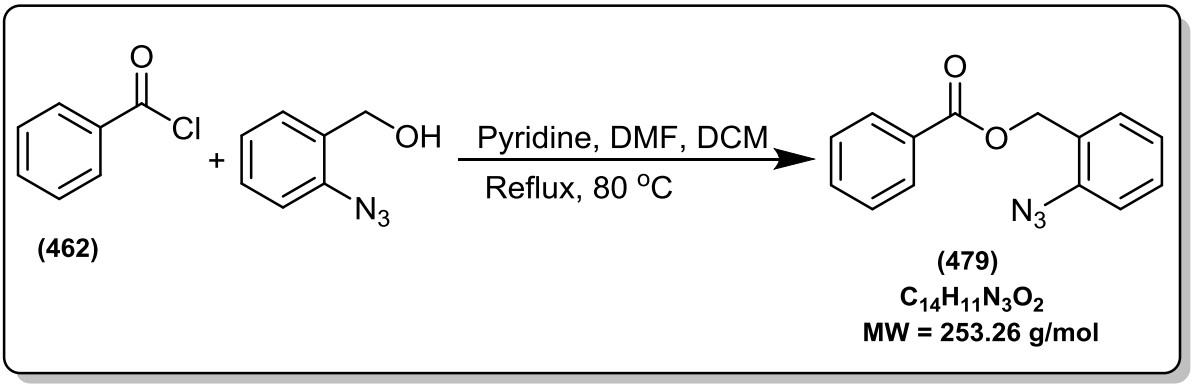
2-Azidobenzoic acide (1.63 g, 10.00 mmol, 1.0 eq) was heated to reflux in a 2M solution of $(COCl)_2$ in dichloromethane (10.35 mL, 20.70 mmol, 2.7 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was cooled to room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 20 mL) to give the crude sulfonyl chloride in as an orange solid (1.5 g, 82 %).

IR: υ_{max} (cm^{-1}): 761.3, 866.8, 1190.6, 1277.2, 1311.0, 1446.3, 1475.3, 1572.1, 1777.7, 2123.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.27-7.33 (2H, m, 2 x Ar**H**), 7.66 (1H, ddd, J^1=8.2 Hz, J^2=8.0 Hz, J^3=1.2 Hz, Ar**H**), 8.15 (1H, dd, J^1=8.0 Hz, J^2=0.9 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 119.83 (CH), 124.70 (CH), 124.83 (qC), 134.42 (CH), 135.39 (CH), 140.73 (qC), 164.10 (C=O) ppm.

8.3.5. Synthesis of 2-azidobenzyl benzoate.



To a stirring solution of 2-azidobenzyl alcohol (500 mg, 3.35 mmol, 2.0 eq) in DCM (10 mL) was added pyridine (135 µL, 132 mg, 1.67 mmol, 1.0 eq) dropwise. The benzoyl chloride (235 mg, 1.677 mmol, 1.0 eq) was added dropwise to this solution followed by addition of a drop of DMF. The mixture was heated to reflux under a nitrogen atmosphere for 48 hours whilst being monitored by TLC. The solvent was removed under vacuum and the mixture was purified by using column chromatography (eluent: petrolum ether/ethyl acetate: 2/1, R_f = 0.23) tpyield the product as a yellow oil (650 mg, 77%).

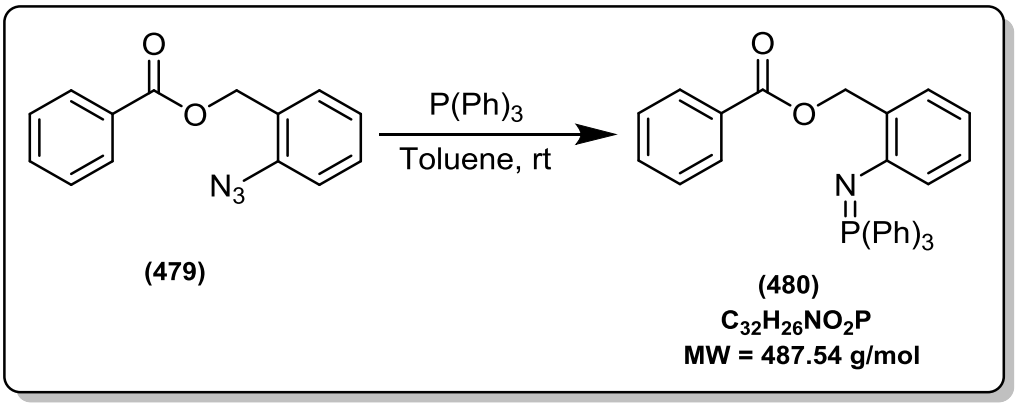
IR: υ_{max} (cm^{-1}): 748.5, 870.1, 990.7, 1041.3, 1122.1, 1173.7, 1269.9, 1372.7, 1450.2, 1584.2, 1719.5, 2117.6, 2980.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.37 (2H, s, C***H*****$_2$**), 7.19 (1H, t, *J*=7.6 Hz, Ar***H***), 7.23 (1H, d, *J*= 8.0 Hz, Ar***H***), 7.40-7.50 (4H, m, 4 x Ar***H***), 7.59 (1H, dd, J^1=7.6 Hz, J^2=7.3 Hz, Ar***H***), 8.10 (2H, d, *J*=7.6 Hz, 2 x Ar***H***), ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 62.26 (CH_2), 118.24 (CH), 124.48 (CH), 127.23 (qC), 128.41 (2 x CH), 129.69 (CH), 129.74 (2 x CH), 130.07 (qC), 130.19 (CH), 133.08 (CH), 138.57 (qC), 166.35 (C=O) ppm.

HRMS (ESI^+): found 276.0742 $[M+Na]^+$, $C_{14}H_{11}N_3O_2Na$ requires 276.0743.

8.3.6. Synthesis of 2-[(triphenyl-λ^5-phosphanylidene)amino]benzyl benzoate.



(479)

(480)
$C_{32}H_{26}NO_2P$
MW = 487.54 g/mol

To a solution of 2-azidobenzyl benzoate (200 mg, 0.790 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added triphenylphosphine (248 mg, 0.949 mmol, 1.2 eq). The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After completion of

the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using column chromatography [petroleum ether/ethyl acetate: 2/1, R_f = 0.19] to yield the product as a pale yellow solid (290 mg, 75 %, m.p.=159-161 ^oC).

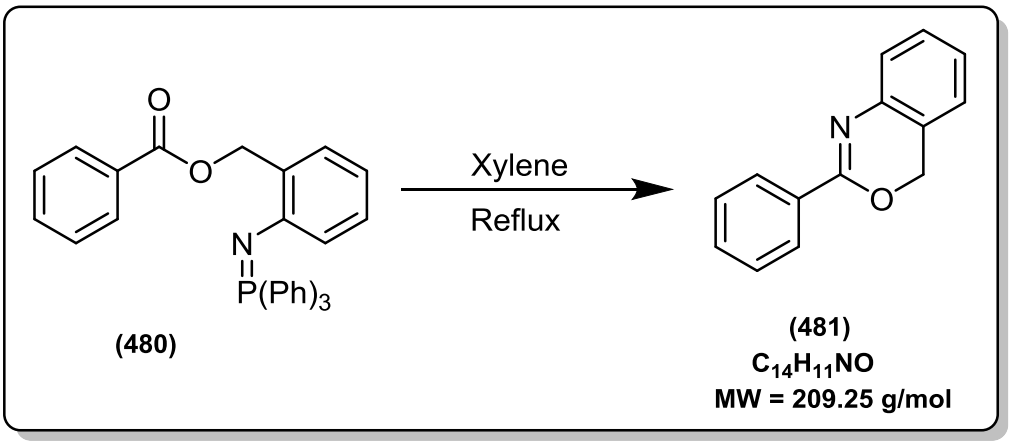
IR: υ_{max} (cm^{-1}): 753.2, 925.2, 1022.4, 1104.9, 1298.6, 1345.0, 1439.4, 1454.0, 1480.8, 1595.3, 1650.4, 1696.8, 1715.9, 2941.3, 3064.1, 2980.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.65 (2H, s, C***H*****$_2$**), 6.39 (1H, d, *J*=7.9 Hz, Ar**H**), 6.59 (1H, t, *J*=7.6 Hz, Ar**H**), 6.79 (1H, t, *J*=7.6 Hz, Ar**H**), 7.24-7.33 (8H, m, 8 x Ar***H***), 7.38-7.45 (4H, m, 4 x Ar***H***), 7.65 (3H, d, *J*=7.8 Hz, 3 x Ar**H**), 7.67 (3H, d, *J*=7.8 Hz, 3 x Ar***H***), 7.96 (2H, d, *J*=7.9 Hz, 2 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 65.69 (CH_2), 117.11 (CH), 121.04 (CH), 128.18 (2 x CH), 128.35 (CH), 128.57 (3 x CH), 128.60 (qC), 128.69 (3 x CH), 129.00 (CH), 129.69 (2 x CH), 129.90 (3 x qC), 130.98 (qC), 131.69 (3 x CH), 132.50 (4 x CH), 132.60 (3 x CH), 149.80 (qC), 167.02 (C=O) ppm.

HRMS (ESI^+): found 488.1777 $[M+H]^+$, $C_{32}H_{27}NO_2P$ requires 488.1774.

8.3.7. Synthesis of 2-phenyl-4*H*-benzo[*d*][1,3]oxazine.



2-[(Triphenyl-λ^5-phosphanylidene)amino]benzyl benzoate (100 mg, 0.205 mmol) was added to dry xylene (10 mL). The mixture was heated at reflux temperature for 24 hours under a nitrogen atmosphere, and monitored by TLC. The solvent was distilled under vacuum. The

residue was purified by using column chromatography [petroleum ether/ethyl acetate: 4/1, R_f = 0.22] to yield the product as a dark yellow oil (40 mg, 93 %).

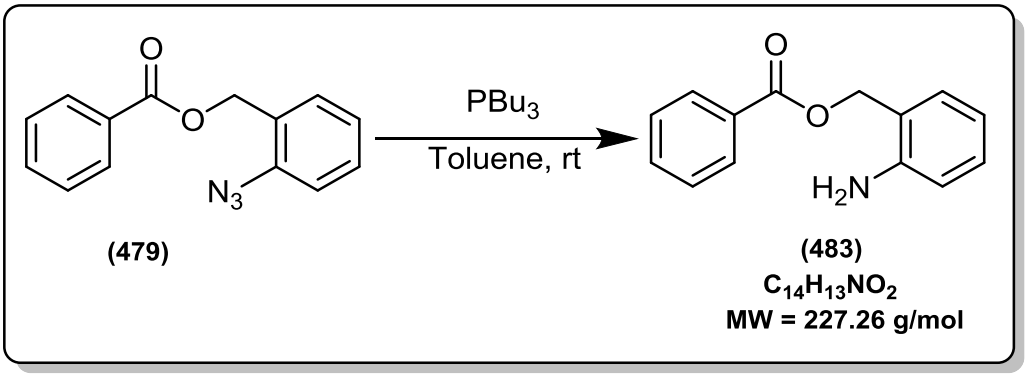
IR: υ_{max} (cm^{-1}): 771.3, 873.2, 930.4, 1000.3, 1109.6, 1227.6, 1246.4, 1315.8, 1379.8, 1490.1, 1567.8, 1593.9, 1612.5, 2868.0, 3039.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.41 (2H, s, C***H*$_2$**), 7.04 (1H, d, *J*=7.4 Hz, Ar***H***), 7.21 (1H, td, J^1=7.3 Hz, J^2=2.1 Hz, Ar***H***), 7.33 (2H, dd, J^1=7.5 Hz, J^2=6.7 Hz, 2 x Ar***H***), 7.47 (2H, dd, J^1=7.8 Hz, J^2=7.8 Hz, 2 x Ar***H***), 7.52 (1H, t, *J*=7.2 Hz, Ar***H***), 8.17 (2H, d, *J*=7.3 Hz, 2 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 66.44 (CH_2), 122.33 (qC), 123.75 (CH), 124.67 (CH), 126.48 (CH), 128.02 (2 x CH), 128.27 (2 x CH), 129.02 (CH), 131.46 (CH), 132.39 (qC), 139.72 (qC), 157.71 (C=N) ppm.

HRMS (ESI^+): found 210.0916 $[M+H]^+$, $C_{14}H_{12}NO$ requires 210.0913.

8.3.8. Synthesis of 2-aminobenzyl benzoate.



(479)

(483)
$C_{14}H_{13}NO_2$
MW = 227.26 g/mol

To a solution of 2-azidobenzyl benzoate (253 mg, 1 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added tributylphosphine (244 mg, 1.2 mmol, 1.2 eq). The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using column chromatography [petroleum ether/ethyl acetate: 3/1, R_f = 0.22] to yield the product as a yellow oil (136 mg, 60 %).

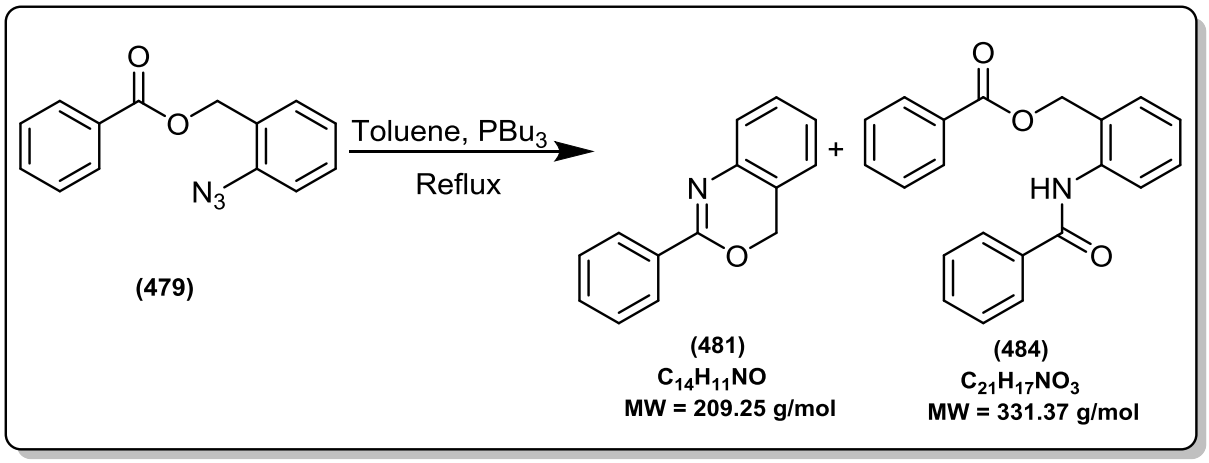
IR: υ_{max} (cm^{-1}): 782.1, 927.7, 996.8, 1025.3, 1068.9, 1105.9, 1266.0, 1314.0, 1451.1, 1496.1, 1584.0, 1602.7, 1705.1, 3063.5, 3376.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 4.70 (2H, bs, N***H***$_2$), 5.38 (2H, s, C**H**$_2$), 6.76 (1H, d, *J*=8.0 Hz, Ar**H**), 6.82 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar***H***), 7.21 (1H, dd, J^1=7.8 Hz, J^2=1.4 Hz, Ar***H***), 7.33 (1H, d, *J*=7.7 Hz, Ar***H***), 7.45 (2H, dd, J^1=7.7 Hz, J^2=7.6 Hz, 2 x Ar***H***), 7.58 (1H, t, *J*=7.5 Hz, Ar***H***), 7.94-8.15 (2H, m, 2 x Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 64.86 (CH_2), 116.28 (CH), 118.50 (CH), 120.27 (qC), 128.45 (2 x CH), 129.74 (2 x CH), 129.97 (qC), 130.19 (CH), 131.54 (CH), 133.19 (CH), 145.98 (qC), 166.86 (C=O) ppm.

The data is identical to that reported in the literature.[244]

8.3.9. Reactivity of 2-azidobenzyl benzoate.



To a solution of 2-azidobenzyl benzoate (150 mg, 0.592 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added tributylphosphine (145 mg, 0.711 mmol, 1.2 eq). The whole was stirred for 6 hours at ambient temperature under a nitrogen atmosphere and after completion of the reaction, monitored by TLC, the mixture was heated at reflux temperature for 24 hours under a nitrogen atmosphere. The solvent was removed under vacuum and the residue was purified by using silica column chromatography to give two products:

2-Phenyl-4*H*-benzo[*d*][1,3]oxazine (481).

[Petroleum ether/ethyl acetate: 3/1, R_f = 0.3] to yield the product as a pale green oil (86 mg, 69 %), data as reported above.

2-Benzamidobenzyl benzoate (484).

[Petroleum ether/ethyl acetate: 3/1, R_f = 0.21] to yield the product as a light yellow (40 mg, 24 %, m.p.=128-130 °C).

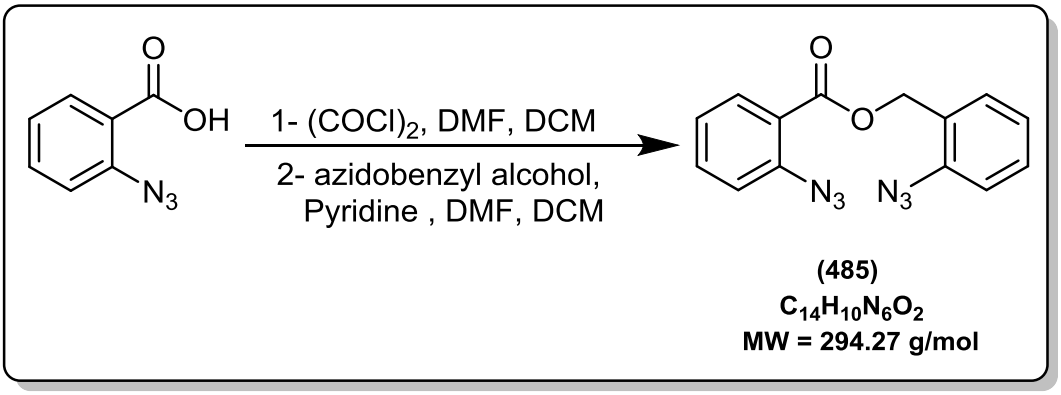
IR: υ_{max} (cm^{-1}): 606.6, 673.3, 753.1, 822.6, 934.3, 1070.8, 1110.9, 1243.9, 1379.3, 1448.9, 1514.8, 1585.8, 1600.9, 1667.7, 1696.1, 2980.6, 3060.7, 3317.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.31 (2H, s, C***H***$_2$), 7.13 (1H, t, *J*=7.5 Hz, Ar***H***), 7.33-7.38 (3H, m, 3 x Ar***H***), 7.40-7.44 (3H, m, 3 x Ar***H***), 7.49 (2H, dd, J^1=7.0 Hz, J^2=6.4 Hz, 2 x Ar***H***), 7.97-8.02 (5H, m, 5 x Ar***H***), 9.69 (1H, bs, N***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 66.12 (CH_2), 124.71 (CH), 125.24 (CH), 126.84 (qC), 127.45 (2 x CH), 128.53 (2 x CH), 128.73 (2 x CH), 129.39 (qC), 129.88 (2 x CH), 130.01 (CH), 131.75 (CH), 131.91 (CH), 133.60 (CH), 134.60 (qC), 136.86 (qC), 165.82 (C=O), 167.47 (C=O) ppm.

HRMS (ESI^+): found 331.1205 $[M]^+$, $C_{19}H_{15}N_4O_2$ requires 331.1195.

8.3.10. Synthesis of 2-azidobenzyl 2-azidobenzoate.



To 2-azidobenzoic acid (800 mg, 4.9 mmol, 2.0 eq) was added a 2M solution of oxalyl chloride in dichloromethane (6.15 mL, 12.3 mmol, 5.0 eq) followed by the addition of DMF (100 µL). The whole was heated to reflux for 15 hours under nitrogen. The excess oxalyl chloride was removed in vacuo and the residue was washed with dichloromethane (3 x 10 mL) to give the crude sulfonyl chloride as an orange solid.

Pyridine (198 µL, 194 mg, 2.46 mmol, 1.0 eq) was added dropwise to a stirring solution of 2-azidobenzyl alcohol (366 mg, 2.46 mmol, 1.0 eq) in DCM (10 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added dropwise to this solution followed by the addition of a drop of DMF. The mixture was heated to reflux under a nitrogen atmosphere for 48 hours whilst being monitored by TLC. The solvent was removed under vacuum and the mixture was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 10/1, R_f = 0.3) which yielded the product as a brown oil (536 mg, 74 %, m.p.=154-156 ^oC).

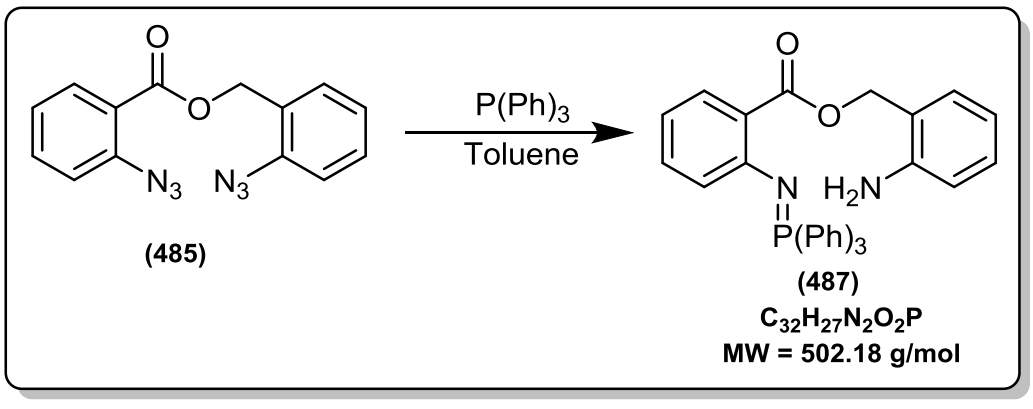
IR: υ_{max} (cm^{-1}): 886.7, 992.3, 1072.8, 1129.3, 1231.6, 1366.4, 1446.0, 1484.8, 1594.1, 1729.9, 2092.8, 2930.2, 3031.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.35 (2H, s, C***H*$_2$**), 7.14-7.27 (4H, m, 4 x Ar***H***), 7.41 (1H, dd, J^1= 7.8 Hz, J^2=7.5 Hz, Ar***H***), 7.51 (1H, d, *J*=8.7 Hz, Ar***H***), 7.56 (1H, dd, J^1=8.0 Hz, J^2=1.2 Hz, Ar**H**), 7.91 (1H, d, *J*=7.8 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 62.63 (CH_2), 118.25 (CH), 119.85 (CH), 122.36 (qC), 124.48 (CH), 124.86 (CH), 126.91 (qC), 129.80 (CH), 130.47 (CH), 131.95 (CH), 133.35 (CH), 138.64 (qC), 140.25 (qC), 164.90 (C=O) ppm.

HRMS (ESI^+): found 317.0764 $[M+Na]^+$, $C_{14}H_{10}N_6O_2Na$ requires 317.0757.

8.3.11. Synthesis of 2-[(triphenyl-λ^5-phosphanylidene)amino]benzyl 2-[(triphenyl-λ^5-phosphanylidene)amino]benzoate.



(485)

(487)

$C_{32}H_{27}N_2O_2P$

MW = 502.18 g/mol

To a solution of 2-azidobenzyl 2-azidobenzoate (100 mg, 0.34 mmol, 1.0 eq) in anhydrous toluene (10 mL), triphenylphosphine (178 mg, 0.68 mmol, 2.0 eq) was added. The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After

completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.21) yielded the product as a light yellow oil (130 mg, 50 %).

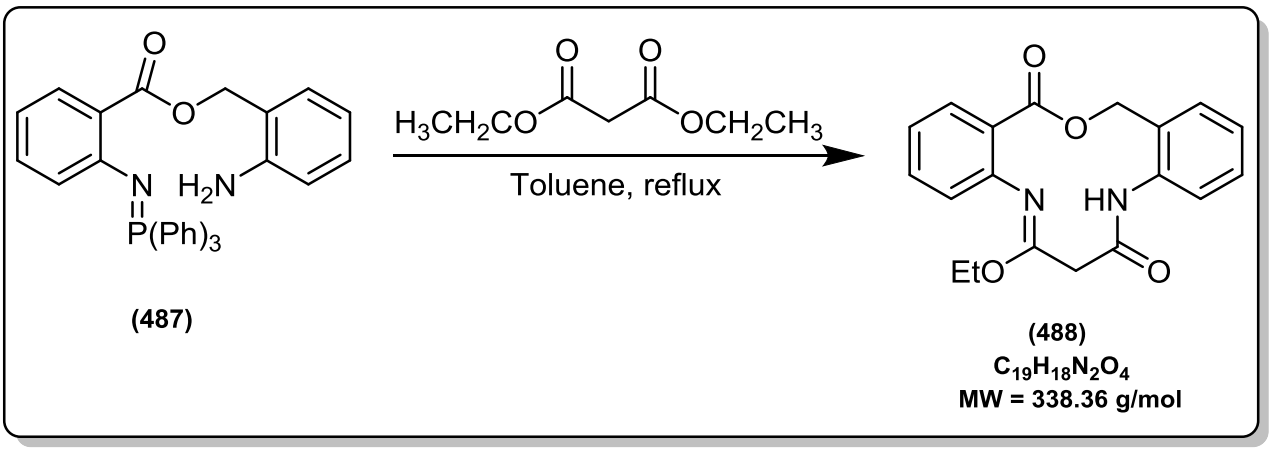
IR: υ_{max} (cm^{-1}): 926.2, 1023.4, 1052.8, 1107.1, 1183.3, 1242.7, 1341.3, 1451.8, 1481.9, 1592.8, 1615.7, 1684.0, 2852.8, 2926.3, 3056.7, 3369.8, 3473.7.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 5.72 (4H, bs, N***H***$_2$ + C***H***$_2$), 6.51 (1H, d, *J*=7.9 Hz, Ar***H***), 6.56 (1H, t, *J*=7.5 Hz, Ar***H***), 6.62 (1H, d, *J*=8.0 Hz, Ar***H***), 6.70 (1H, t, *J*=7.5 Hz, Ar***H***) 6.90 (1H, t, *J*=7.5 Hz, Ar***H***), 7.23 (1H, t, *J*=7.5 Hz, Ar***H***), 7.39 (1H, d, *J*=7.2 Hz, Ar***H***), 7.44-7.47 (6H, m, 6 x Ar***H***), 7.51-7.55 (3H, m, 3 x Ar***H***), 7.78 (6H, m, 6 x Ar***H***), 7.93 (1H, d, *J*=8.0 Hz, Ar***H***) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 65.14 (CH_2), 111.76 (qC), 116.13 (CH), 116.54 (CH), 117.03 (CH), 120.98 (CH), 124.34 (CH), 128.57 (3 x CH), 128.69 (3 x CH), 129.13 (CH), 129.95 (qC), 130.17 (qC), 130.79 (qC), 131.66 (3 x CH), 131.73 (CH), 131.78 (qC), 132.50 (3 x CH), 132.60 (3 x CH), 133.67 (CH), 149.92 (qC), 150.21 (qC), 168.52 (C=O) ppm.

HRMS (ESI^+): found 503.1883 $[M+H]^+$, $C_{14}H_{10}N_6O_2Na$ requires 503.1884.

8.3.12. Synthesis of (*Z*)-8-ethoxy-5,16-dihydro-6*H*-dibenzo[c,J][1]oxa [5,9]diazacyclododecine-6,14(7*H*)-dione.



(487)

(488)
$C_{19}H_{18}N_2O_4$
MW = 338.36 g/mol

To a solution of 2-((triphenyl-λ^5-phosphanylidene)amino)benzyl 2-((triphenyl-λ^5-phosphanylidene)amino)benzoate (105 mg, 0.138 mmol, 1.0 eq) in anhydrous toluene (10 mL) was added diethyl malonate (26 mg, 0.165 mmol, 1.2 eq). The whole was heated for 24 hours at reflux under a nitrogen atmosphere, whilst being monitored by TLC. The solvent was removed under vacuum. The residue was purified by using column chromatography (eluent: petroleum ether/ethyl acetate: 3/1, R_f = 0.25) which yielded the product as a light yellow oil (30 mg, 65 %).

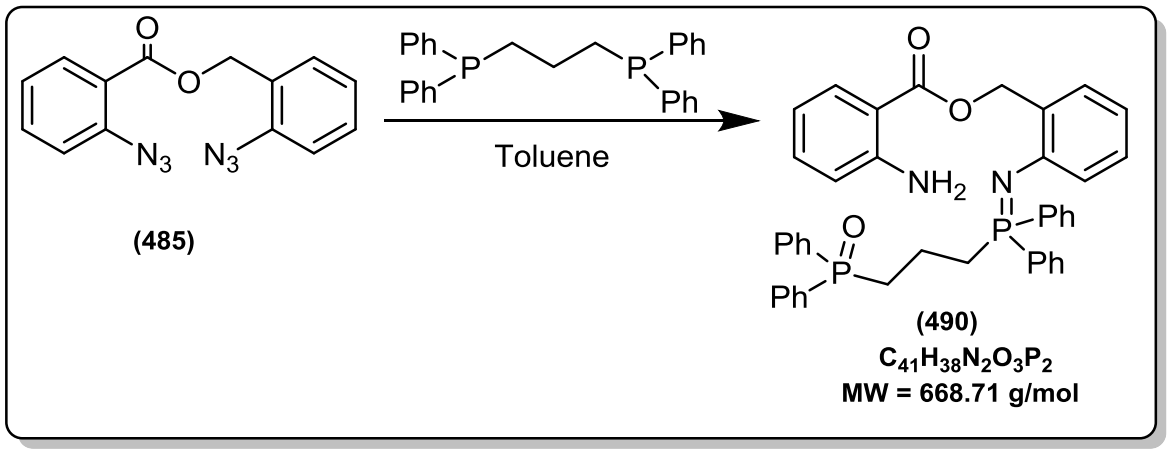
IR: υ_{max} (cm^{-1}): 762.5, 950.8, 1030.9, 1072.7, 1162.1, 1237.9, 1262.0, 1378.9, 1446.2, 1460.9, 1574.1, 1600.7, 1650.5, 1692.5, 1737.6, 2927.8, 2979.8.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.20 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 3.50 (2H, s, CH_2-C=O), 4.17 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 5.34 (2H, s, OCH_2), 6.97 (1H, d, *J*=7.4 Hz, Ar***H***), 7.04 (1H, dd, *J*=7.6 Hz, J^2=7.5 Hz, Ar***H***), 7.14-7.22 (2H, m, 2 x Ar***H***), 7.27 (1H, dd, *J*=7.4 Hz, J^2=7.3 Hz, Ar***H***), 7.41 (1H, dd, *J*=7.6 Hz, J^2=7.5 Hz, Ar***H***), 7.95 (1H, d, *J*=7.6 Hz, Ar***H***), 8.64 (1H, d, *J*=8.0 Hz, Ar***H***), 13.27 (1H, bs, ***H***N) ppm.

^{13}C NMR δ_c (100 MHz, $CDCl_3$): 14.15 (CH_3), 45.74 (CH_2), 61.63 (CH_2), 66.48 (CH_2), 116.82 (qC), 120.40 (CH), 121.72 (qC), 122.74 (CH), 124.01 (CH), 124.12 (CH), 127.23 (CH), 128.94 (CH), 129.23 (CH), 132.85 (CH), 137.85 (qC), 140.19 (qC), 158.17 (C=N), 163.94 (C=O), 167.46 (C=O) ppm.

HRMS (ESI^+): found 338.1278 $[M]^+$, $C_{19}H_{18}N_2O_4$ requires 338.1267.

8.3.13. Synthesis of 2-{[(3-(diphenylphosphoryl)propyl)diphenyl-λ^5-phosphanylidene]amino}benzyl 2-aminobenzoate.



To a solution of 2-azidobenzyl 2-azidobenzoate (100 mg, 0.34 mmol, 1.0 eq) in anhydrous toluene (10 mL), 1,3-bis(diphenylphosphanyl)propane (280 mg, 0.34 mmol, 1.0 eq) was added. The mixture was stirred for 12 hours at ambient temperature under a nitrogen atmosphere. After completion of the reaction, monitored by TLC, the solvent was removed under vacuum. The residue was purified by using slica column chromatography (eluent: petroleum ether/ethyl acetate: 2/1, R_f = 0.23) which yielded the product as a pale yellow oil (92 mg, 41 %).

IR: υ_{max} (cm^{-1}): 729.3, 907.9, 1024.1, 1107.9, 1291.1, 1371.6, 1435.7, 1481.4, 1591.5, 1614.8, 1682.1, 2853.9, 2924.2, 3056.5, 3367.5, 3471.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.93 (2H, t, *J*=7.3 Hz, O=PCH$_2$CH$_2$C***H$_2$***), 2.08-2.24 (2H, m, O=PCH$_2$C***H$_2$***CH$_2$), 2.55-2.69 (2H, m, O=PC***H$_2$***CH$_2$CH$_2$), 5.50 (2H, s, OC***H$_2$***), 5.56 (2H, bs, N***H$_2$***), 6.26 (1H, t, *J*=7.0 Hz, Ar***H***), 6.46 (1H, m, Ar***H***), 6.53 (1H, t, *J*=7.9 Hz, Ar***H***), 6.59 (1H, t, *J*=7.0 Hz, Ar***H***), 6.81 (1H. bs, Ar***H***), 7.12-7.21 (7H, m, 7 x Ar***H***), 7.27-7.47 (11H, m, 11 x Ar***H***), 7.63-7.67 (4H, m, 4 x Ar***H***), 7.81 (1H, d, *J*=7.9 Hz, Ar***H***) ppm.

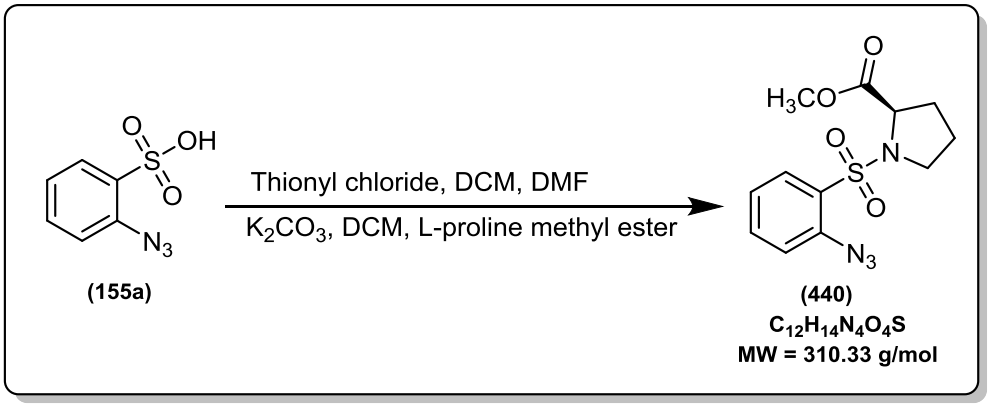
^{13}C NMR δ_c (100 MHz, $CDCl_3$): 15.05 (CH_2), 18.27 (CH_2), 29.72 (CH_2), 64.93 (CH_2), 111.63 (qC), 116.58 (2 x CH), 116.71 (CH), 120.56 (CH), 128.37-129.07 (m, 11 x CH), 130.63 (2 x CH), 130.77 (2 x qC), 131.43 (2 x CH), 131.52 (3 x CH), 131.63 (2 x CH), 131.67 (CH), 132.11 (qC), 132.54 (CH), 132.73 (CH), 133.08 (qC), 133.65 (CH), 138.02 (2 x qC), 150.23 (qC), 168.37 (C=O) ppm.

HRMS (ESI$^+$): found 652.2437 $[M]^+$, $C_{41}H_{38}N_2O_3P_2$ requires 652.2409.

9. Chapter 9: Experimental for chapter 5: Attempted synthesis of circumdatin and fuligocandin analogues.

9.1. Synthesis of the 10,10-dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]benzothiadiazepin-4-one.

9.1.1. Synthesis of methoxycarbonyl-1-(2'- azidobenzenesulfonyl) pyrrolidine.



2-Azidobenzenesulfonic acid (603 mg, 3.030 mmol, 2.5 eq) was heated at reflux at 80 ^oC in a 2M solution of thionyl chloride in dichloromethane (3.03 mL, 6.06 mmol, 5.0 eq) with a drop of DMF under an inert atmosphere of nitrogen for 5 hours. The reaction was allowed to reach room temperature before the crude acid chloride was concentrated and the residue was washed with dichloromethane (2 x 10 mL) to give the crude sulfonyl chloride as an orange solid.

A solution of potassium carbonate (919 mg, 6.66 mmol, 5.5 eq) in water (20 mL) was added in one portion to L-proline methyl ester (200 mg, 1.212 mmol, 1.0 eq) in dichloromethane (20 mL). The sulfonyl chloride was dissolved in dichloromethane (5 mL) and was added dropwise to this solution. The reaction was allowed to stir at room temperature for 20 hours before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by

silica column chromatography [petroleum ether/ethyl acetate: 3/1, Rf= 0.23] to yield the product as a yellow oil (300 mg, 58 %).

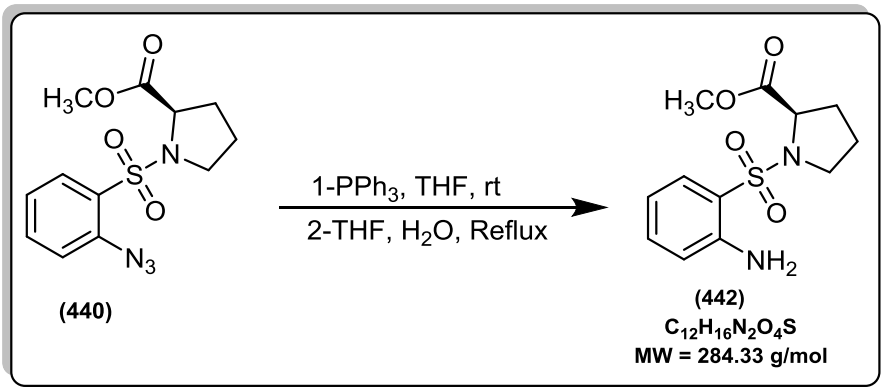
IR: υ_{max} (cm^{-1}): 759.7, 1019.9, 1079.9, 1155.5, 1285.8, 1335.8, 1471.1, 1736.7, 2119.7, 2883.1, 2980.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.79-1.88 (1H, m, C***H***H), 1.91-2.04 (2H, m, C**H**$_2$), 2.08-2.18 (1H, m, C***H***H), 3.34-3.40 (1H, m, C***H***H), 3.56-3.61 (4H, m, C**H**$_3$ + C**H**), 4.62 (1H, dd, J^1=8.5 Hz, J^2=3.0 Hz, NC**H**), 7.16 (H, dd, J^1=7.6 Hz, J^2=7.7 Hz, Ar**H**), 7.21 (H, d, J=8.0 Hz, Ar**H**) 7.51 (1H, ddd, J^1=7.7 Hz, J^2=7.6 Hz, J^3=1.3 Hz, Ar**H**), 7.93 (1H, dd, J=8.0 Hz, J=1.8 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.70 (CH_2), 31.02 (CH_2), 48.35 (CH_2), 52.33 (CH), 60.41 (CH), 119.70 (CH), 124.57 (CH), 130.23 (qC), 131.75 (CH), 133.19 (CH), 138.19 (qC), 172.65 (C=O) ppm.

HRMS (ESI^+): found 333.0630 $[M+Na]^+$, $C_{12}H_{14}N_4O_4S$ requires 333.0628.

9.1.2. 2-Methoxycarbonyl-1-(2'-aminobenzenesulfonyl)pyrrolidine.



To a solution of the azido ester (426 mg, 1.37 mmol, 1.0 eq) in dry THF was added triphenylphosphine (PPh_3) (360 mg, 1.37 mmol, 1.0 eq) and the mixture was stirred for 24 hours at room temperature. After completion of the reaction, monitored by TLC, water (10 mL) was added. The mixture was heated at reflux overnight.

The solvent was distilled under vacuum and the mixture was purified by using silica column chromatography (petroleum ether/ethylacetate: 2/1, Rf = 0.25) to give the product as a light yellow in 390 mg and 64 % yield, m.p=121-122 ^oC (lit. m.p = 118-119 ^oC[245]).

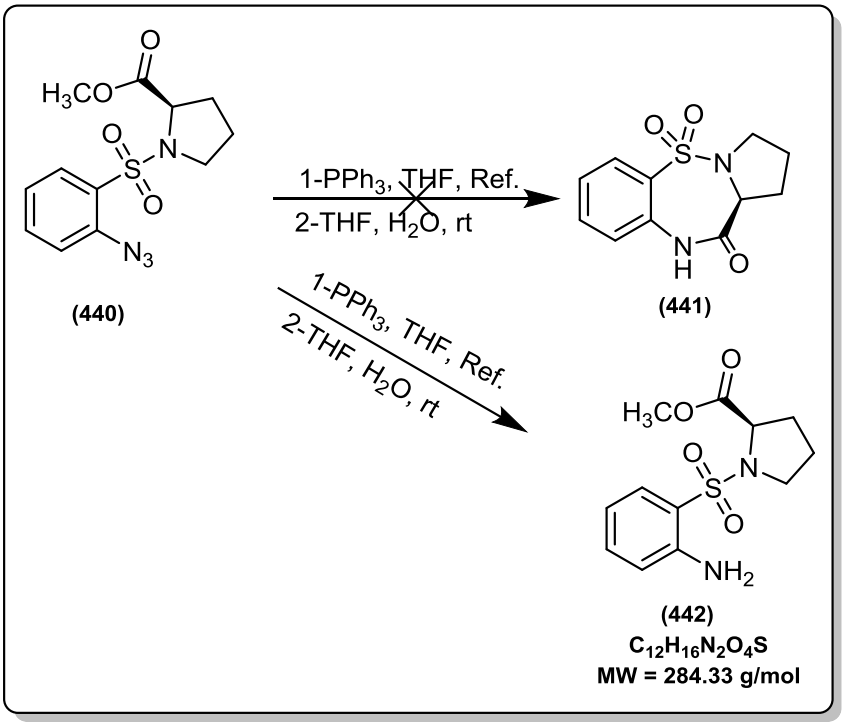
IR: υ_{max}(cm^{-1}): 752.1, 997.2, 1086.8, 1137.3, 1276.9, 1433.7, 1486.2, 1620.7, 1724.1, 2900.5, 2951.9, 3370.4, 3474.2.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.82-1.91 (1H, m, C***H***H), 1.93-2.07 (2H, m, C**H$_2$**), 2.15-2.24 (1H, m, CH***H***), 3.39 (2H, t, *J*=6.9 Hz, C**H$_2$**), 3.73 (3H, s, C**H$_3$**), 4.52 (1H, dd, J^1=8.7 Hz, J^2=4.3 Hz, NC**H**), 5.24 (2H, s, N**H$_2$**), 6.74 (2H, dd, J^1=8.5 Hz, J^2=8.3 Hz, 2 x Ar**H**), 7.31 (1H, ddd, J^1=8.5 Hz, J^2=8.3 Hz, J^3=1.1 Hz, Ar**H**), 7.71 (1H, dd, J^1=8.5 Hz, J^2=0.9 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.86 (CH_2), 31.02 (CH_2), 48.60 (CH_2), 52.51 (CH), 59.48 (CH), 116.89 (CH), 117.56 (CH), 119.11 (qC), 130.23 (CH), 134.50 (CH), 146.40 (qC), 173.03 (C=O) ppm.

HRMS (ESI$^+$): found 285.0905 $[M+H]^+$, $C_{12}H_{17}N_2SO_4$ requires 285.0904.

9.1.3. 2-Methoxycarbonyl-1-(2'-aminobenzenesulfonyl)pyrrolidine.

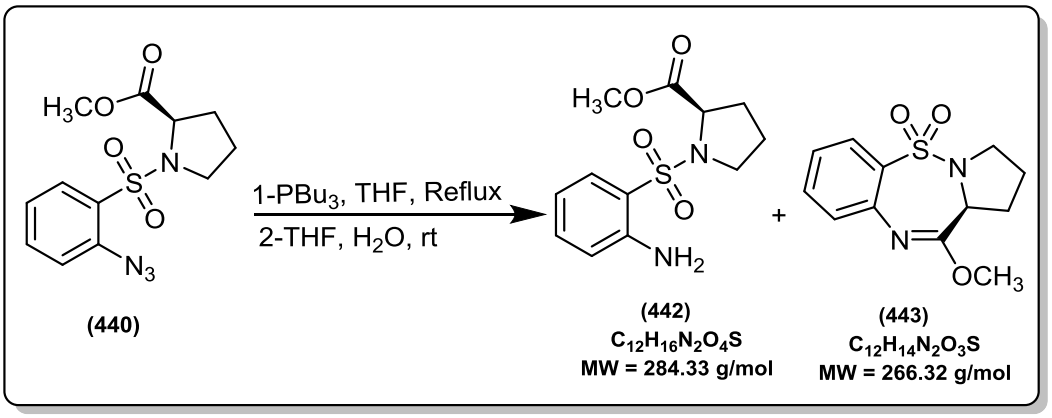


To a solution of the azido ester **(425)** (426 mg, 1.37 mmol, 1.0 eq) in dry THF (10 mL) was added triphenylphosphine (PPh_3) (360 mg, 1.37 mmol, 1.0 eq) and the mixture was stirred for

24 hours at room temperature. After completion of the reaction, monitored by TLC, water (10 mL) was added. The mixture was heated at reflux overnight.

The solvent was removed under vacuum and the mixture was purified by using silica column chromatography (petroleum ether/ethyl acetate: 2/1, Rf = 0.2) to give the product which was identical to that isolated above (100 mg, 25 %, m.p.=121-122 ^{o}C, lit. m.p = 118-119 ^{o}C[245]).

9.1.4. 2-Methoxycarbonyl-1-(2'-aminobenzenesulfonyl)pyrrolidine.



To a solution of the azido ester (426 mg, 1.37 mmol, 1.0 eq) in dry THF (10 mL) was added tributyl phosphine (279 mg, 1.37 mmol, 1.0 eq) and the mixture was stirred for 24 hours at room temperature. After completion of the reaction, monitored by TLC, water (10 mL) was added. The mixture was heated at reflux overnight.

The solvent was distilled under vacuum and the mixture was purified by using column chromatography with (petroleum ether/ethyl acetate: 2/1, Rf = 0.2) to give two products.

Methyl[(2-aminophenyl)sulfonyl] prolinate (442).

[yellow solid (150 mg, 39 %)], data as reported above.

11-Methoxy-1,2,3,11a-tetrahydrobenzo[*f*]pyrrolo[1,2-*b*][1,2,5]thiadiazepine 5,5-dioxide (443).

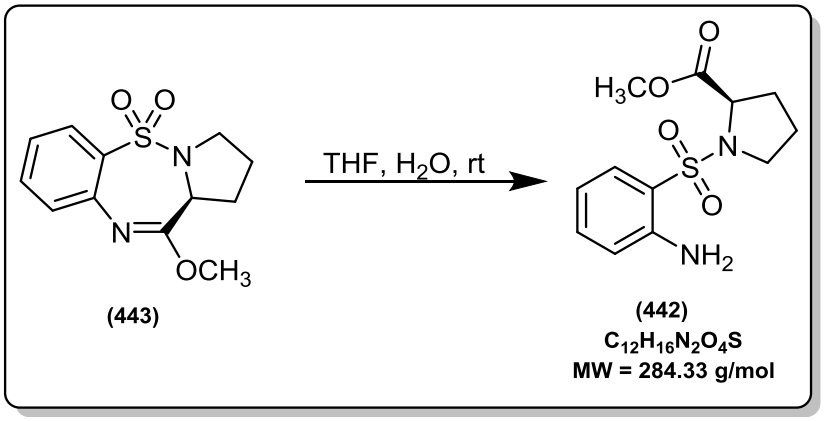
[white oil, 200 mg, 54 %]

IR: υ_{max} (cm^{-1}): 761.0, 952.7, 1069.4, 1128.1, 1160,5, 1335.6, 1372.6, 1434.2, 1588.9, 1673.5, 2866.1, 2969.0, 3334.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.62-1.71 (1H, m, C***H***H), 1.76-1.95 (1H, m, C**H$_2$**), 2.21-2.30 (1H, m, CH***H***), 2.80-2.86 (1H, m, C***H***H), 3.27-3.32 (1H, m, C***H***H), 3.71 (3H, s, C**H$_3$**), 4.50 (1H, t, *J*=7.0 Hz, NC**H**), 7.02 (1H, dd, J^1=7.7 Hz, J^2=7.5 Hz, Ar**H**), 7.12 (1H, d, *J*=7.9 Hz, Ar**H**), 7.39 (1H, dd, J^1=7.7 Hz, J^2=7.5 Hz, Ar**H**), 7.69 (1H, d, *J*=7.9 Hz, Ar**H**) ppm.

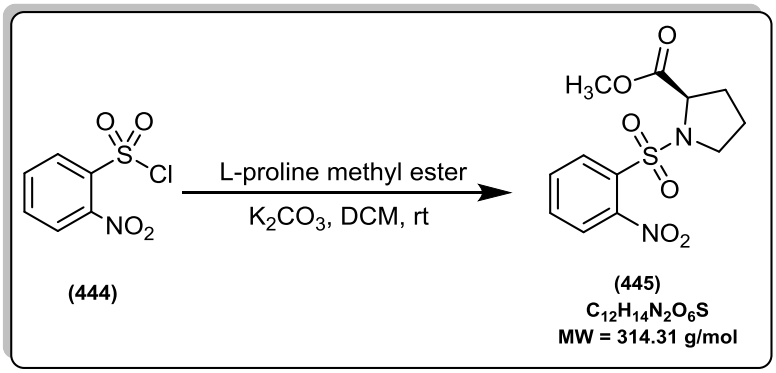
^{13}C NMR δ_c (100 MHz, DMSO): 24.53 (CH_2), 31.85 (CH_2), 48.88 (CH_2), 53.80 (CH), 63.75 (CH_3), 123.47 (CH), 128.13 (CH), 128.26 (CH), 131.69 (qCH), 133.73 (CH), 140.48 (qC), 164.49 (qC) ppm.

9.1.5. 2-Methoxycarbonyl-1-(2'-aminobenzenesulfonyl)pyrrolidine.



To a solution of compound **(428)** (200 mg, 0.75 mmol, 1.0 eq) in THF (10 mL) was added water (10 mL) and the solution was stirred at room temperature for 24 hours. After completion of the reaction, monitored by TLC, the solvent was removed under vacuum and the mixture was purified by using column chromatography with (*petroleum ether/ethyl acetate*: 2/1, Rf = 0.2) which gave the product (190 mg, 90 %), identical in all respects to that isolated above.

9.1.6. Synthesis of 2-Methoxycarbonyl-1-(2'-nitrobenzenesulfonyl) pyrro-lidine.



A solution of potassium carbonate (4.27 g, 31.00 mmol, 5.5 eq) in water (10 mL) was added in one portion to a stirred solution of L-proline methyl ester (930 mg, 5.63 mmol, 1.0 eq) in DCM (10 mL). The sulfonyl chloride (3.23 g, 14.65 mmol, 2.6 eq) dissolved in DCM (5 mL) was added dropwise to this solution and the whole was stirred for 18 hours. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by silica column chromatography (ethyl acetate/ hexane: 1/2, Rf = 0.2) to give the product as a colorless oil (1.800 g, 84 %, lit. m.p = 86-88 ^oC[245])

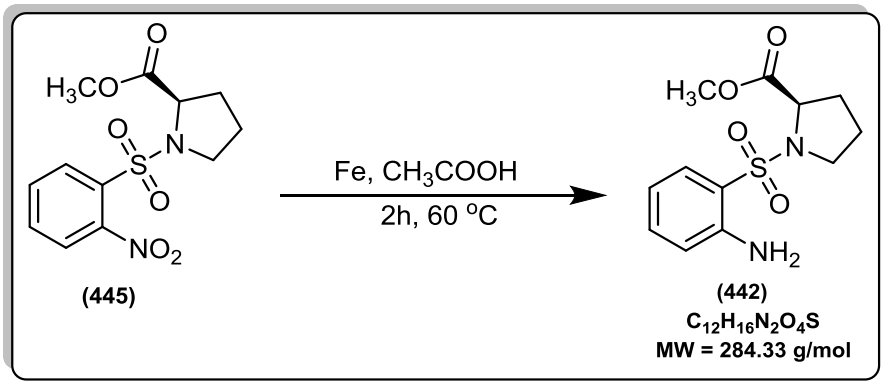
IR: υ_{max} (cm^{-1}): 741.8, 851.8, 1021.9, 1081.9, 1126.5, 1158.7, 1201.0, 1343.3, 1437.4, 1540.6, 1589.6, 1741.9, 2955.8, 3098.4.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.95-2.18 (3H, m, C**H$_2$** + C***H***H), 2.23-2.33 (1H, m, CH***H***), 3.53-3.59 (1H, m, C***H***H), 3.62-3.67 (1H, m, CH***H***), 3.68 (3H, s, C**H$_3$**), 4.61 (1H, dd, J^1=5.5 Hz, J^2=3.0 Hz, NC**H**), 7.64-7.67 (1H, m, Ar**H**), 7.71 (2H, m, 2 x Ar**H**), 8.12 (1H, m, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.55 (CH_2), 30.96 (CH_2), 48.51 (CH_2), 52.45 (CH), 60.91 (CH), 124.06 (CH), 131.07 (CH), 131.66 (CH), 132.85 (qC), 133.56 (CH), 148.08 (qC), 172.31 (C=O) ppm.

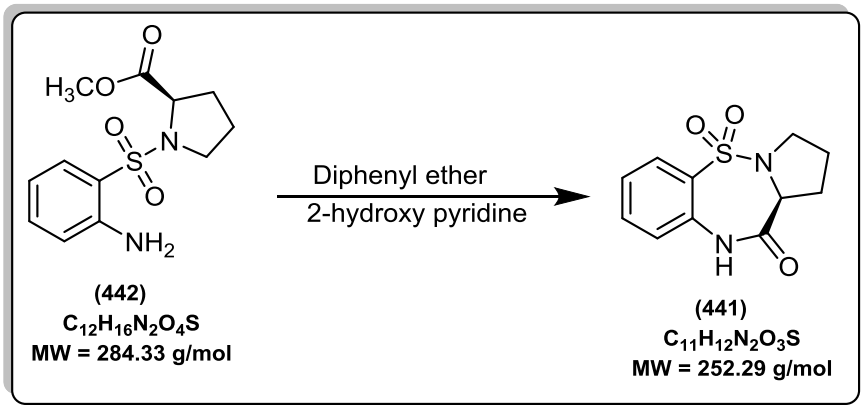
HRMS (ESI^+): found 315.0643 $[M+H]^+$, $C_{12}H_{15}N_2SO_6$ requires 315.0645.

9.1.7. Synthesis of 2-Methoxycarbonyl-1-(2'-aminobenzenesulfonyl) pyrrolidine.



To a solution of the nitroester (1.8 g, 5.73 mmol, 1.0 eq) in glacial acetic acid (25 mL), iron powder (1.6 g, 28.662 mmol, 5.0 eq) was added over 30 minutes. The reaction mixture was stirred and heated at 60 ^{o}C for 2 hours. Removal of the solvent gave a gummy residue which was extracted with ethyl acetate (4 x 30 mL). The organic extracts were combined, washed with sodium bicarbonate, brine and dried. Concentration in vacuo afforded the aminoester as a yellow solid (1.19 g, 74 %), identical to that isolated previously.

9.1.8. Synthesis of 10,10-dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]-benzothiadiazepin-4-one.



A mixture of the aminoester (177 mg, 0.58 mmol, 1.0 eq), 2-hydroxypyridine (56 mg, 0.58 mmol, 1.0 eq), and diphenyl ethyl ether (10 mL) was heated at 205 ^{o}C while monitoring via TLC overnight. On cooling the crude reaction mixture was poured over n-hexane (10 mL) and allowed to stand for 10 min. The clear supernatant was discarded and the solid was dissolved

in $CHCl_3$ and purified on a silica column to afford the cyclised compound as a brown solid (100 mg, 63 %. m.p.= 291-292 ^oC, lit. m.p.=292-293 ^oC[233]).

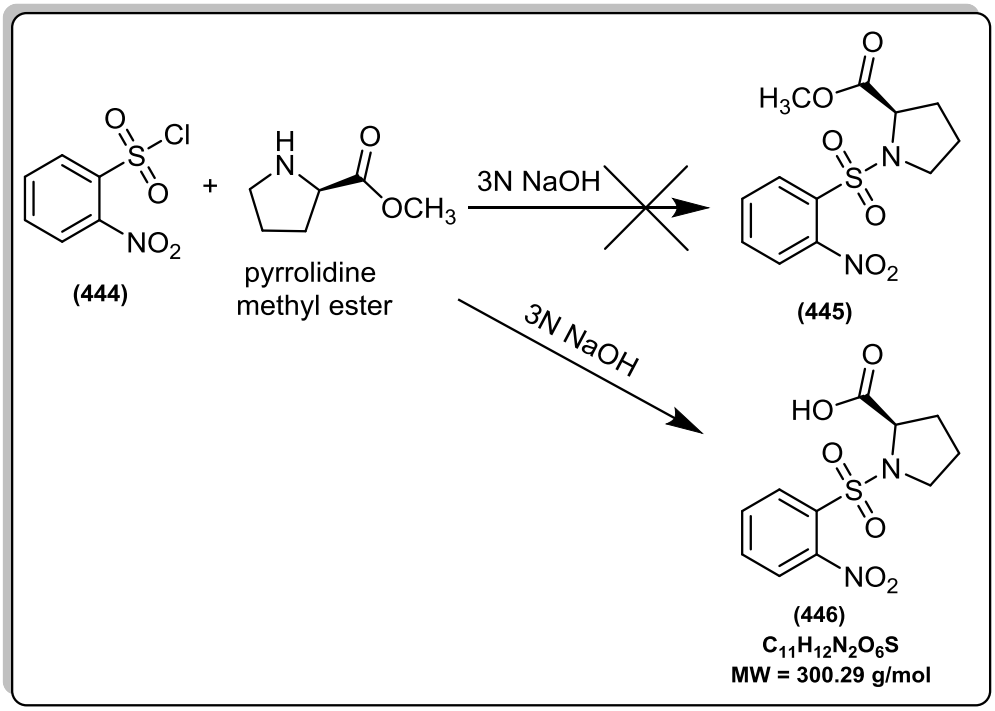
IR: υ_{max} (cm^{-1}): 755.4, 1007.2, 1078.4, 1191.5, 1341.8, 1384.2, 1478.5, 1583.2, 1661.4, 2891.7, 2933.1, 2985.4, 3063.3, 3204.1.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.82-1.92 (1H, m, C***H***H), 1.95-2.07 (1H, m, C***H***H), 2.19-2.27 (1H, m, C***H***H), 2.46-2.55 (1H, m, C***H***H), 3.00-3.06 (1H, m, C***H***H), 3.42-3.54 (1H, m, C***H***H), 4.65 (1H, dd, J^1=7.9 Hz, J^2=5.9 Hz, NC**H**), 7.18 (1H, d, J=8.0 Hz, Ar**H**), 7.22 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.53 (1H, ddd, J^1=7.8 Hz, J^2=7.6 Hz, J^3=1.4 Hz, Ar**H**), 7.91 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar**H**), 9.20 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.64 (CH_2), 32.47 (CH_2), 58.47 (CH_2), 63.65 (CH), 121.58 (CH), 123.78 (CH), 129.03 (CH), 129.39 (qC), 134.10 (CH), 134.54 (qC), 174.91 (C=O) ppm.

HRMS (ESI^+): found 253.0639 $[M+H]^+$, $C_{11}H_{13}N_2SO_3$ requires 253.0641.

9.1.9. 1-(2-Nitrobenzenesulfonyl)pyrrolidine-2-carboxylic acid.



2-Azidobenzenesulfonyl chloride (2.0 g, 9.02 mmol, 1.0 eq) was added portionwise over a period of 5 min to a well stirred and ice-cooled solution of pyrrolidine methyl ester (1.494 g,

9.024 mmol, 1.0 eq) in 3N sodium hydroxide (7 mL). 30 mins of vigorous stirring resulted in a clear yellow solution which was acidified with concentrated HCl dropwise and then extracted into ethyl acetate (3 x 15 mL). The organic extracts were combined, dried and evaporated to give as a pale yellow oil (2.066 g, 76 %) in excellent purity that was directly carried forward without further purification.

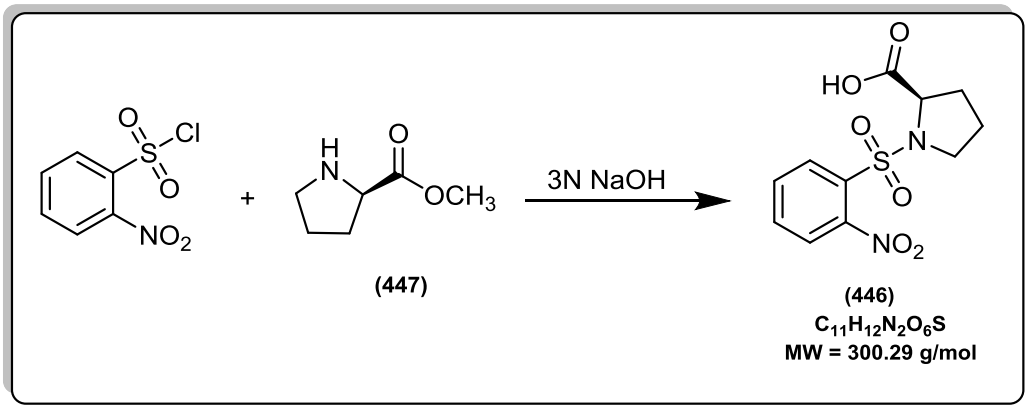
IR: υ_{max} (cm^{-1}): 568.5, 601.1, 726.4, 909.1, 1125.2, 1159.5, 1348.2, 1540.5, 1716.6, 2980.6, 3275.3.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.89-1.97 (2H, m, C**H**$_2$), 2.05-2.13 (1H, m, C***H***H), 2.18-2.27 (1H, m, CH***H***), 3.44 (1H, app. q, J^1=7.4 Hz, C***H***H), 3.55-3.60 (1H, m, CH***H***), 4.53 (1H, dd, J^1=8.6 Hz, J^2=2.9, C***H***), 7.56-7.58 (1H, m, Ar**H**), 7.62-7.67 (2H, m, 2 x Ar**H**), 8.01 (1H, dd, J^1=8.7 Hz, J^2=1.7 Hz Ar**H**), 9.13 (1H, s, O**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.48 (CH_2), 30.96 (CH_2), 48.47 (CH_2), 60.69 (CH), 124.16 (CH), 131.0478 (CH), 131.83 (CH), 132.38 (qC), 133.84 (CH), 148.03 (qC), 177.40 (C=O) ppm.

The data is identical to that reported in the literature[233].

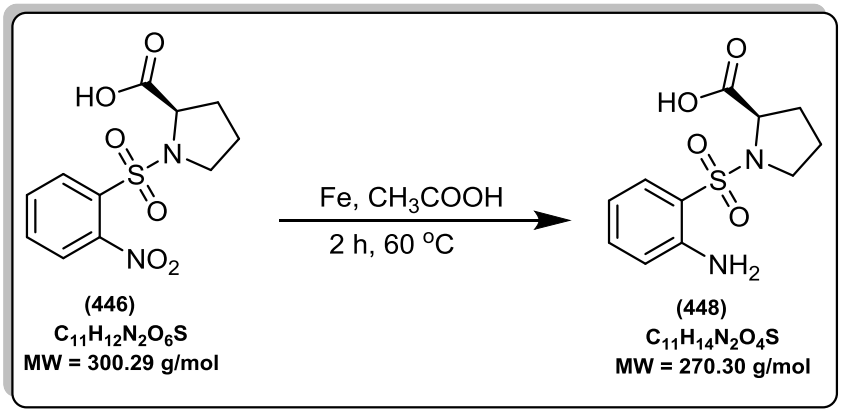
9.1.10. 1-(2-Nitrobenzenesulfonyl)pyrrolidine-2-carboxylic acid.



2-Nitrobenzenesulfonyl chloride (2.00 g, 9.00 mmol, 1.0 eq) was added portionwise over a period of 5 min to a well stirred and ice-cooled solution of pyrrolidine-2-carboxylic acid (1.04 g, 9.024 mmol, 1.0 eq) in 3N sodium hydroxide (7 mL). 30 min of vigorous stirring resulted in a clear yellow solution which was acidified with conc. HCl dropwise and then extracted into ethyl acetate (3 x 15 mL). The organic extracts were combined, dried and evaporated to

give as a pale yellow oil (2.30 g) in 85 % yield and excellent purity which was directly carried forward without any purification. The data obtained was identical to that obtained above.

9.1.11. 1-(2-Aminobenzenesulfonyl)pyrrolidine-2-carboxylic acid.



(446)
$C_{11}H_{12}N_2O_6S$
MW = 300.29 g/mol

(448)
$C_{11}H_{14}N_2O_4S$
MW = 270.30 g/mol

To a solution of the nitroester (2.0 g, 6.67 mmol, 1.0 eq) in glacial acetic acid (25 mL), iron powder (1.86 g, 33.34 mmol, 5.0 eq) was added over 30 minutes. The reaction mixture was stirred and heated at 60 ^{o}C for 2 hours. Removal of the solvent gave a gummy residue which was extracted with ethyl acetate (4 x 30 mL). The organic extracts were combined, washed with sodium bicarbonate, brine and dried. Concentration in vacuo afforded the amino acid as a yellow oil (1.45 g, 76 %).

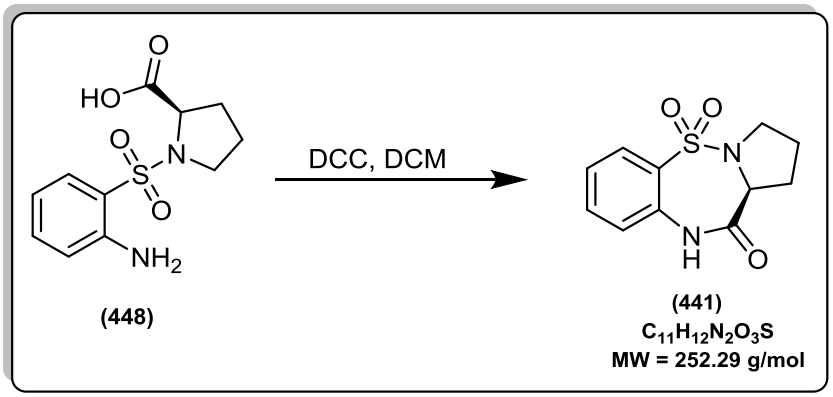
IR: υ_{max} (cm^{-1}): 756.1, 1141.6, 1319.6, 1453.5, 1483.7, 1616.8, 1727.7, 2980.1, 3375.9, 3469.9.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.75-1.93 (2H, m, C**H_2**), 2.07-2.16 (2H, m, C**H_2**), 3.31 (2H, dd, J^1=7.6 Hz, J^2=1.7 Hz, C**H_2**), 3.55-3.60 (1H, m, C***H***H), 4.46 (1H, dd, J^1=7.9 Hz, J^2=5.1 Hz, C***H***), 6.63-6.72 (2H, m, 2 x Ar**H**), 7.12 (3H, bs, N**H_2 + OH**), 7.26 (1H, ddd, J^1=8.0 Hz, J^2=7.8 Hz, J^3=1.5 Hz Ar**H**), 7.63 (1H, dd, J^1=8.0 Hz, J^2=1.5 Hz, Ar**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.85 (CH_2), 30.92 (CH_2), 48.83 (CH_2), 59.69 (CH), 117.44 (CH), 117.95 (CH), 118.95 (qC), 130.38 (CH), 134.81 (CH), 146.31 (qC), 176.93 (C=O) ppm.

HRMS (ESI^+): found 271.0753 $[M+H]^+$, $C_{11}H_{15}N_2SO_4$ requires 271.0747.

9.1.12. 10,10-Dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5] benzothia-diazepin-4-one.



(448)

(441)
$C_{11}H_{12}N_2O_3S$
MW = 252.29 g/mol

DCC (1.297 g, 0.629 mmol) dissolved in dichloromethane (3 mL) was added to a solution of compound **(433)** (1.7 g, 0.629 mol, 1.0 eq) in dichloromethane (6 mL) at 0 ^{o}C, and the mixture was stirred at ambient temperature overnight. After filtration through Celtite, the organic phase was washed with 2 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and water (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford a solid residue, which was purified by flash silica chromatography (petroleum ether/ethyl acetate: 1/1, Rf = 0.23) to give the title compound (1.00 g, 63 %, m.p.= 291-292 ^{o}C) as a white solid, lit. m.p.292-293 ^{o}C[233].

IR: υ_{max} (cm^{-1}): 755.4, 1007.2, 1078.4, 1191.5, 1341.8, 1384.2, 1478.5, 1583.2, 1661.4, 2891.7, 2933.1, 2985.4, 3063.3, 3204.1.

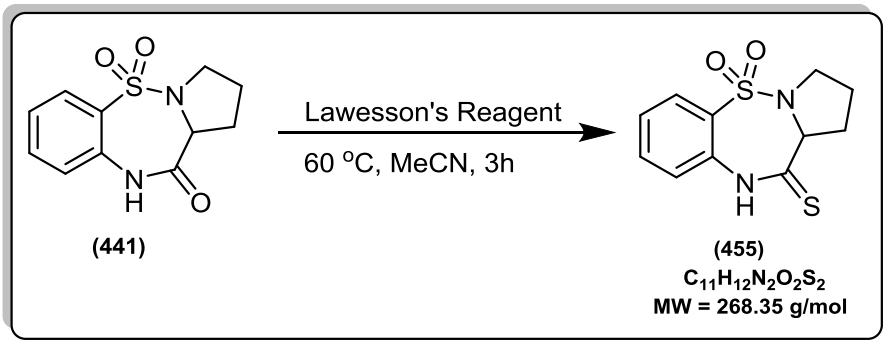
^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.82-1.92 (1H, m, C***H***H), 1.95-2.07 (1H, m, CH***H***), 2.19-2.27 (1H, m, C***H***H),2.46-2.55 (1H, m, CH***H***), 3.00-3.06 (1H, m, CH***H***), 3.49-3.54 (1H, m, C***H***H), 4.65 (1H, dd, J^1=7.9 Hz, J^2=5.9 Hz, NC**H**), 7.18 (1H, d, J=8.0 Hz, Ar**H**), 7.22 (1H, dd, J^1=7.8 Hz, J^2=7.6 Hz, Ar**H**), 7.53 (1H, ddd, J^1=7.8 Hz, J^2=7.6 Hz, J^3=1.4 Hz, Ar**H**), 7.91 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar**H**), 9.20 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.64 (CH_2), 32.47 (CH_2), 58.47 (CH_2), 63.65 (CH), 121.58 (CH), 123.78 (CH), 129.03 (CH), 129.39 (qC), 134.10 (CH), 134.54 (qC), 174.91 (C=O) ppm.

HRMS (ESI^+): found 253.0639 $[M+H]^+$, $C_{11}H_{13}N_2SO_3$ requires 253.0641.

9.2. Attempted Synthesis of fuligocandin Analogues.

9.2.1. 10,10-Dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5] benzothia-diazepine-4-thione.



Lawesson's reagent (404 mg, 1.0 mmol, 0.5 eq) was added to a MeCN solution (25 mL) of compound **(441)** (504 mg, 2.0 mmol, 1.0 eq) and the mixture was heated to reflux at 60 °C for 3h during which time a yellow precipitate was formed. The reaction mixture was allowed to stand at room temperature overnight. The product was vacuum-filtered and washed with a small amount of cold MeCN and purified by silica column chromatography [petroleum ether/ ethyl acetate: 2/1, Rf = 0.23] to yield the product as a yellow solid (50 mg, 9 %, m.p: 262-264 °C (lit. m.p: 268-270 °C[143])).

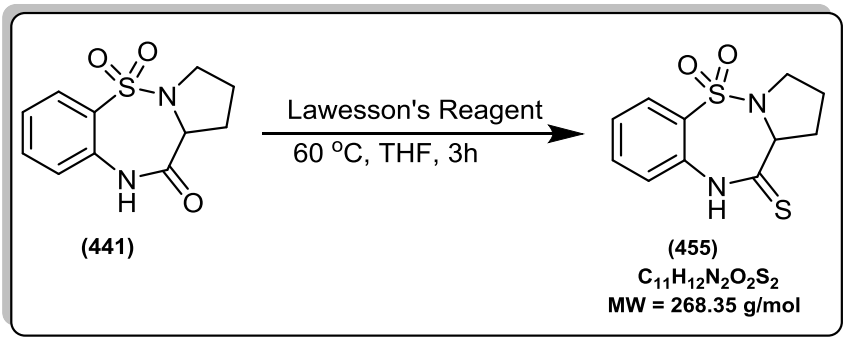
IR: υ_{max} (cm^{-1}): 580.90, 697.40, 751.10, 1004.80, 1051.30, 1169.90, 1339.80, 1384.00, 1470.60, 1529.10, 1589.00, 2868.60, 2922.50, 2955.80, 3150.20.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 1.70-2.19 (1H, m, C***H***H), 1.95-2.07 (1H, m, CH***H***), 2.30-2.41 (1H, m, C***H***H), 2.50 (1H, s, CH***H***), 2.87-2.93 (1H, m, C***H***H), 3.32-3.47 (1H, m, CH***H***), 4.80 (1H, t, *J*=7.5 Hz, NC**H**), 7.39 (1H, dd, J^1=7.6 Hz, J^2=7.5 Hz, Ar**H**), 7.44 (1H, d, *J*=7.9 Hz, Ar**H**), 7.72 (1H, ddd, J^1=7.6 Hz, J^2=7.5 Hz, J^3=1.2 Hz, Ar**H**), 7.77 (1H, d, *J*=7.9 Hz, Ar**H**), 12.35 (1H, s, N**H**) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 24.15 (CH_2), 35.18 (CH_2), 49.79 (CH_2), 70.81 (CH), 124.00 (CH), 125.77 (CH), 128.27 (CH), 130.68 (qC), 134.94 (CH), 135.25 (qC), 206.32 (C=S) ppm.

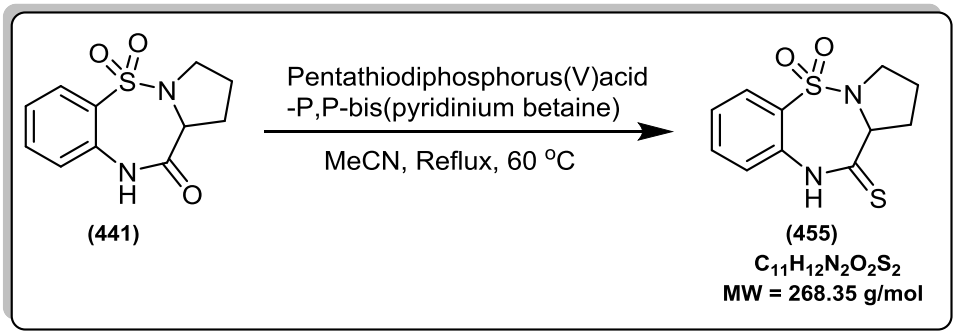
HRMS (ESI^+): found 269.0403 $[M+H]^+$, $C_{11}H_{13}O_2N_2S_2$ requires 269.0413

9.2.2. 10,10-Dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]-benzothiadiazepine-4-thione.



Lawesson's reagent (404 mg, 1.0 mmol, 0.5 eq) in one portion was added to a solution of compound (**441)** (504 mg, 2.0 mmol, 1 eq) in a dry THF (30 mL) at room temperature, under a nitrogen atmosphere, with stirring. The mixture was stirred 1hour at room temperature after which time all solid had dissolved to give a clear for yellow solution. The reaction mixture was heated at reflux for a further hour (monitored for completion by TLC). Upon cooling to room temperature the solution was concentrated and purified using flash silica column chromatography [Eluent: petroleum ether/ ethyl acetate: 2/1, Rf = 0.23] to yield the product as a yellow solid (60 mg, 11%, m.p: 262-264 °C). The data was identical to that obtained above.

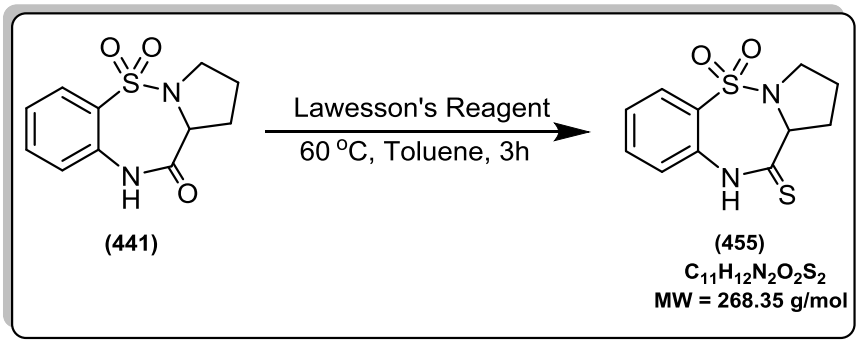
9.2.3. 10,10-Dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]benzothia-diazepine-4-thione.



The P_2S_5-py_2 reagent (230 mg, 0.6 mmol) was added to a MeCN solution (25 mL) of compound (**426**) (504 mg, 2.0 mmol) and the mixture was heated at reflux for 3h during which time a yellow precipitate was formed.[246] The reaction mixture was left at room temperature overnight in order to precipitate fully. The product was filtered and washed with a small amount of cold MeCN and purified by silica column chromatography [petroleum

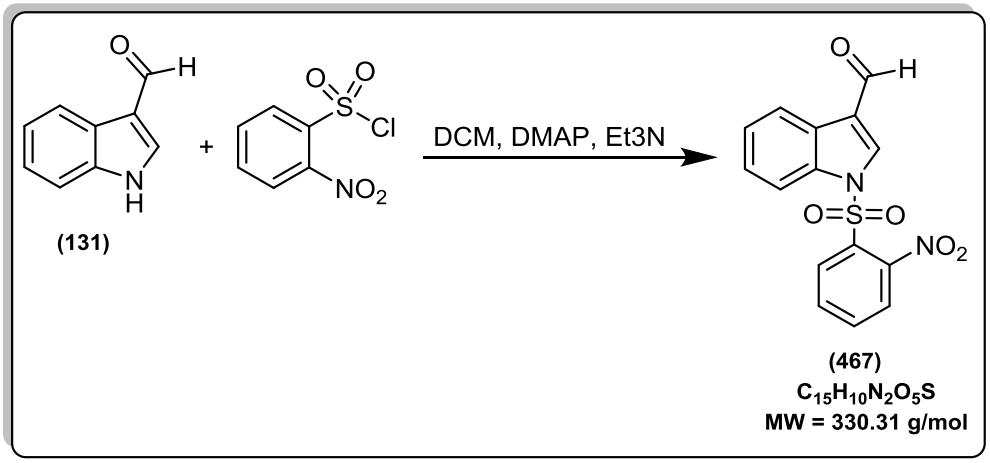
ether/ ethyl acetate: 2/1, Rf = 0.23] to yield the product as a yellow solid (100 mg, 19 %, m.p: 262-264 ^{o}C), identical to that isolated above.

9.2.4. 10,10-Dioxo-2,3,3a,5-tetrahydro-1*H*-pyrrolo[1,2-*b*][1,2,5]benzothia-diazepine-4-thione.



To a toluene solution (25 mL) of compound **(441)** (504 mg, 2.0 mmol, 1.0 eq) was added Lawesson's Reagent (404 mg, 1.0 mmol, 0.5 eq) and the mixture was heated to 60 ^{o}C for 3h during which time a yellow precipitate was formed. The reaction mixture was allowed to stand at room temperature overnight in order to precipitate fully. The product was vacuum-filtered and washed with a small amount of cold MeCN and purified by silica column chromatography [petroleum ether/ ethyl acetate: 2/1, Rf = 0.23] to yield the product as a yellow solid (60 mg, 11 %, m.p.= 262-264 ^{o}C) with data identical to that given above.

9.2.5. 1-(2-Nitrophenylsulfonyl)-indole-3-carbaldehyde.



A dichloromethane suspension (12 mL) of indole-3-carbaldehyde (0.9 g, 6.2 mmol, 1.0 eq), DMAP (0.061 g, 0.5 mmol, 0.08 eq), and triethylamine (1.3 mL, 9.3 mmol, 1.5 eq) was stirred for 10 min at room temperature, and then 2-nitrophenylsulfonyl chloride (1.5 g, 6.82 mmol, 1.1 eq) in 12 mL of dichloromethane was added dropwise over 10 min. The reaction mixture was allowed to stir at room temperature overnight and thereafter quenched with 30 mL of aq. HCl (5 %). The organic phase was separated, and the aqueous phase was extracted several times with dichloromethane. The combined dichloromethane phases were dried with $MgSO_4$ and flushed through a short silica plug. Evaporation of the yellow filtrate in vacuo gave the product (2.0 g, 98 %, m.p.=132-134 ^{o}C) as a beige solid.

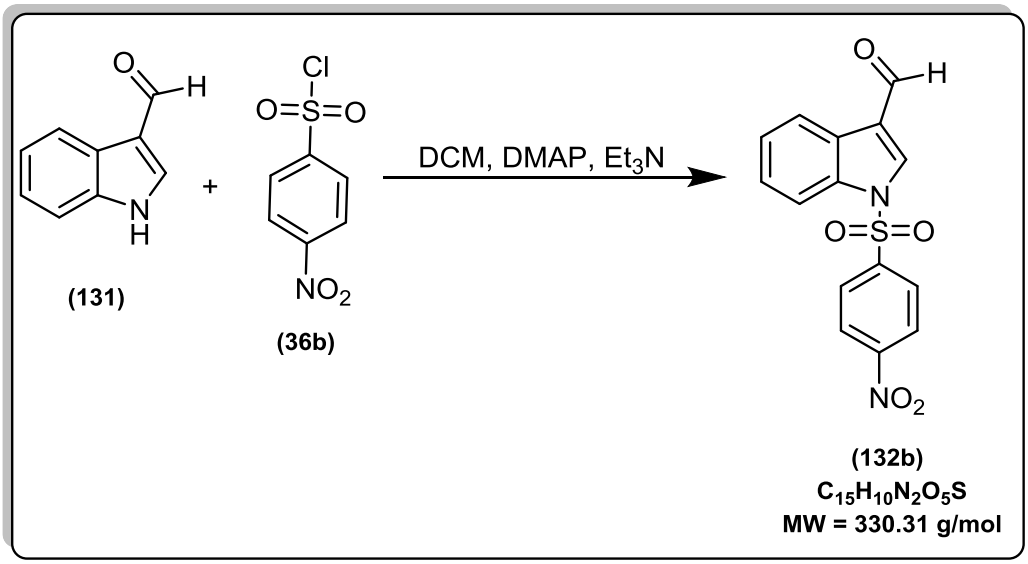
IR: υ_{max} (cm^{-1}): 747.8, 778.5, 969.6, 1117.9, 1182.7, 1372.0, 1388.3, 1439.5, 1541.1, 1583.4, 1675.6, 2840.0, 2912.1, 3147.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.43-7.53 (2H, m, 2 x Ar**H**), 7.86 (1H, dd, J^1=7.0 Hz, J^2=2.0 Hz, Ar**H**), 7.96 (1H, ddd, J^1=7.8 Hz, J^2=1.2 Hz, Ar**H**), 8.05 (1H, td, J^1=7.7 Hz, J^2=1.3 Hz, Ar**H**), 8.17-8.22 (2H, m, Ar**H**), 8.33 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar**H**), 8.82 (1H, s, **H**C=O) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 113.60 (CH), 121.82 (qC), 122.56 (CH), 125.98 (CH), 126.98 (qC), 126.13 (qC), 126.42 (CH), 127.01 (CH), 128.83 (qC), 131.54 (CH), 134.32 (CH) 134.76 (qC), 137.86 (CH), 139.68 (CH), 147.73 (CH), 187.65 (C=O) ppm.

HRMS (ESI^+): found 329.0237 $[M-H]^+$, $C_{15}H_8O_3N_4S$ requires 329.0231.

9.2.6. 1-(2-Nitrophenylsulfonyl)-indole-3-carbaldehyde.



A dichloromethane suspension (12 mL) of indole-3-carbaldehyde (0.9 g, 6.2 mmol, 1.0 eq), DMAP (0.061 g, 0.5 mmol, 0.08 eq), and triethylamine (1.3 mL, 9.3 mmol, 1.5 eq) was stirred for 10 min at room temperature, and then 4-nitrophenylsulfonyl chloride (1.5 g, 6.82 mmol, 1.1 eq) in 12 mL of dichloromethane was added dropwise over 10 min. The reaction mixture was allowed to stir at room temperature overnight and thereafter quenched with 30 mL of aq. HCl (5 %). The phases were separated, and the aqueous phase was extracted several times with dichloromethane. The combined dichloromethane phases were dried with $MgSO_4$ and flushed through a short silica plug. Evaporation of the light yellow filtrate in vacuo gave the product as a beige solid (1.2 g, 59 %, m.p.= 159-161^{o}C, lit. m.p=160 ^{o}C[143]).

IR: υ_{max} (cm^{-1}): 778.5, 969.6, 1117.9, 1182.7, 1372.0, 1388.3, 1439.5, 1541.1, 1583.4, 1675.6, 2840.0, 2912.1, 3147.5.

^{1}H NMR: δ_H (400 MHz, $CDCl_3$): 7.43-7.53 (2H, m, 2 x Ar**H**), 7.86 (1H, dd, J^1=7.0 Hz, J=2.0 Hz, Ar**H**), 7.96 (1H, ddd, J^1=7.8 Hz, J^2=7.7 Hz, J^3=1.3 Hz, Ar**H**), 8.05 (1H, ddd, J^1=7.8 Hz, J^2=7.7 Hz, J^3=1.3 Hz, Ar**H**), 8.17-8.22 (2H, m, 2 x Ar**H**), 8.33 (1H, dd, J^1=8.0 Hz, J^2=1.3 Hz, Ar**H**), 8.82 (1H, s, **H**C=O) ppm.

^{13}C NMR δ_c (100 MHz, DMSO): 113.60 (CH), 121.82 (qC), 122.56 (CH), 125.98 (CH), 126.98 (qC), 126.13 (qC), 126.42 (CH), 127.01 (CH), 128.83 (qC), 131.54ppm. (CH), 134.32 (CH) 134.76 (qC), 137.86 (CH), 139.68 (CH), 147.73 (CH), 187.65 (C=O) ppm.

HRMS (ESI^{+}): found 331.0381 $[M+H]^+$, $C_{15}H_{11}O_5N_2S$ requires 331.0383.

IV. Conclusions.

In conclusion for the first project (Chapter 2) of this PhD the aims have been partially achieved. We have been successful in applying a series of multi-component reactions (MCR) to aldehydes incorporating the azide functional group. Some of the reactions investigated with *o*-azidobenzaldehyde gave the desired MCR and a new product with an azide but the azide did not react with the nitrile. Some of the reactions resulted in the attempted MCR stopping after one reaction between just two of the components. Some of these, however, had azides and nitriles in them which did react to form tetrazoles, a previously unreported process with these starting materials.

In conclusion for the second project (Chapter 3) of this thesis the aims have been achieved. We have been successful in the preparation of tetra- and triazolo-analogues of the pyrrolobenzothiadiazepines and benzothiadiazepines. However, some of the attempted reactions resulted in products that did not react the azide moiety with the nitriles or alkynes, and ring-size appeared to be an important factor.

In conclusion for the third project (Chapter 4.1) of this PhD the aims have been achieved. We have been successful in making new products from azides. The 2-azidobenzamide with alkyl bromides gave mixtures of benzotriazinones and quinazolinones. Some of the alkyl bromides with 2-azidobenzamide gave just benzotriazinones and some of the alkyl bromides did not react. The benzotriazinones did not react with diphenylcyclopropenone to produce new compounds.

In conclusion for the fourth project (Chapter 4.2) of this thesis the aims have been achieved. We have been successful in the preparation of 1,2,4-oxadiazole analogues. 1,3-Dipolar cycloaddition of 2-azido-N'-hydroxybenzimidamide with the acid chlorides, ethyl 2-chloro-2-oxoacetate and oxalyl chloride gave new 1,2,4-oxadazole analogues. The 1,2,4-oxadiazoles reacted with dimethylacetylene dicarboxylate (DMAD) to produce new compounds. This process should be more thoroughly investigated in future.

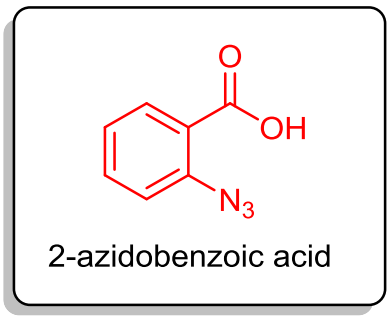
In conclusion for the fifth project (Chapter 4.3) of this thesis significant progress has been made. We have been successful in the preparation of a 6H-1,3-oxazine. We have been successful in synthesising diazides as starting materials but these did not react to form the desired products, with the exception of the synthesis of one macrocycle.

In conclusion for the final project (Chapter 5) of this thesis the aims have not been achieved. We have not been successful in developing a synthetic route for sulfonamide analogues circumdatin or fuligocandin, but we have shown that this appears not to be a valid route.

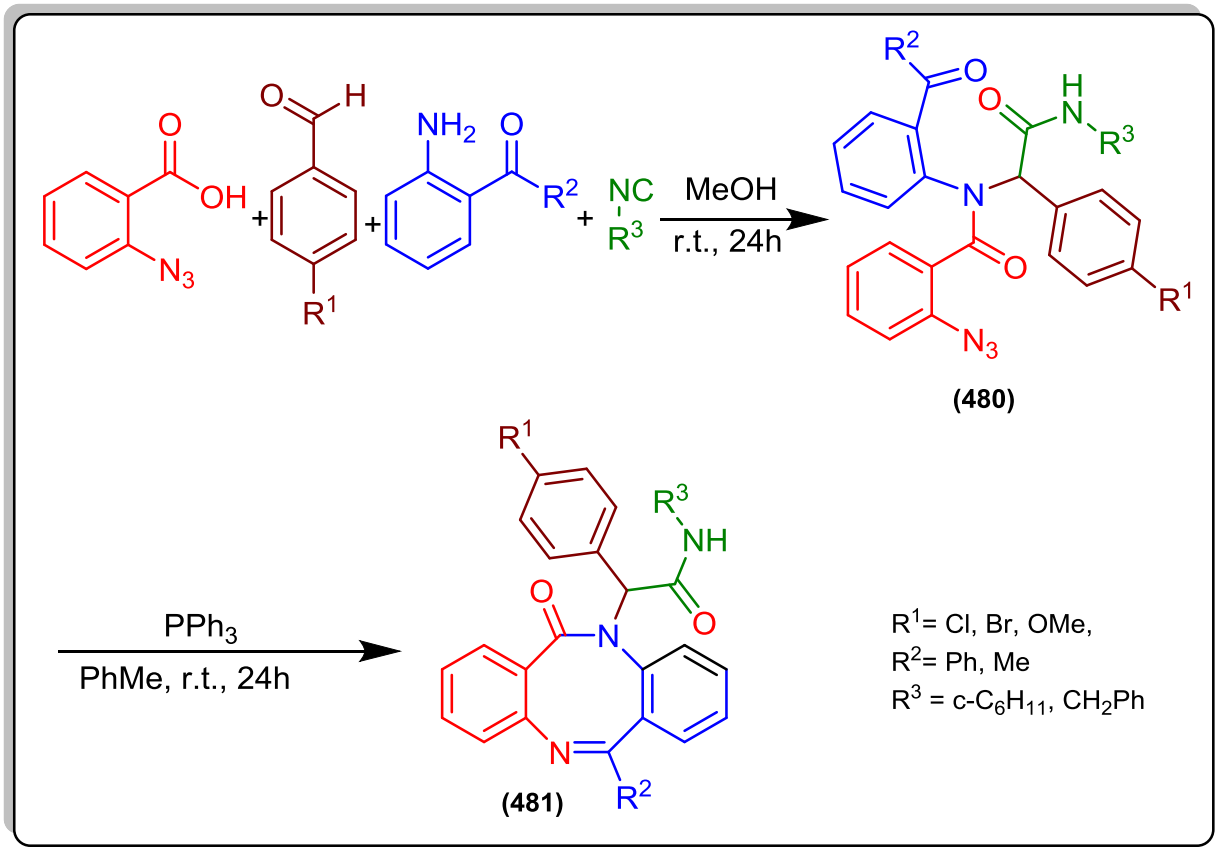
V. Future work

1. *N*-((phenylcarbamoyl)(phenyl)methyl)-*N*-(2-acetylphenyl)-2-azidobenzamide derivative.

In the future 2-azidobenzoic acid will be synthesized which will be useful for the future study of azide-containing MCRs in which the azide can hopefully undergo post-MCR modification. It is hoped that 2-azidobenzoic acid will not undergo the condensation reaction that the 2-azidobenzaldehyde underwent. It is clear from the MCR work that 2-azidobenzaldehyde / nitrile reactions are a problem due to the cycloaddition occurring before the MCR and stopping the MCR.

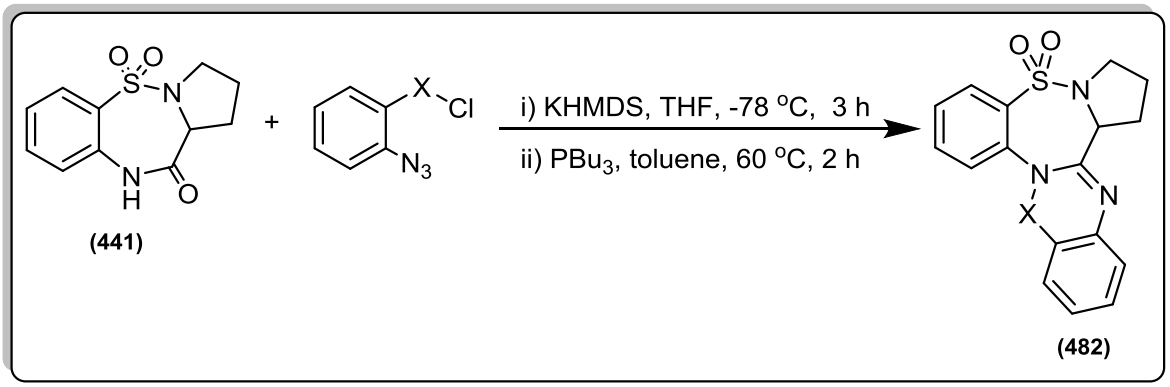


For example, 2-azidobenzoic acid will be studied for the reaction shown below, in which it could be attempted to react the azide present in compound **(480)** after MCR in an aza-Wittig reaction[247].



1. Synthesis of Sulfonamide Analogues of the Circumdatins.

All attempts to reacted the amide **(441)** with 2-azidobenzoyl chloride or 2-azidobenzenesulfonyl chloride and provide precursors for circumdatin analogue synthesis were not successful. However, it was thought that compound **(482)** might be prepared by adapting a procedure in the literature[248]. The proposed reaction is shown below:



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