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**Some Aspects of the Chemistry of Small
Ring Organic Molecules: 1-Azetines,
1-Azetidinones, 3-Oxo- β -sultams and
Cyclopropenones**

Paul A. O’Gorman

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

University of Huddersfield
Department of Chemical & Biological Sciences

May 2009

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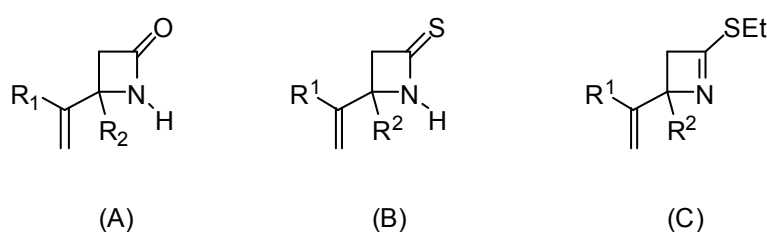
Paul O’Gorman - May 2009.

bp - Boiling Point
Cbz – 1-aminocyclopropane-1-carboxylic acid
CNS - Central Nervous System
COSY - Correlation Spectroscopy
CSI - Chlorosulfonyl isocyanate
DCM - Dichloromethane
DMAP - dimethylaminopyridine
DMF - Dimethylformamide
DNA - Deoxyribo Nucleic Acid
DPP - Diphenylcyclopropenone
EDCI - 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
ES - Electrospray
HMBC - Heteronuclear Multiple Bond Correlation
HSQC - Heteronuclear Single Quantum Correlation
IR - Infrared
LDA - Lithium diisopropylamide
MS - Mass Spectroscopy
NACHR - Nicotinic Acetylcholine Receptor
NBS - N-Bromosuccinimide
NCS - N-Chlorosuccinimide
NMR - Nuclear Magnetic Resonance
NOESY - Nuclear Overhauser Effect Spectroscopy
Nu - Nucleophile
PBD - Pyrrolobenzodiazepine
PBSD - pyrrolobenzothiadiazepines
ppm - Parts Per Million
RNA - Ribo Nucleic Acid
RT - Room Temperature
 S_N2 - Substitution Nucleophilic Second Order
TBAF - tetrabutylammonium fluoride
TEA - Triethanolamine
TFA - Trifluoroacetic acid
TFSA – Trifluoromethyl Sulfonic Acid
THF - Tetrahydrofuran
TLC - Thin Layer Chromatography

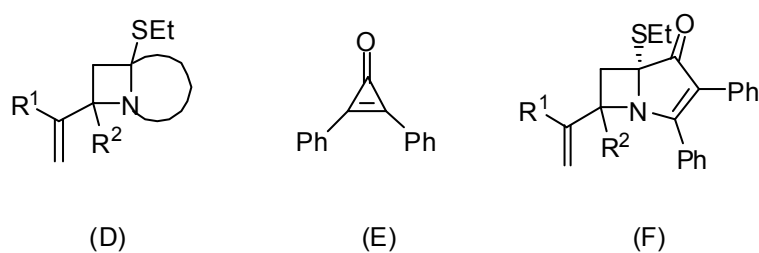
Abstract

The β -lactams and the related β -sultams are attractive targets for synthesis because of their central importance in antibiotics such as the penicillins. These heterocycles are of further interest because of their potential as inhibitors of the serine protease class of enzymes¹³, believed to be responsible for diseases such as rheumatoid arthritis and cystic fibrosis.

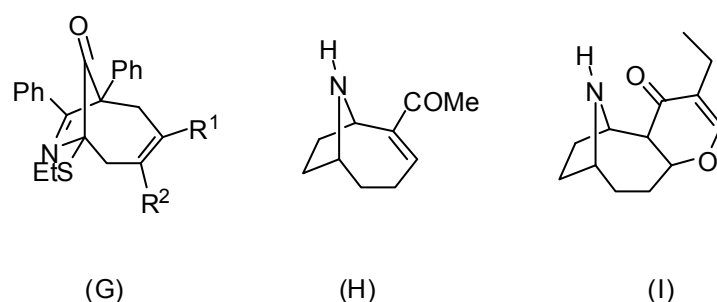
This thesis will describe the synthesis of the 4-vinyl beta lactams (A)²⁵, thiation of these compounds using Lawesson's reagent to yield thio lactams (B) and subsequent conversion into the corresponding 1-azetine (C) using Meerwein's reagent.



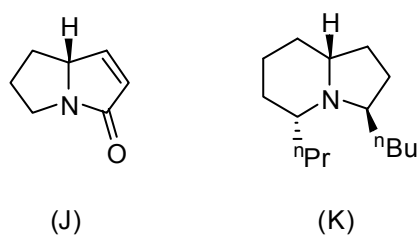
Compound (C) provided a template for a series of cycloaddition reactions in order to produce a series of bicyclic heterocycles, represented by general structure (D). One reaction that was explored in this series was that between 1-azetines (C) and diphenylcyclopropenone (DPP) (E) which should have yielded the bicyclic adducts (F).⁹³



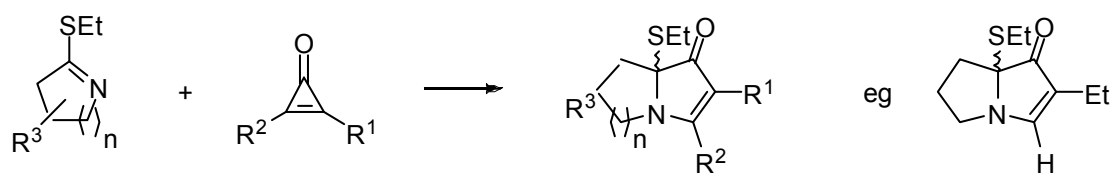
In the event the products isolated were not the anticipated cycloadducts (F) but rather the ring expanded compounds (G)¹¹⁴ obtained via sigmatropic rearrangement, the nucleus of which is an isomer of the azabicyclononane system, present in many important⁷² alkaloids such as anatoxin-a (H) and pinnamine (I).



The project subsequently evolved to look at the possibility of synthesising other alkaloid nuclei such as the pyrrolizidines, indolizidines and pyrroloazepines through the reaction of the appropriate imines with cyclopropenones. These bicyclic systems are present in many natural products⁷² such as pyrrolam A (J) and indolizidine 223AB (K) and are of great interest for synthesis because of the wide range of biological activities they possess, such as the ability to block the nicotinic receptor channels.

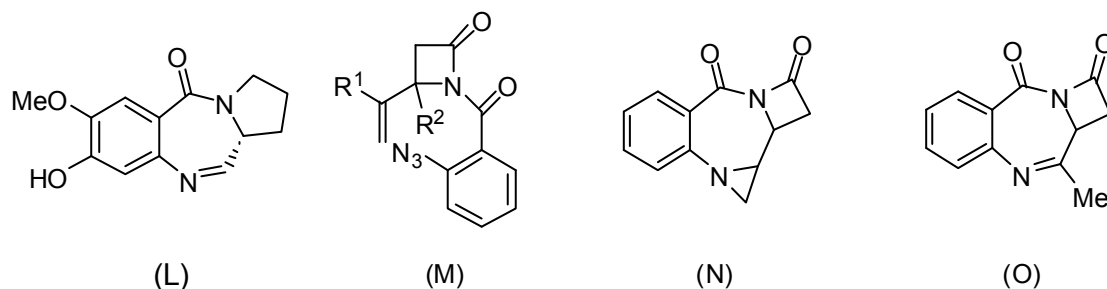


This thesis will therefore describe an effective synthesis of the heterocycles shown in Scheme A (where $n = 1, 2$ or 3).



Scheme A

Further research into the reactions of 4-vinyl β -lactams (A) has also been conducted with a view to synthesising analogues of the pyrrolobenzodiazepine, antitumour, antibiotic natural products, of which DC-81 (L) is an example.¹¹⁵ Thus, reaction of (A) with *o*-azidobenzoylchloride gave the *N*-substituted β -lactam (M). Ring closure via an azide-alkene cycloaddition and loss of nitrogen gave either the aziridine compound (N) or the methyl imine (O).



Overall the work described in this thesis pioneers initial research into the reactions of electron rich imines with cyclopropenones, positively demonstrating their use in the synthesis of analogues of alkaloid natural products.

Introduction

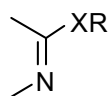
Chapter 1: Introduction

1.0 Introduction

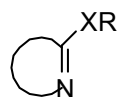
Imino ethers (1a, X=O), also known as imidates (the terms will be used interchangeably throughout this thesis) together with the corresponding imino thioethers, also known as thioimidates (1a, X=S), are a sub-class of the larger and more well known imine class of compound. The latter are well established as expedient starting materials, intermediates and synthetic targets in organic synthesis.

In this thesis, the discussion will centre on the synthesis and reactions of cyclic thioimidates (imino thioethers) (1b, X=S). This Introduction will focus on the synthesis of all types of thioimidates and imidates and their use as key building blocks for the formation of a wide variety of compounds. Where the imidates/thioimidates concerned are cyclic, this introduction will be limited to the non-fully conjugated (non-aromatic) systems.

In the Discussion of this thesis, cyclic thioimidates (1b, X=S) will be used in the synthesis of heterocyclic nuclei which are of importance as the central core of several classes of alkaloid natural products. For this reason a very brief overview of the use of cyclic imines (including imidates and thioimidates, where appropriate) in the synthesis of alkaloids will form the latter part of this introduction, followed by a very general introduction to the indolizidine, pyrrolizidine, pyrroloazepine and homotropane alkaloids.



(1a)



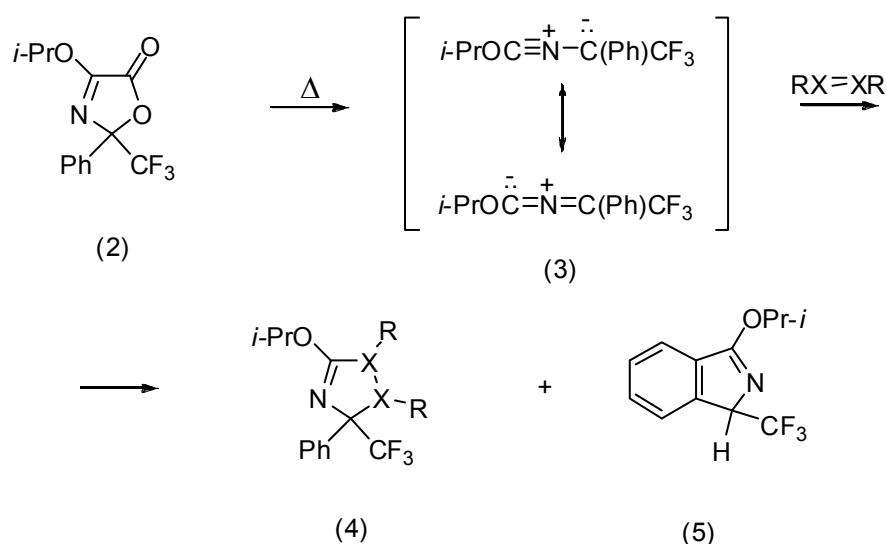
(1b)

X = O or S

R = alkyl group

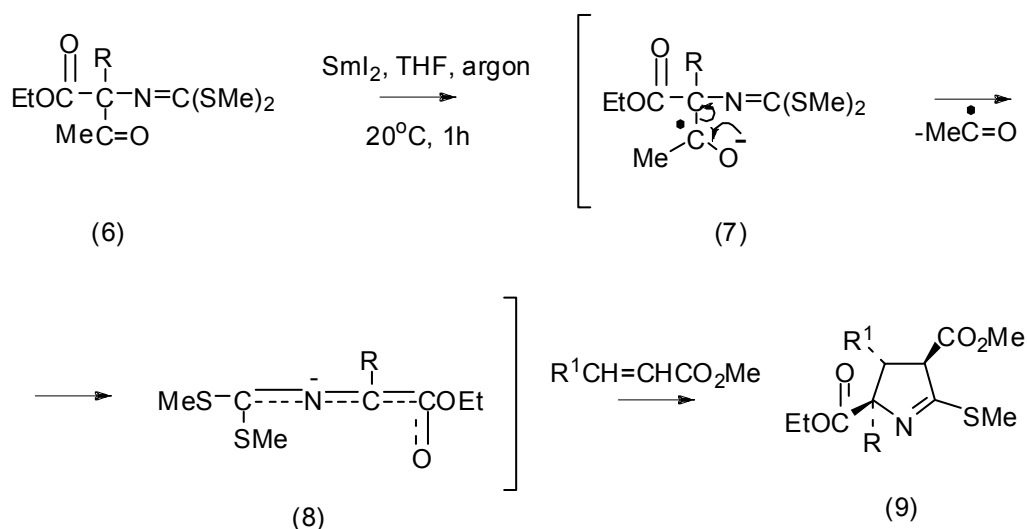
1.1 Synthesis of imidates and thioimidates

Oxazolone derivatives (2) that contain a pre-existing imidate functionality undergo thermolysis reactions in the presence of unsaturated compounds (RX=XR) in toluene to produce a new cyclic imidate, the pyrroline (4, X=C).¹ The process involves a thermal ring opening, with decarboxylation to give a nitrile ylide (3), which subsequently undergoes an *in situ* 1,3-dipolar cycloaddition reaction with the unsaturated compound RX=XR to form compound (4) together with the iso-indole (5) (Scheme 1). It can be seen that the nitrile ylide (3) functions as an excellent provider of the imidate functionality present in compound (4).



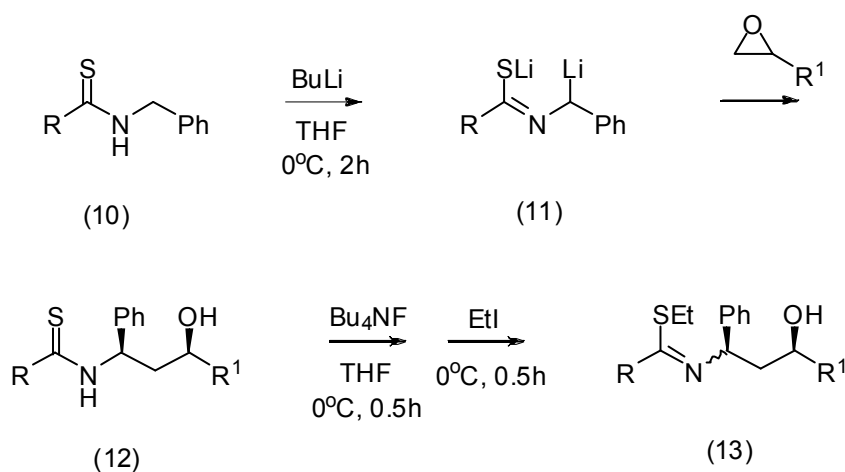
Scheme 1

Cyclic pyrrolines containing imidate or thioimidate functionality can also be formed from acyclic starting materials.¹ Thus, using powdered Sml₂, compound (6) is converted into ylide (8) via the intermediate radical species (7). Anion (8) undergoes *in situ* reaction with esters to yield cyclic thioimidates (9).



Scheme 2

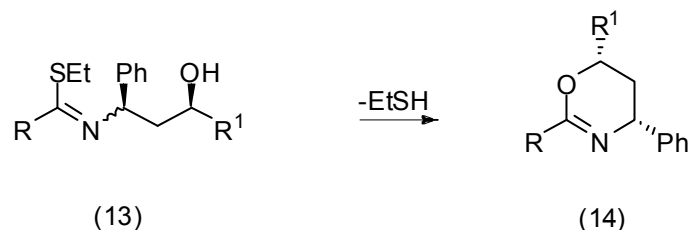
Non-cyclic thioimidates² such as compound (13) have been synthesised from the corresponding thioamide (12) as shown in Scheme 3. Thus, the thioamides (10) undergo double deprotonation producing dianions (11). Further reaction with a propylene oxide yielded the thioamides (12), which produced the acyclic thioimidates (13), after reaction with ethyl iodide in the presence of tetrabutylammonium fluoride (TBAF).



E.g. R = Ph, R¹ = ^tBu

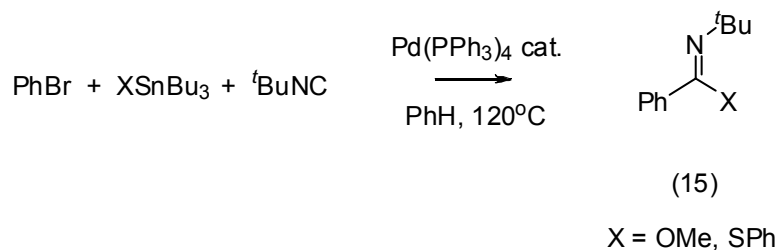
Scheme 3

It is of interest to note that the acyclic thioimide (13) in turn functions as a precursor for the synthesis of the cyclic imide (14), as shown in Scheme 4.^{2,3}



Scheme 4

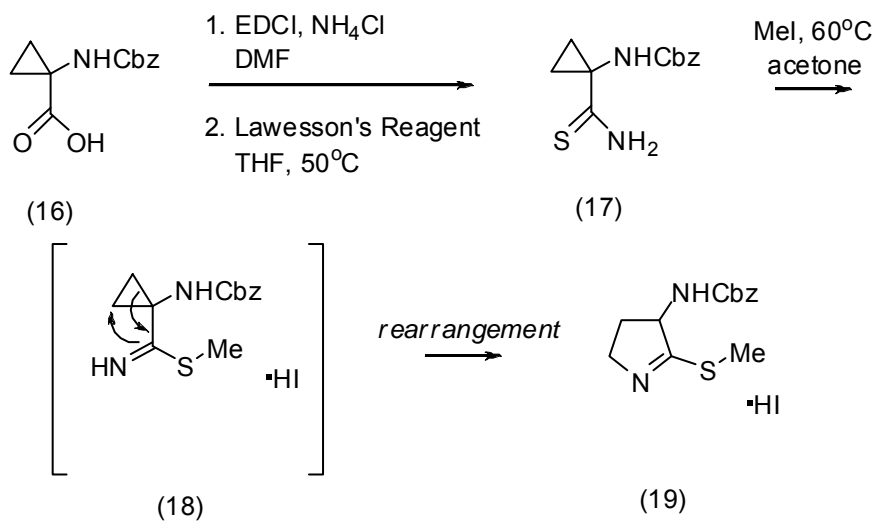
The synthesis of imidates and thioimides using isocyanides has been achieved.⁴ Thus, the synthesis of imide (15, X=OMe) or thioimide (15, X=SPh) was carried out *in situ* using a palladium catalysed coupling between bromobenzene, tert-butyl isocyanide and tributylstannyl methoxide or thiophenoxide (Scheme 5).



Scheme 5

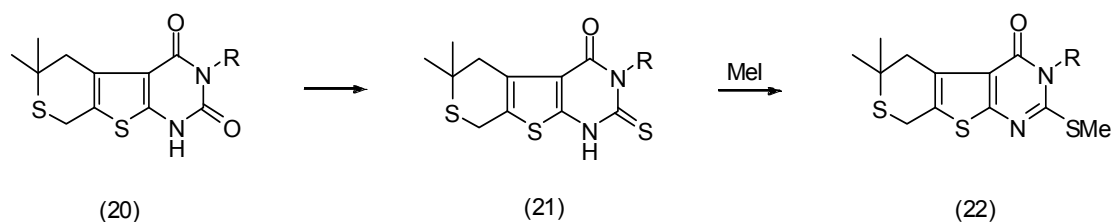
A traditional and well-established route to imidates/thioimides⁵ is from the alkylation of the corresponding amides and thioamides, respectively, a process highlighted in the last step of Scheme 3. Scheme 6 highlights an interesting variation of this process starting from commercially available Cbz protected 1-aminocyclopropane-1-carboxylic acid (16).⁵ This compound initially undergoes conversion to the corresponding amide using EDCI and NH₄Cl in DMF and subsequent treatment with Lawesson's reagent yields thioamide (17). Upon reaction of thioamide (17) with methyl iodide in acetone at 60°C, the expected thioimide intermediate (18) underwent a rapid

rearrangement process, resulting in exclusive formation of the cyclic thioimidate (19).



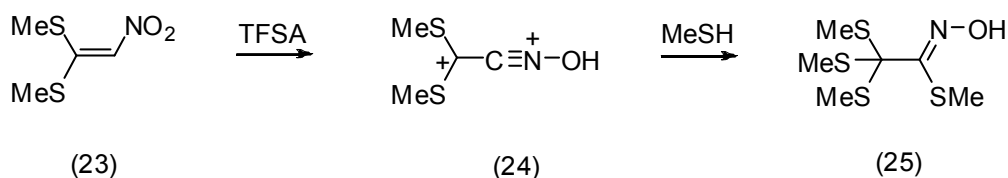
Scheme 6

The conversion of amides (20) into the thioamides (21) and subsequent alkylation with MeI gave the cyclic thioimidates (22) (Scheme 7).⁶ This method is a further example of the classic process by which amides are converted into thioimidates/iminoethers.



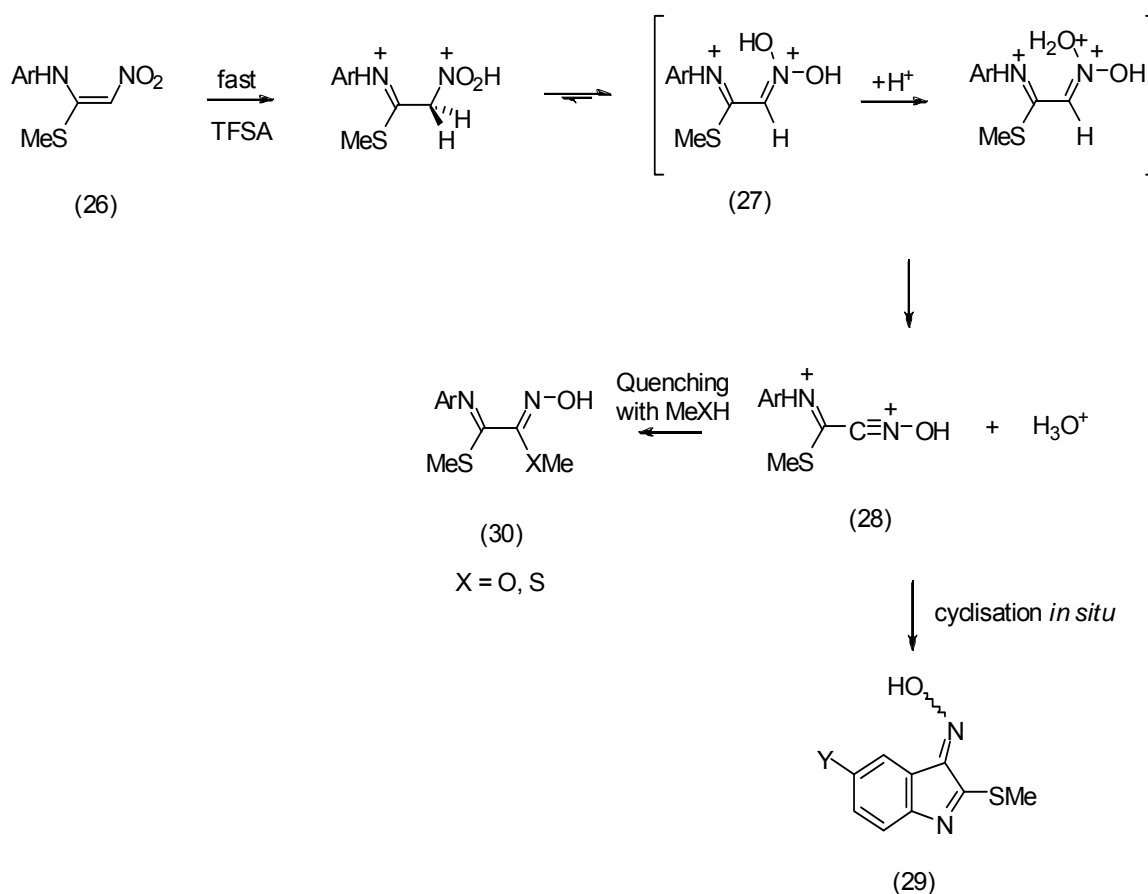
Scheme 7

By dissolving nitro derivative (23) in TFSA at low temperature, hydroxynitrilium ion (24) is formed, which can be trapped with methyl thiol to yield the non-cyclic thioimidate (25) (Scheme 8).⁷



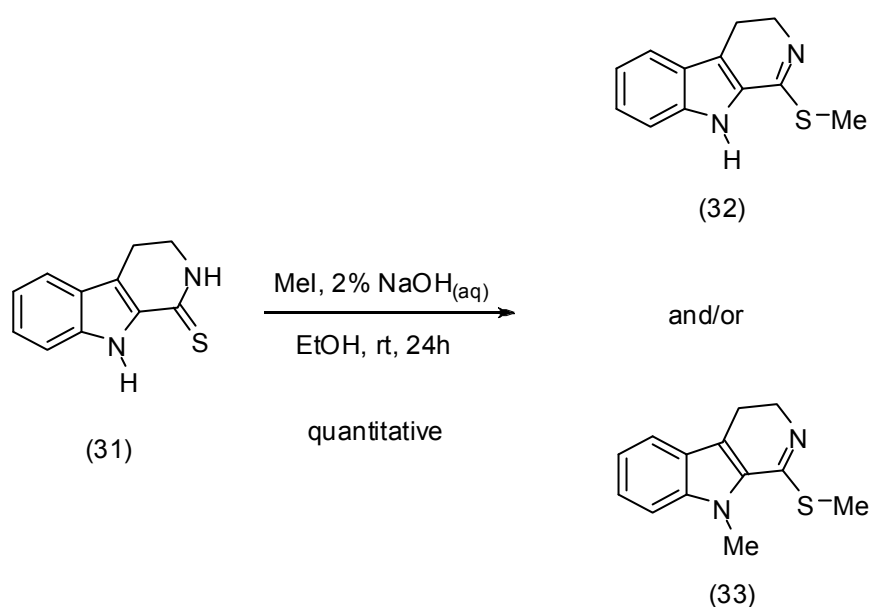
Scheme 8

Protonation of nitro compound (26) followed by tautomerisation to give intermediate (27) allows further protonation and loss of water to yield the stable hydroxynitrilium (28). Intramolecular cyclisation gave the thioimide (29). Alternatively, quenching of hydroxynitrilium (28) with an excess of a suitable nucleophile such as MeOH or MeSH, yielded the acyclic imide (30, X=O) and thioimide (30, X=S)⁸ as products of the reaction (Scheme 9).



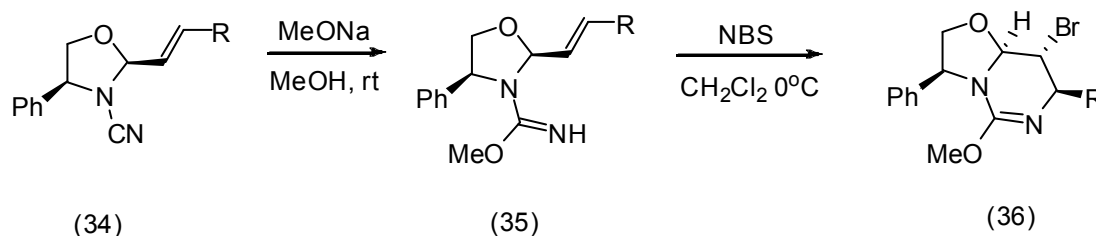
Scheme 9

The thione (31) readily undergoes S-alkylation in one step, with a stoichiometric amount of methyl iodide in ethanol at room temperature, to give triheterocyclic imino-thioether (32) in quantitative yield.⁹ If an excess of methyl iodide was employed, the reaction was found to yield both S-alkylated (32) and the N,S-dialkylated (33) products (Scheme 10).



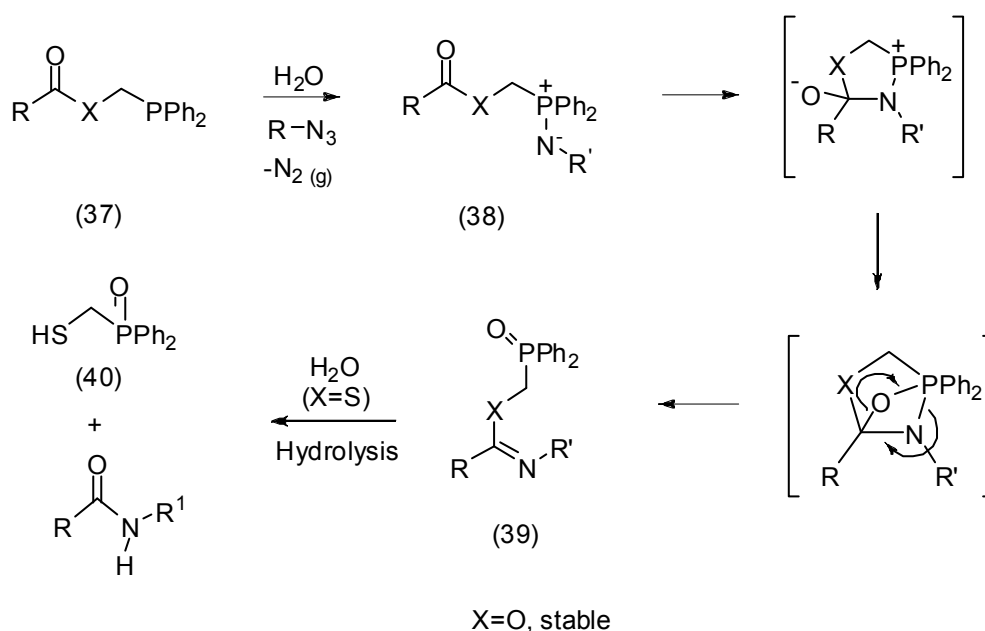
Scheme 10

Imidate (36) was synthesised from *N*-cyanooxazolidine (34) via nucleophilic attack at the carbon of the C≡N bond and protonation via MeOH to yield iminoether (35).¹⁰ The iminoether then underwent bromocyclisation at 0°C to yield quantitatively bicyclic product (36) (Scheme 11).



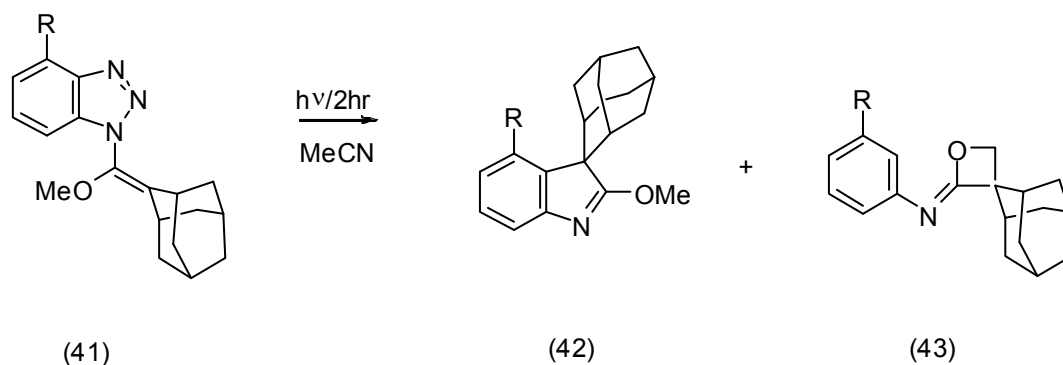
Scheme 11

Reaction of the phosphines (37, X=O) with an azide gave the iminophosphoranes (38), which then underwent an intramolecular aza-Wittig¹¹ reaction to produce the stable imidate (39, X=O) as shown in Scheme 12.¹² There is also literature precedent for the reaction occurring when X=S i.e. with the iminophosphorane (38, X=S) which is formed from the corresponding phosphinothioester (37, X=S). This procedure gives the thioimidate (39, X=S) after intramolecular aza-Wittig reaction, which has not been isolated, but rather undergoes hydrolysis to give the sulfide (40) together with an amide.¹³ This latter process is the now well known Staudinger ligation (Scheme 12), whereby amides are produced from carboxylic acids via the formation of phosphines (37, X = S) as intermediates.



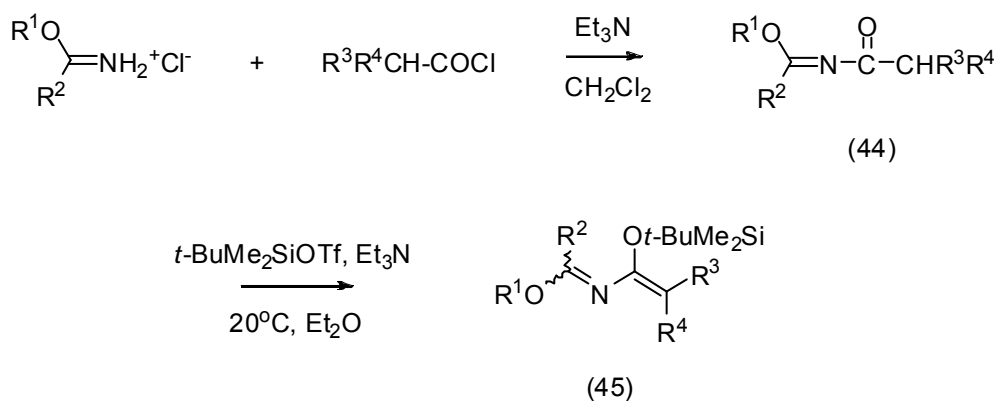
Scheme 12

Photoinduced elimination¹⁴ of nitrogen from the benzotriazole (41) produces an intermediate which then cyclises to yield the cyclic imidate (42) together with the unusual oxetane containing imidate species (43) (Scheme 13).



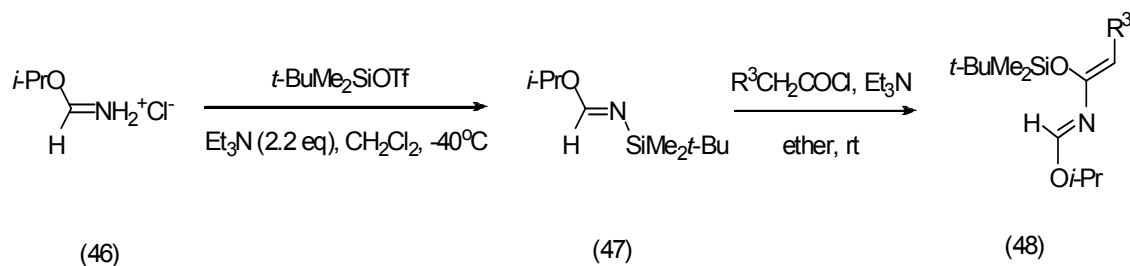
Scheme 13

Ghosez¹⁵ and others¹⁶ have shown that iminoether hydrochlorides react with acid chlorides, in the presence of a base such as triethylamine *via* an acylation process, to form the acylimidates (44). These then undergo *O*-silylation at ambient temperature to give the corresponding imidate based 2-azadienes (45) in good to excellent yield (Scheme 14). The starting iminoether hydrochlorides were obtained by alkylation of the corresponding amide, a common route to such iminoethers.



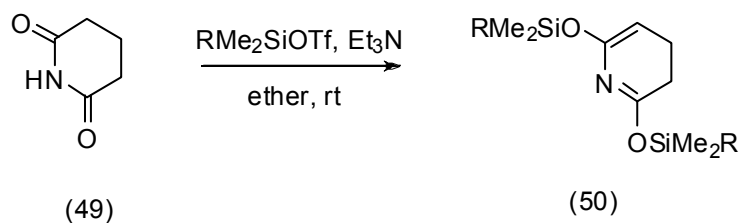
Scheme 14

An alternative route to 2-azadienes has also been developed by the same research group¹⁵ and is shown in Scheme 15. In this method, *N*-silylation of the iminoether hydrochloride (46) gave *N*-silylated imidate (47). Desilylation, *N*-acylation and re-silylation at the carbonyl oxygen gave the silyl containing imidate based azadiene (48).



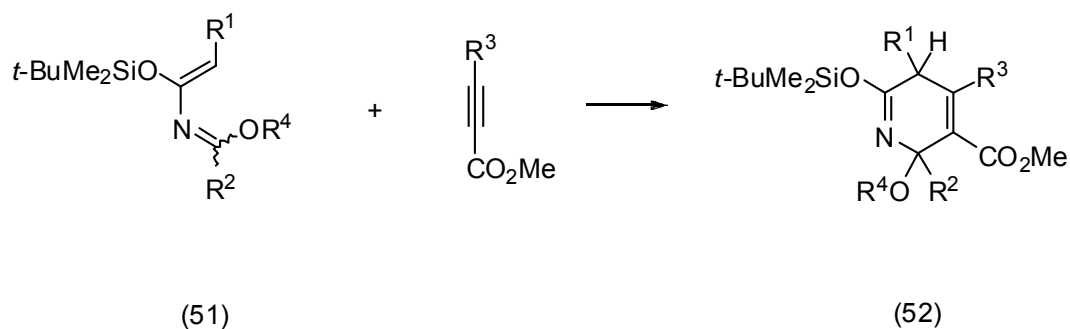
Scheme 15

In parallel with the synthesis of the acyclic imidate based 2-azadienes detailed above, cyclic^{15,17} versions have also been synthesised, using the silylation method shown in Scheme 16. The product (50) is obtained directly from the silylation of the corresponding imide (49) with a trialkyltriflate.



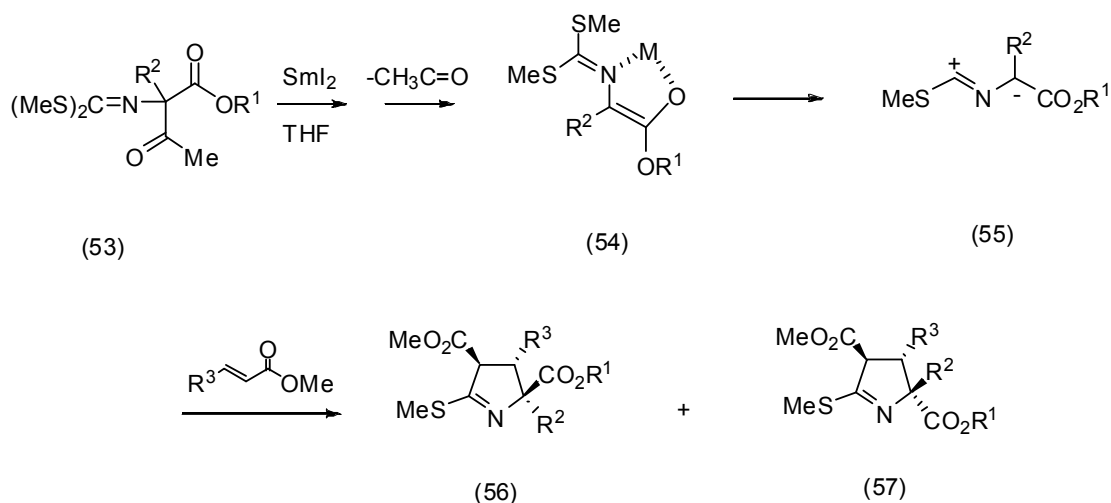
Scheme 16

Dienes such as those shown in Scheme 14-16 have been shown^{15,18} to react in Diels-Alder cycloadditions. An example is shown in Scheme 17 whereby the imidate based azadiene (51) reacts with an alkyne to form the cyclic *O*-silylated imidate (52).



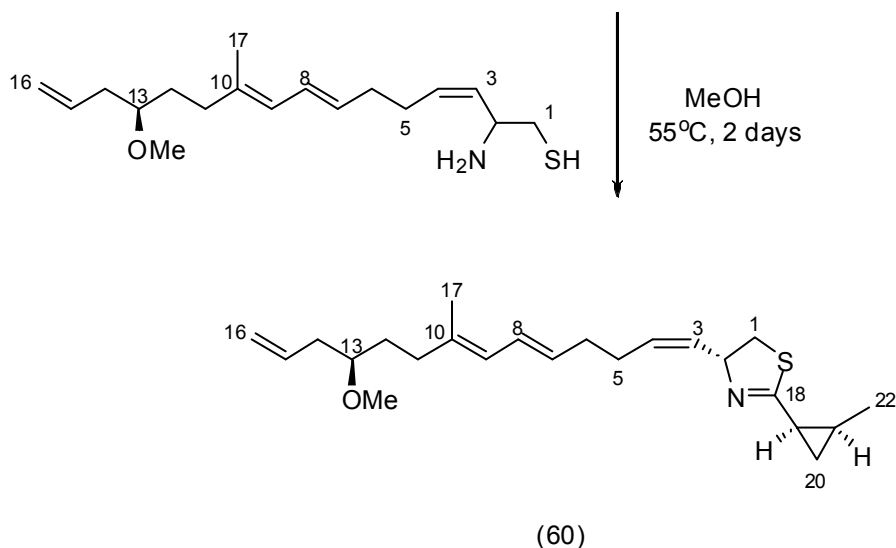
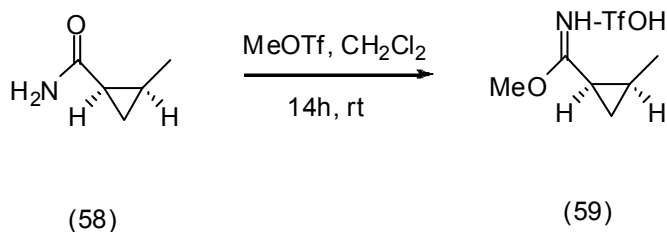
Scheme 17

In a single electron transfer process, compound (53) undergoes loss of an MeCO fragment to form the metal complex (54). Loss of MSMe gives the ylide (55) which then undergoes 1,3-dipolar cycloaddition with an unsaturated ester, to yield pyrrolines (56) and (57) which contain the thioimide moiety (Scheme 18). 1,3-Dipole (55) represents an excellent precursor for the synthesis of cyclic thioimides with diverse substituents.¹⁹



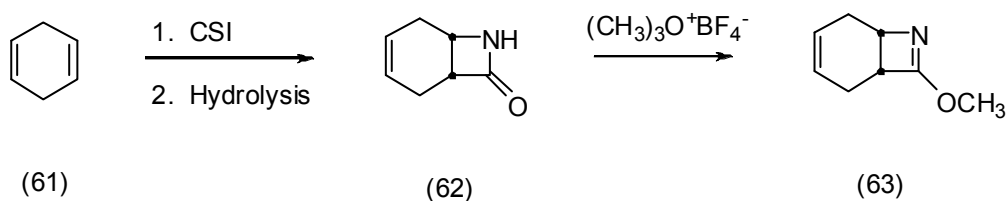
Scheme 18

As well as the alkylation discussed in Schemes 6, 7 and 10, for example, iminoethers have also been synthesised from the respective amide using triflates, as shown in the conversion of compound (58) into compound (59). Compound (59) (the imidate)²⁰ can then undergo further reaction with an aminothiols in the presence of methanol to yield the natural product curacin A²¹ (60), which is itself an example of a cyclic thioimide (Scheme 19).



Scheme 19

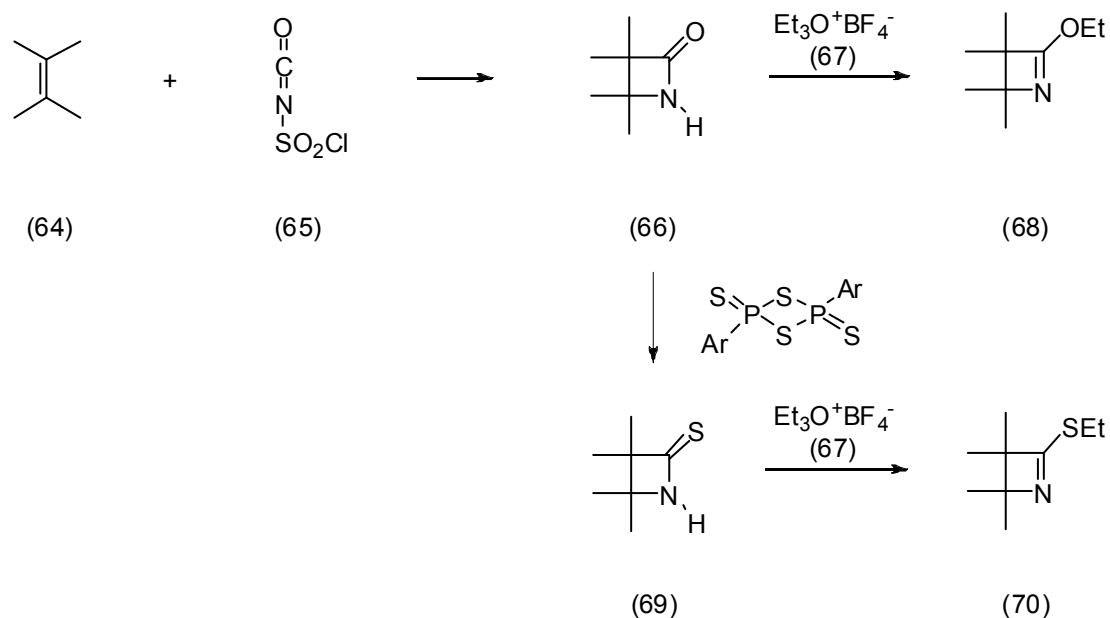
1,4-cyclohexadiene (61) undergoes standard [2+2] cycloaddition to chlorosulfonyl isocyanate²² to yield the bicyclic β-lactam (62). Subsequent O-methylation²³ of lactam (62) with trimethyloxonium fluoroborate results in the isolation of imidate (63).²⁴



Scheme 20

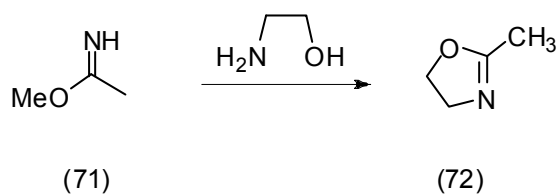
Similar [2+2] cycloaddition of alkene (64) to chlorosulfonyl isocyanate (65)²⁵ results in the synthesis of β-lactam (66).^{26,27,28} This lactam undergoes direct ethylation with Meerwein's reagent (67) to yield the cyclic iminoether (68) in good yield. The corresponding iminothioether is accessible via thiation of

β -lactam (66) using Lawesson's reagent²⁹ to give thioxo compound (69). Ethylation using Meerwein's reagent yields cyclic iminothioether (70) (Scheme 21).²⁸

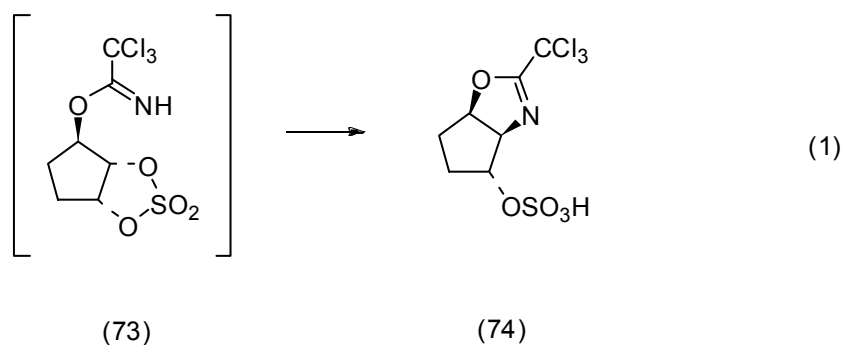


Scheme 21

Cyclic iminoether (72) is a rare example³⁰ of an iminoether that is commercially available. It is available via reaction of imidate (71) with ethanolamine as shown below, a reaction similar to that used in Scheme 19.

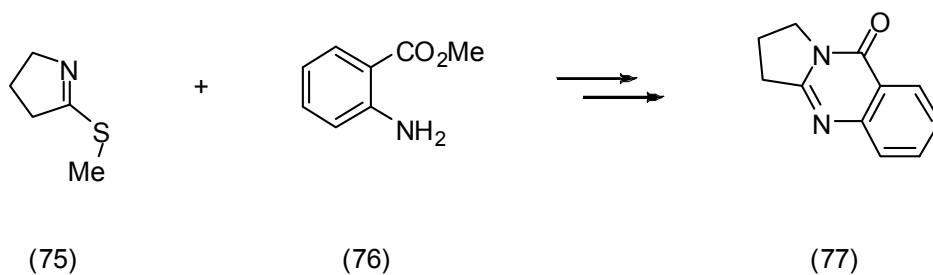


Access to the cyclic iminoether (74) was achieved via thermally promoted intramolecular nucleophilic attack of the cyclic sulfonate (73).³¹



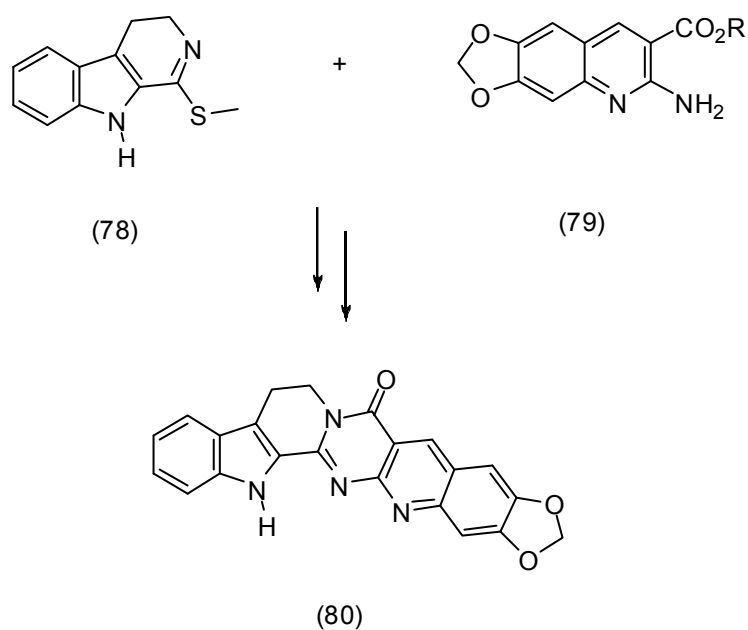
1.2 Reactions of Imidates and Thioimidates with Nucleophiles other than Water

Iminothioether (75) underwent nucleophilic displacement^{9,32} of SMe with compound (76), which was then followed by a second intramolecular nucleophilic attack at the ester carbonyl moiety resulting in the formation of tricyclic alkaloid (77), in excellent yield (Scheme 22).



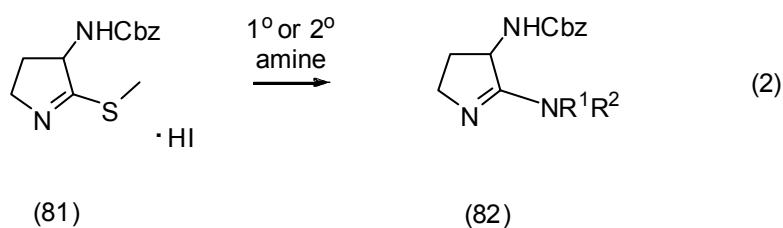
Scheme 22

As detailed in Scheme 23, this process³² is also applicable to the reaction of iminothioether (78) with compound (79) hence allowing the production of *N*-polyheterocyclic system (80).

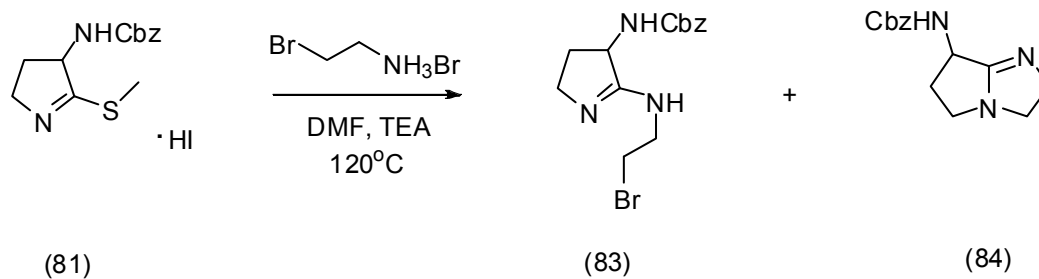


Scheme 23

Kuduk⁵ has shown that pyrrolothioimidate (81) can undergo nucleophilic displacement reactions with a variety of primary and secondary amines to afford 2,3-diaminodihydropyrroles of the type (82) shown in equation (2), in moderate to good yields.

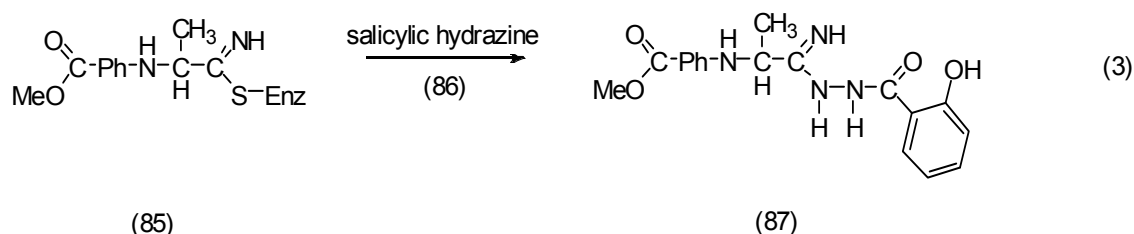


Thioimidate (81) (equation 2) can also undergo nucleophilic displacement with 2-bromoethylamine to form compound (83), which upon heating to 120°C undergoes partial conversion into the bicyclic compound (84) (Scheme 24).⁵

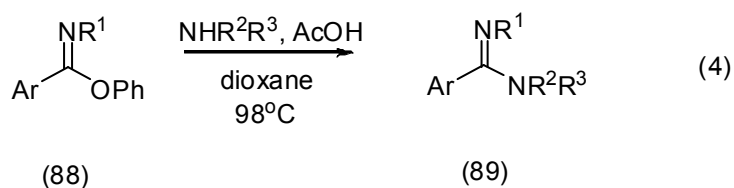


Scheme 24

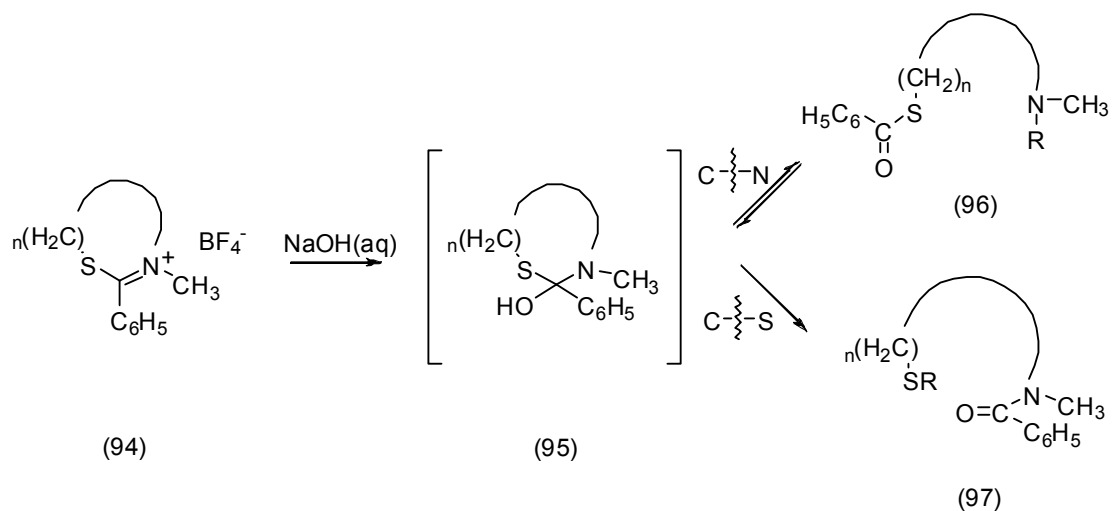
Nucleophilic attack at the imino carbon of enzyme adduct (85) by salicylic hydrazine (86) resulted in the formation of the corresponding amidrazone (87) (equation 3).³³



Acyclic imino ethers of the type (88) undergo conversion into the corresponding amidine (89) in dioxane solvent at 98°C in good to excellent yields (equation 4).⁴

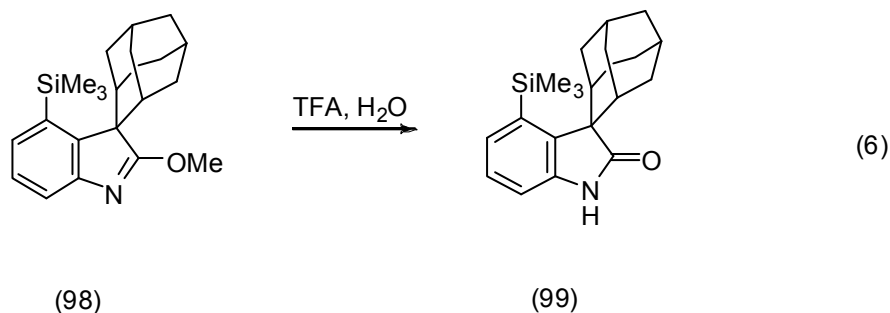


The imidates and thioimidates (15) (see Scheme 5) also react readily with amines to give amidines.⁴

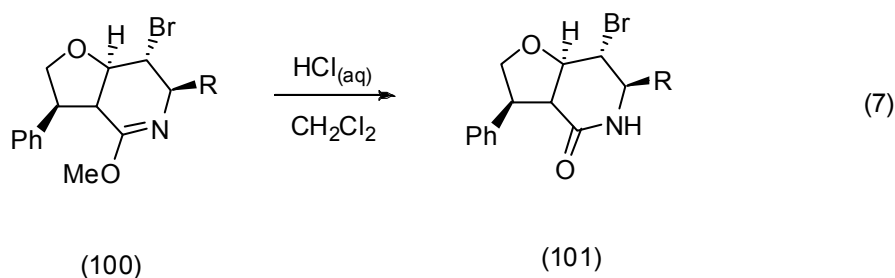


Scheme 26

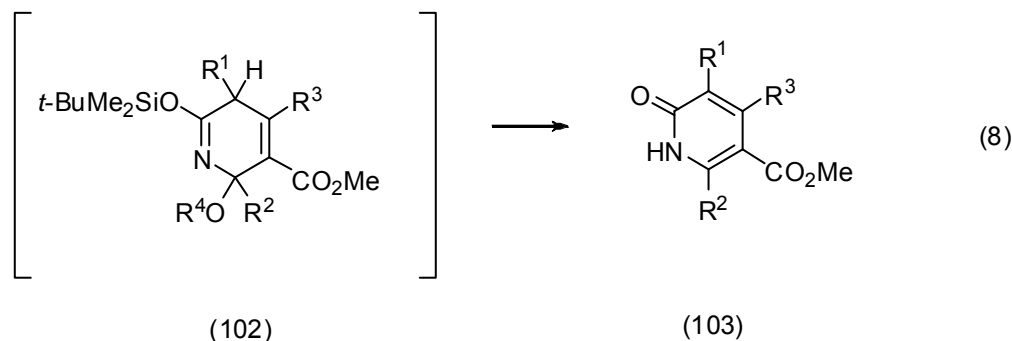
Cyclic iminoether (98) undergoes hydrolysis¹⁴ in TFA to give the corresponding oxindole (99) in a yield of 85% (equation 6).



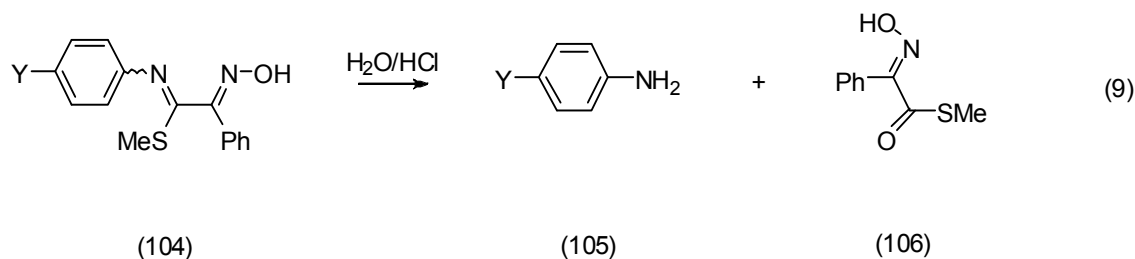
The treatment¹⁰ of iminoether (100) with aqueous hydrochloric acid in dichloromethane results in the acidic hydrolysis of the iminoether moiety to give the amide (101) (equation 7).



Access to pyridinones (103) is accomplished via the hydrolysis (methanolysis of the same compound has also been reported) of adduct (102) (equation 8).¹⁸

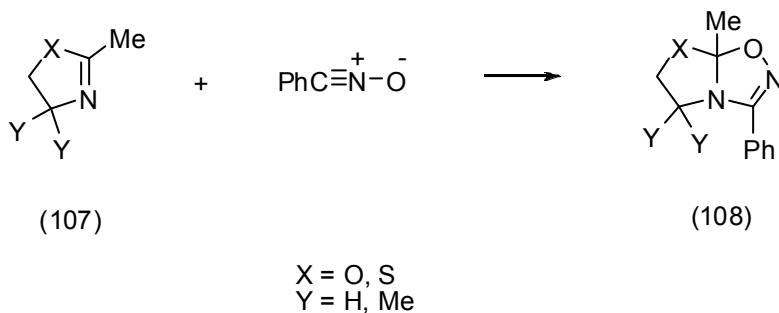


Acyclic iminothioether (104) undergoes partial hydrolysis resulting in a mixture of *para*-substituted aniline (105) and *S*-methyl α -hydroxyiminophenylthioglyoxylate (106), shown in equation 9.³⁵ This process is noteworthy in that it results in C=N cleavage exclusively (i.e. no C-S cleavage was seen).



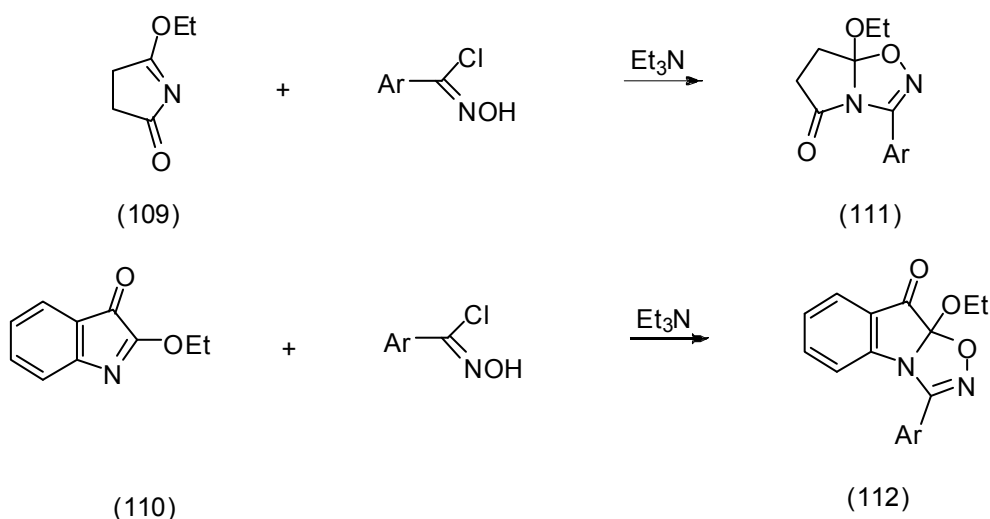
1.4 Cycloaddition reactions

One of the main parts of the discussion (see later) will deal with cycloadditions to cyclic imino ethers and imino thioethers. Previous literature in this area will therefore be reviewed. Heterocyclic systems (107) consisting of 5 atoms, in which the imidate or thioimidate functionality is found as part of the ring itself, have been shown³⁶ to readily undergo reaction with benzonitrile oxide to give a range of cycloadducts of the type (108) (Scheme 27).

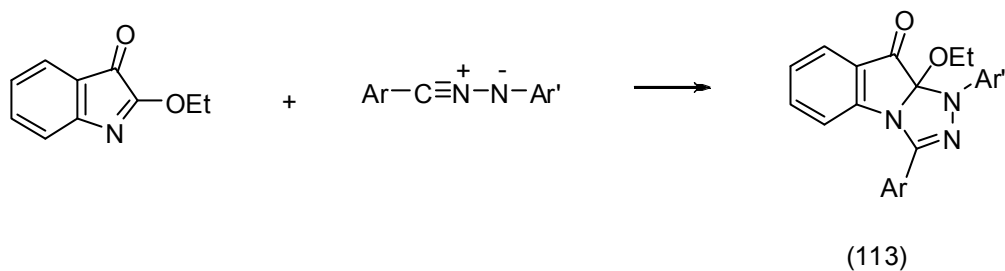


Scheme 27

Rings of larger size also containing the imidate functionality can be readily synthesised³⁶ using the above methodology but have been reported by Miller and Scrowston to be unreactive towards 1,3-dipoles.³⁶ A plausible reason for the decreased reactivity is a reduction in the ring strain exhibited by heterocyclic systems of larger size and thus their overall increased stability. It has also been reported by the same group, in an attempt to increase the reactivity of larger ring systems towards 1,3-dipoles, that the C=N double bond within the ring can be conjugated with an appropriate carbonyl group. The resulting imidate esters undergo reaction with nitrile oxides (Scheme 28) and nitrile imines (Scheme 29) to yield the respective cycloadducts (111), (112) and (113).

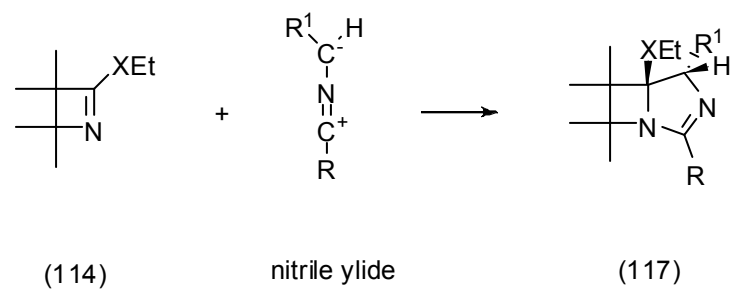
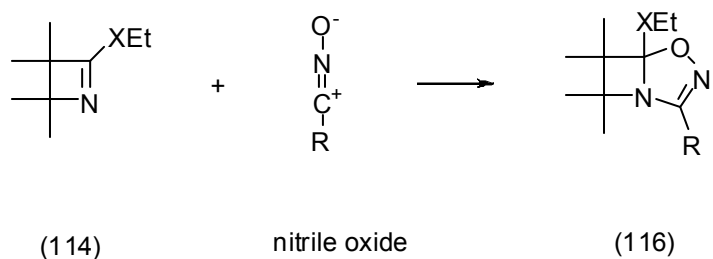
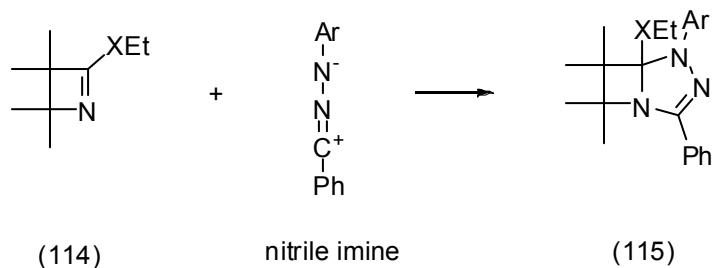


Scheme 28



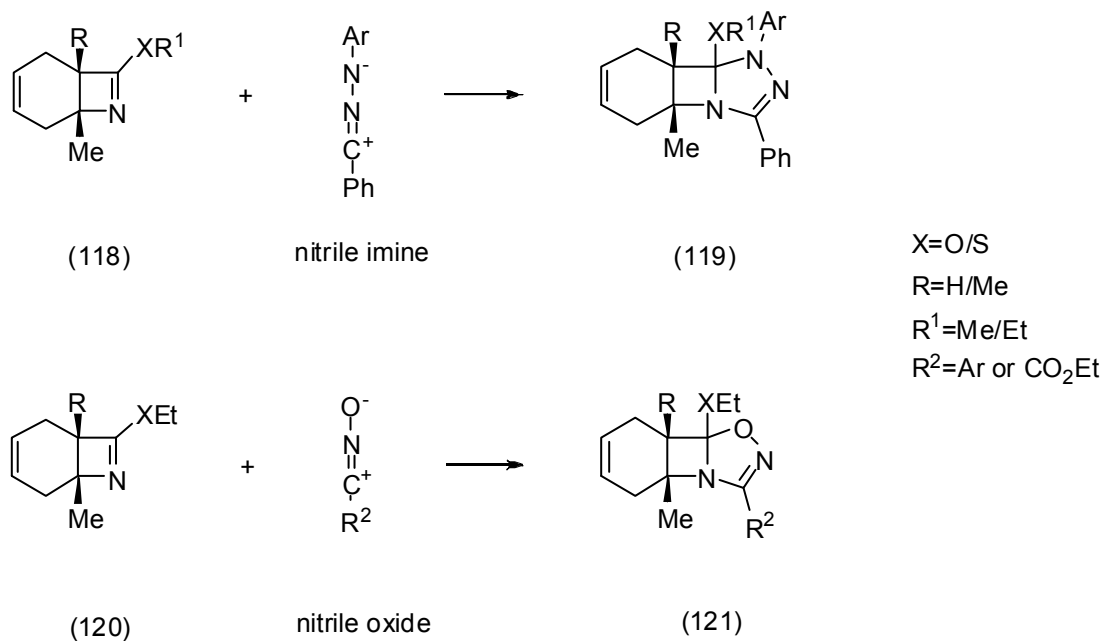
Scheme 29

In work of direct relevance to this thesis, Hemming and Smalley^{26,28} have also shown that the 4-membered cyclic iminoethers (114, X=O) and iminothioethers (114, X=S) can also undergo 1,3-dipolar cycloaddition reactions with nitrile imines, nitrile oxides and nitrile ylides to yield cycloadducts (115), (116) and (117) (Scheme 30), respectively.



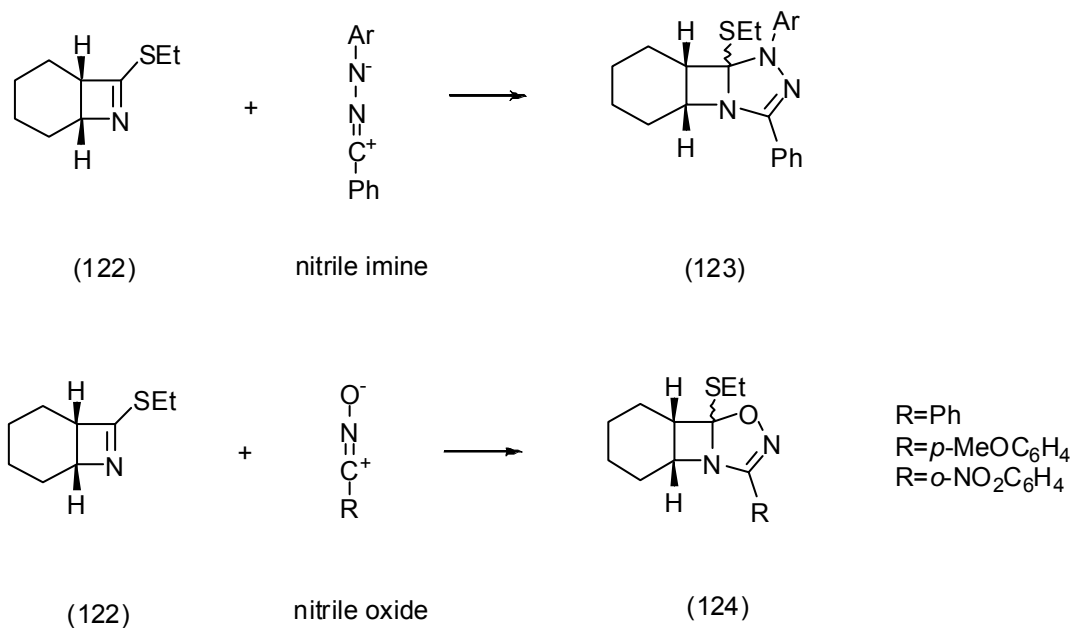
Scheme 30

The corresponding bicyclic iminoethers (118, X=O) and imino thioethers (118, X=S) have also been shown by the same research group²⁷ to undergo 1,3-dipolar cycloaddition reactions with nitrile imines to yield cycloadducts (119). In the equivalent reaction with nitrile oxides, bicyclic compounds (120, X=O or S) undergo cycloaddition, resulting in the formation of cycloadducts (121) (Scheme 31).



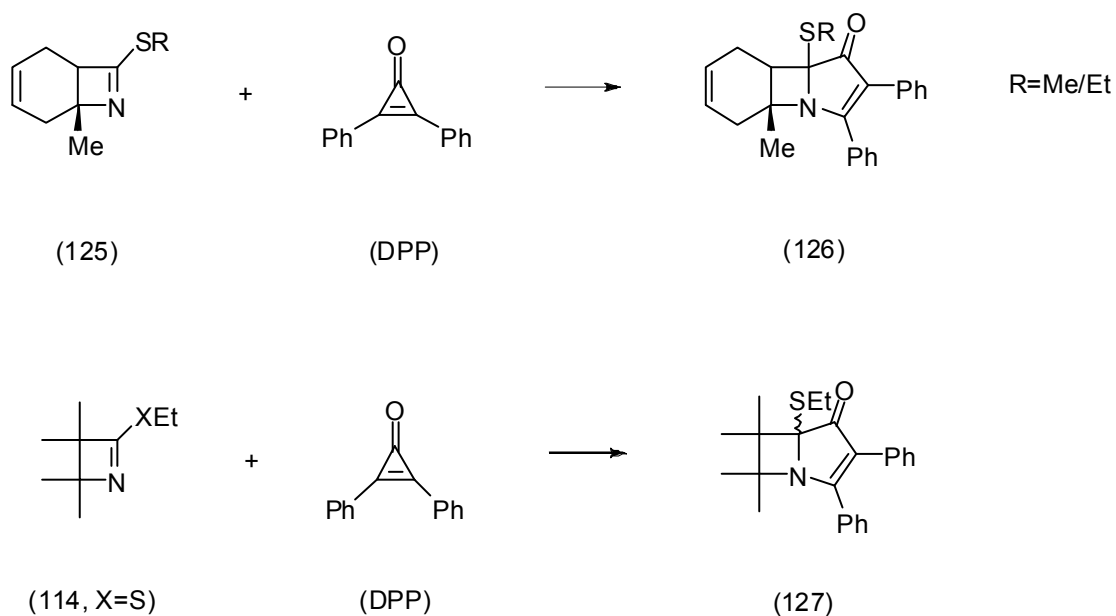
Scheme 31

The same process also works with the related imino thioether (122) which gives cycloadducts (123) and (124) (Scheme 32), after reaction with nitrile imines and nitrile oxides, respectively.²⁷



Scheme 32

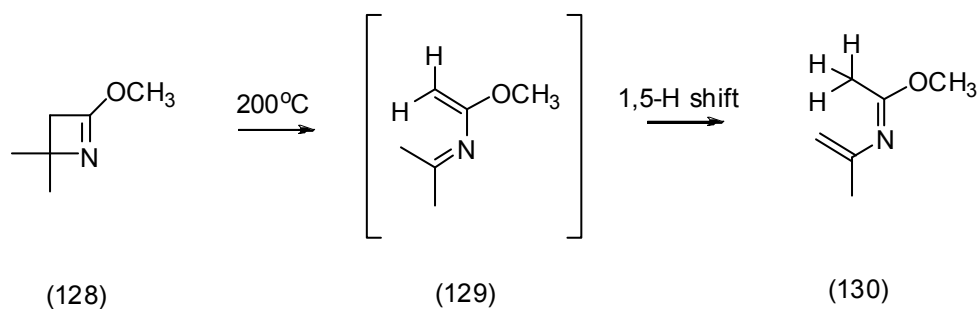
In a related reaction, the bicyclic imino thioether (125) undergoes a formal [3+2] cycloaddition with diphenylcyclopropenone (DPP) to yield cycloadducts (126) in good yield (Scheme 33). The same reaction also works with cyclic imino thioether (114, X=S), producing cycloadduct (127).²⁷



Scheme 33

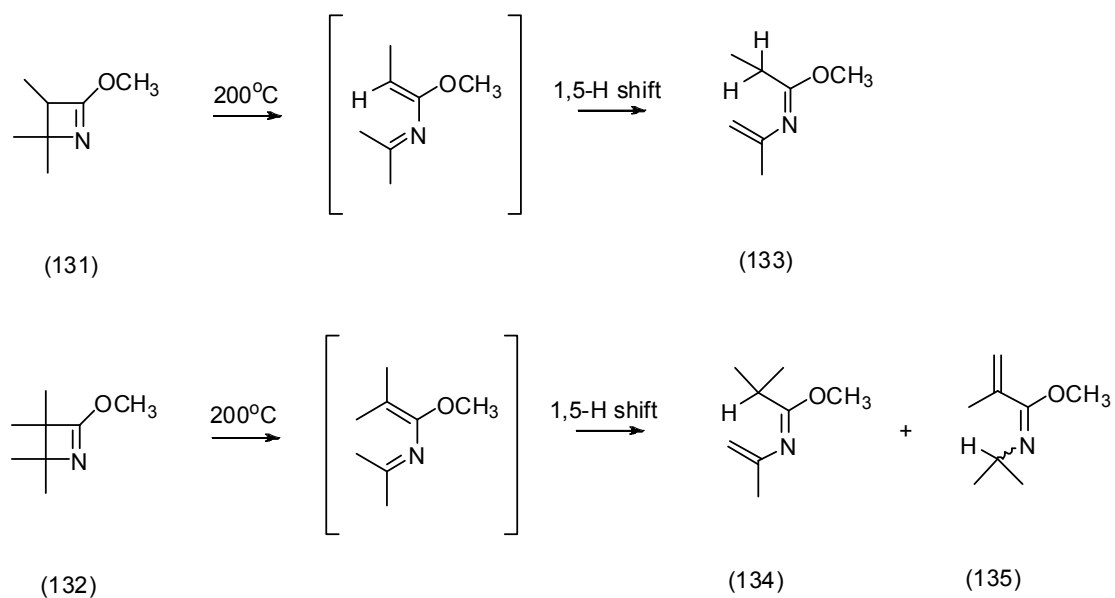
1.5 Rearrangement reactions

Cyclic iminoether (128) undergoes thermal ring opening at 200°C to give intermediate (129) which then undergoes a 1,5-H shift to yield the corresponding unsaturated iminoether (130) (Scheme 34).³⁹



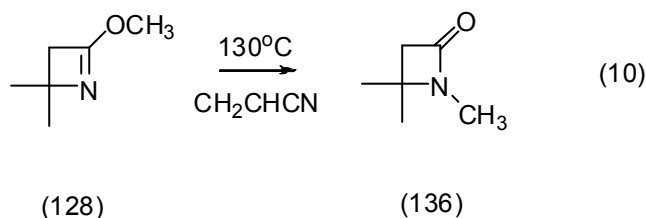
Scheme 34

In an analogous reaction^{39,40} cyclic iminoethers (131) and (132) undergo complete conversion into the corresponding unsaturated iminoethers (133), (134) and (135) (Scheme 35), with the latter reaction giving a mixture of products.

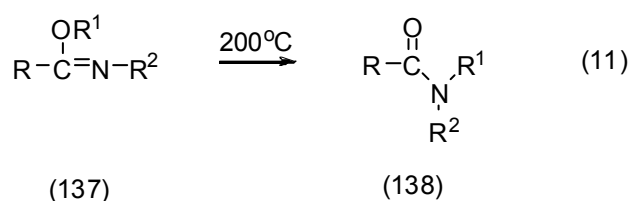


Scheme 35

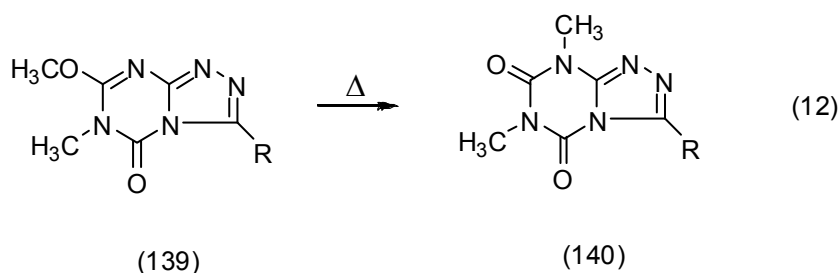
Interestingly, iminoether (128) also undergoes an intramolecular³⁹ Chapman rearrangement^{39,42} at 130°C to yield the corresponding beta lactam (136) (equation 10).



Acyclic iminoethers (137) undergo pseudo Chapman rearrangement at 200°C via oxygen to nitrogen shift of an alkyl group to yield the corresponding amides (138) (equation 11).⁴²⁻⁴⁴

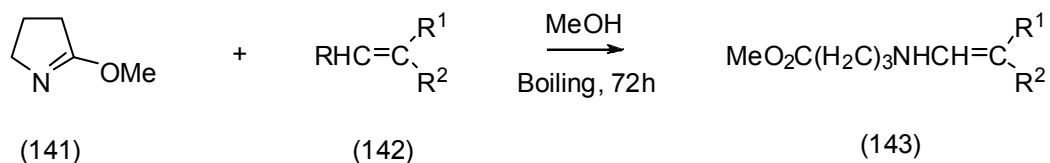


In a photolytic rearrangement, cyclic iminoether (139) is converted into cyclic amide (140) involving the shift of a methyl group from oxygen to nitrogen (equation 12).⁴³



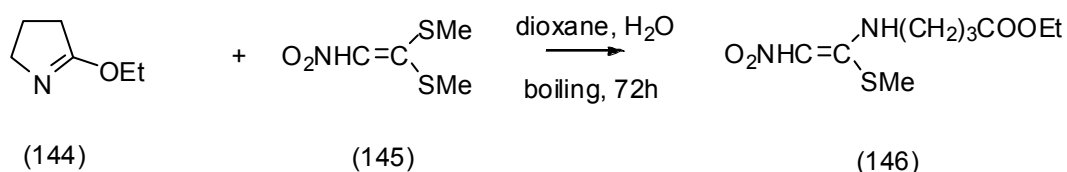
1.6 Miscellaneous reactions

When heated at reflux in methanol with 1,2,2-trisubstituted ethylenes (142), the cyclic imidate (141) yields a non-cyclic product (143) (Scheme 36).⁴⁵



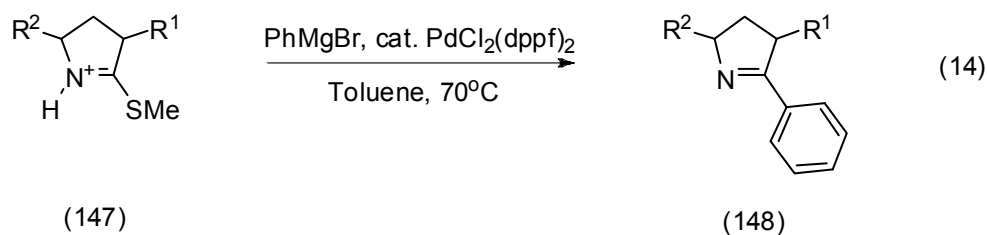
Scheme 36

A similar example to that shown in Scheme 36 is the reaction of 5-ethoxy-3,4-2*H*-dihydropyrrole (144) with alkene (145) in aqueous solution yielding compound (146). This product is formed with a different regiochemical outcome to that detailed for compound (143) (Scheme 37).⁴⁵



Scheme 37

In a palladium-catalysed cross coupling⁴⁶ reaction, phenylmagnesium bromide reacts with the protonated pyrrolothiomethylimidate (147) in toluene at 70°C, to form 2,5-disubstituted pyrroline (148) (equation 14).

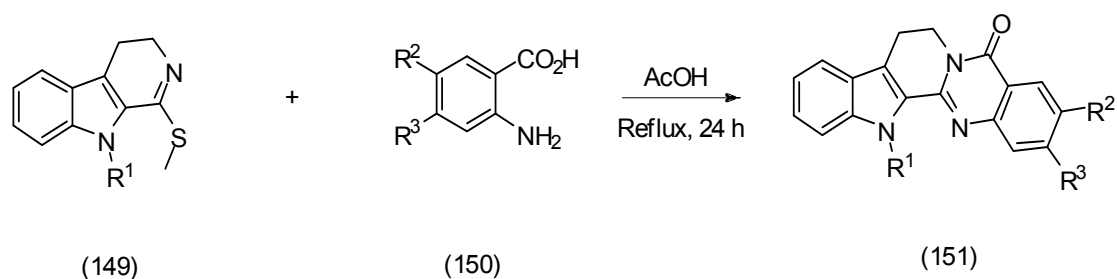


This thesis will deal with work on the use of cyclic imidates and cyclic thioimidates in the synthesis of four classes of alkaloids, the homotropanes, pyrrolizidines, indolizidines and pyrroloazepines. This introduction will therefore move on to discuss briefly the use of cyclic imines in general (i.e. not just the systems covered above) as precursors in the synthesis of alkaloids, before moving on to describe the above four classes in a little more detail.

2.0 Cyclic imines as precursors for alkaloids

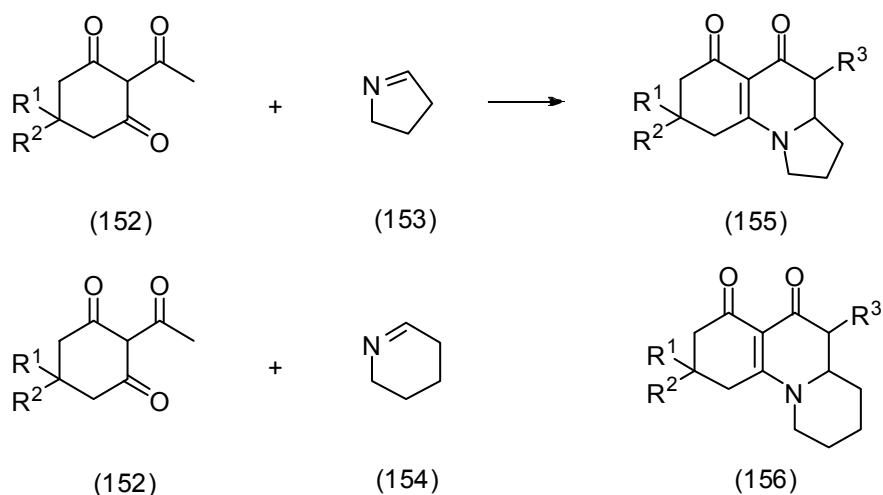
Cyclic imines are established^{47,48} as expedient starting materials in the synthesis of alkaloids in general and in the synthesis of the indolizidine, pyrrolizidine, pyrroloazepine and homotropane alkaloids targeted in this thesis. The alkaloids are ubiquitous in nature and are found, for example, in plants, trees, amphibian skin and microorganisms.⁴⁹

Triheterocyclic thioiminoether (149) undergoes a condensation reaction¹¹ with a variety of different aryl amino acids (150), at reflux and in the presence of acetic acid, to yield polyheterocyclic compounds (151) (Scheme 38).



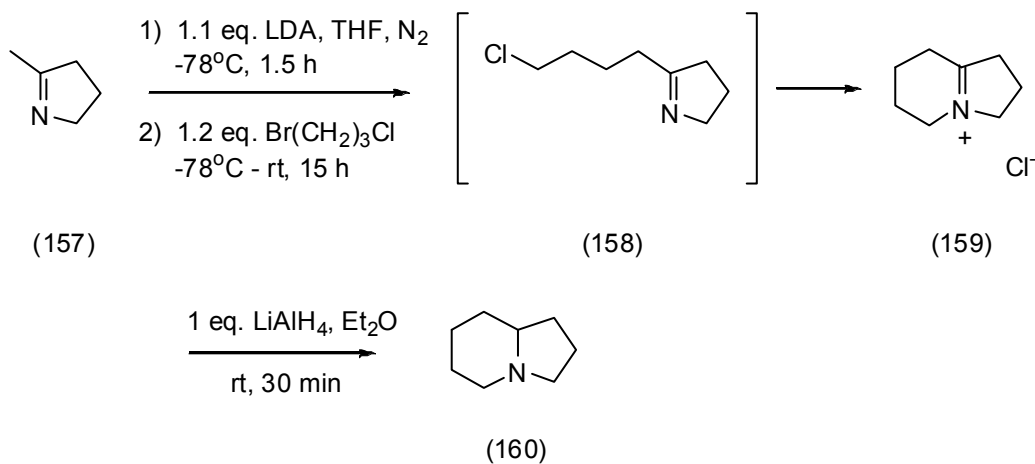
Scheme 38

The 2-acylcycloalkane-1,3-diones (152) undergo cyclocondensation reactions with simple cyclic azomethines (153) and (154), which act as Schiff bases to form triheterocyclic compounds (155) and (156) (Scheme 39).⁴⁸ This synthesis is applied to the formation of both naturally occurring compounds and their synthetic analogues.



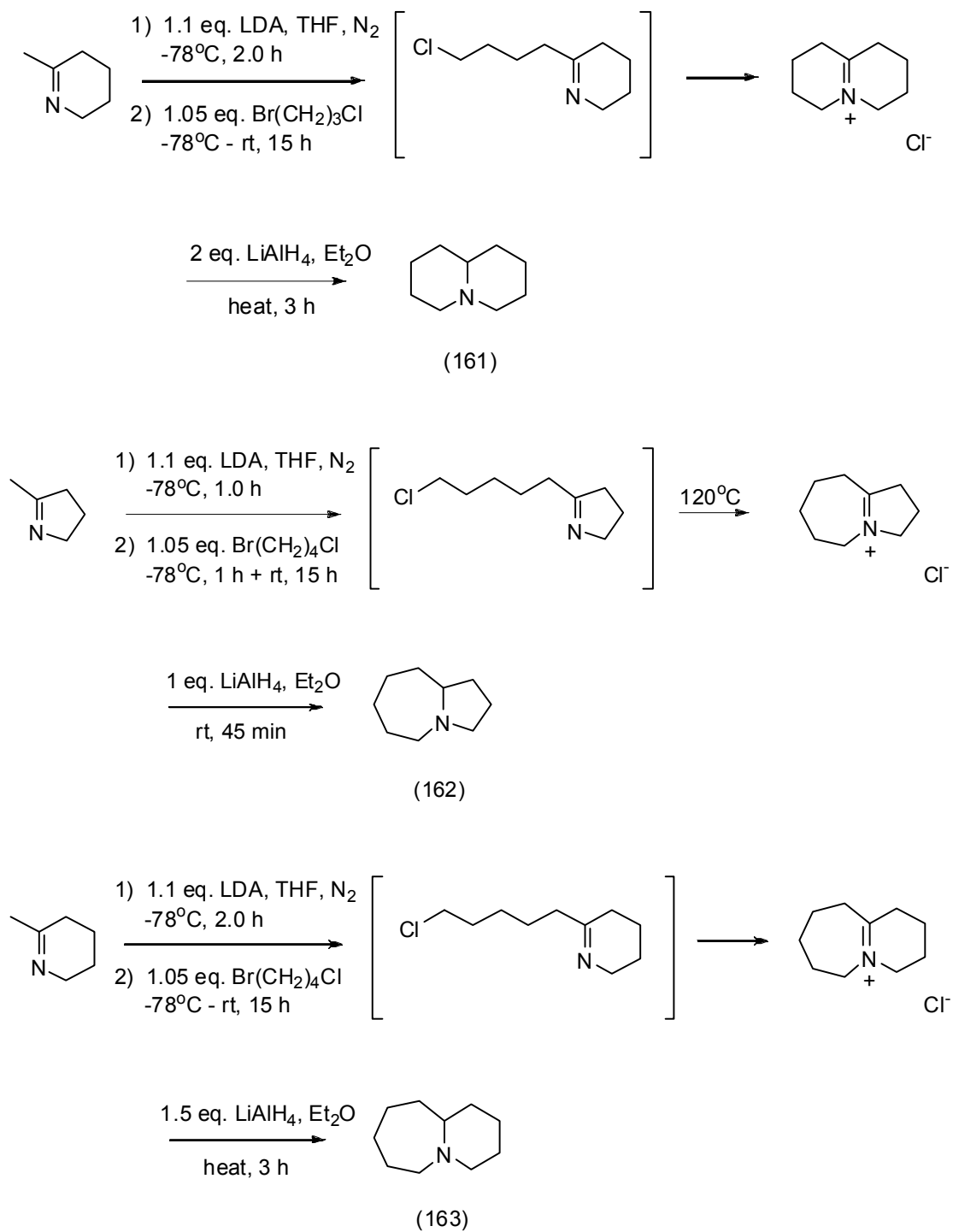
Scheme 39

The indolizidine and quinolizidine nuclei are readily accessible from the corresponding cyclic imine.⁴⁷ In a reaction with LDA, deprotonation of cyclic imine (157), followed by addition of a haloalkane results in the formation of a bicyclic iminium salt (159) via intermediate (158). This compound then undergoes reduction using lithium aluminium hydride, to yield the desired indolizidine adduct (160) in 59% yield (Scheme 40).



Scheme 40

In analogous reactions the corresponding quinolizidine (161), pyrroloazepine (162) and azabicyclo[5.4.0]undecane (163) bicyclic systems were also synthesised in yields of 68 – 70% (Scheme 41).⁴⁷



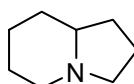
Scheme 41

3.0 The alkaloids

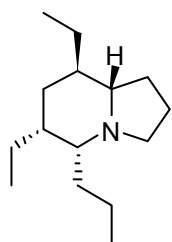
The synthesis of alkaloids^{49,52-56} continues to attract significant attention in the literature, with new approaches to the vast array of natural product targets being developed on a regular basis. Synthetic chemists continue to discover novel and interesting routes to these compounds, particularly because of their usefulness in a wide array of medical applications including the development of new anticancer, antiviral, antibiotic and neurotransmission agents.⁵⁷⁻⁶⁰ Synthetic routes to many of these compounds are highly sought after due to the tiny amounts of the natural product that are available from the natural source. Many classes of alkaloids are alkylated and hydroxylated compounds,^{61,62} and provide interesting regio and stereochemical challenges to synthetic chemists which must be addressed when designing routes to the synthesis of the natural compounds. A brief overview of four classes of alkaloids, the indolizidines, pyrrolizidines, pyrroloazepines and homotropans will be discussed in the following section, along with some selected examples from the literature. This section is not intended to be a comprehensive survey, but is designed to serve as an introduction to the four classes of alkaloid that are of relevance to this thesis.

3.1 Indolizidine alkaloids

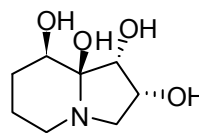
The indolizidines⁴⁹ are a large class of alkaloid, ubiquitous in nature. These have been isolated from a wide variety of natural sources, including extracts from the skin secretions of certain poison frogs,^{63,64} where they are used as part of the animals' defence mechanisms to guard against predation. The core azabicyclic nucleus (164) forms the framework for what are often referred to as "simple" indolizidines. These can be simple alkyl or hydroxy containing compounds^{61,62} such as indolizidine 223A (165) and swainsonine (166) or more complex polysubstituted ones such as cyclizidine (167) and pumiliotoxin (168).⁴⁹



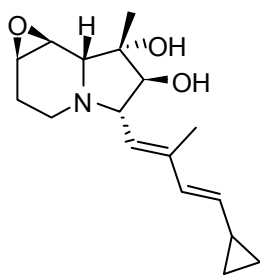
(164)



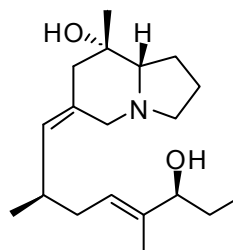
(165)



(166)

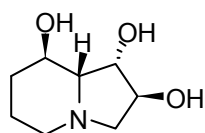


(167)

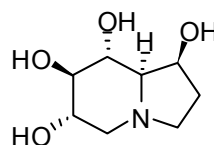


(168)

Many of the indolizidines exhibit significant pharmacological properties^{52,53,64} and are routinely tested for use in the treatment of a wide range of diseases. For example, 2-epi-swainsonine (169) and castanospermine (170) exhibit glycosidase inhibitory properties and have been tested for the treatment of cancer, HIV and immunological disorders.⁶² Some of these types of compounds have been shown to inhibit the infectivity of retroviruses, especially the human immunodeficiency virus (HIV), which has resulted in the synthesis of a spate of analogues in an attempt to find a useful compound to combat this particular virus.

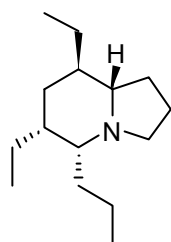


(169)

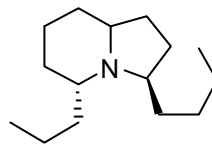


(170)

Some alkylated indolizidine alkaloids, for example indolizidine 223A (165) and (-)-indolizidine 223AB (171) exhibit non-competitive blockage of nicotinic receptor channels and consequently have the potential for use in the treatment of neurotransmission diseases.⁶⁵



(165)

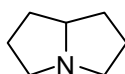


(171)

It is this medical usefulness coupled with their interesting structure that makes indolizidines current targets for synthesis and explains why they continue to attract significant attention from many synthetic chemists. The absolute configuration of the stereogenic centres is a crucial factor for the biological activity of the indolizidines. There is a considerable number of existing synthetic routes to indolizidine compounds, that have been developed over a number of years many of which are now commonly used for the synthesis of new indolizidine targets, the detail and explanation of which are beyond the scope of this thesis.

3.2 Pyrrolizidine alkaloids

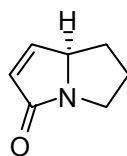
As with their indolizidine counterparts, the pyrrolizidine alkaloids are a large class of nitrogen containing compounds, which contain the azabicyclic nucleus (172).^{57,66,67} In nature they are more commonly found in certain plants and insects, acting as anti-feedants that not only guard against predation, but also serve as starting materials for the biosynthesis of attractants/deterrents.⁶⁸



(172)

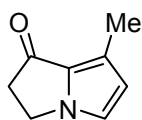
Many of the naturally occurring pyrrolizidine alkaloids are similar in structure to that of compound (173) and have been found to exhibit hepatotoxic, mutagenic and carcinogenic properties, which are thought to be related to the presence of the double bond within the molecule.^{57,69} Carbonyl groups, often in the form of a lactam moiety, are another common feature,^{57,70,71} and thus

this provides synthetic chemists with a natural lead in the pursuit of synthetic analogues of the naturally occurring compounds.

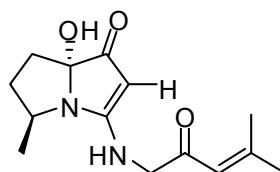


(173)

Alkaloids (174) and (175) are examples of naturally occurring pyrrolizidines that contain similar structural characteristics to that of compound (173).⁷⁰

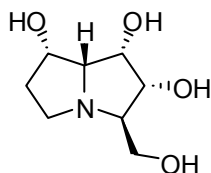


(174)

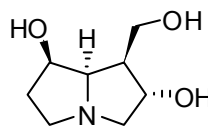


(175)

There are also examples of the pyrrolizidine alkaloids that contain hydroxyl functionality⁷¹ similar to that of the corresponding indolizidines (section 3.1). The alkaloids (+)-1-epiaustraline (176) and (-)-rosmarinicine (177) are examples of polyhydroxylated pyrrolizidines and research into these types of compounds is rapidly becoming important in the field of glycobiology, due to the potential for them to mimic the behaviour of glycosidase inhibitors. This is due to similarities in the structural characteristics of the respective pyrrolizidines to that of glycosidase inhibitors. These include an array of hydroxyl groups that could fit into the active site of an enzyme and also a basic nitrogen at physiological pH which plays an important role in the glycosidic processes. This area of research is of particular interest to chemists and biologist alike, as glycosidase inhibitors are known to play a key role in diseases such as diabetes, AIDS and cancer. Thus, the ability to access new therapeutic targets for such diseases would be potentially advantageous in finding new treatments. Access to polyhydroxylated pyrrolizidines and suitable synthetic precursors is thus of some importance.

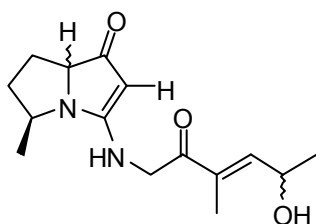


(176)

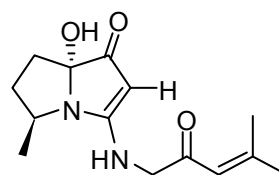


(177)

The naturally occurring pyrrolizidines (178) and (175) are thought to have potential use in the treatment of cancer and have been made available by total synthesis.⁷⁰ This is extremely advantageous in the area of medical research as it provides a continuous and reliable source of the naturally occurring compound that would otherwise be in short supply, allowing a wider range of research to be carried out on such compounds, and allowing access to analogues.



(178)

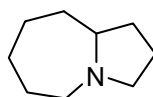


(175)

There are many other areas of pharmacological and biological research involving the pyrrolizidine alkaloids. These include their use as tools to probe the interaction of acetylcholine-related enzymes⁷² and their receptors, which have implications both in the area of neurotransmission diseases and also in understanding the chemical defence in plants and animals against herbivores and predators. Studies carried out on animals have shown that some pyrrolizidine alkaloids have an effect on the heart and may serve as a model for human heart disease associated with pulmonary hypertension. There have also been studies into certain pyrrolizidine alkaloids that are converted into compounds that are known toxic metabolites and have potentially harmful effects on the liver, leading to liver disease in humans.⁵⁷

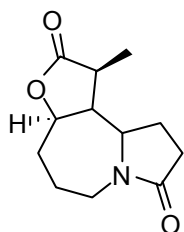
3.3 Pyrroloazepine alkaloids

The azabicyclic nucleus shown in structure (180) forms the structural framework for what are a smaller and less well-known sub-class of alkaloid, the pyrroloazepines.^{59,73a}

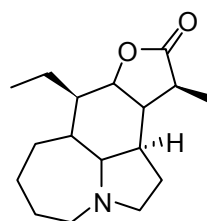


(180)

These alkaloids have been isolated from plant roots, stemoamide (181) and stenine (182) being two relatively well documented examples of natural products that contain the azabicyclic skeleton (180) and are found in the roots of *stemona tuberosa*. Several such pyrroloazepines have been used for many years in Chinese traditional medicine, in the treatment of a range of common respiratory ailments, including bronchitis and tuberculosis. Some have also been found to have potent insecticidal activity.⁷⁴

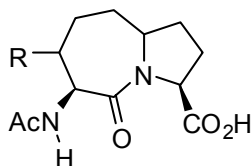


(181)



(182)

Other pyrroloazepines such as bicyclic lactam (183) have attracted the attention of synthetic chemists⁷³ because they have the potential to be used as protease inhibitors, which are implicated in a range of diseases such as such as cystic fibrosis and rheumatoid arthritis. Due to the restricted nature of the of the amide bonds in such compounds and the amino acid side chains, these compounds act as peptide mimics, and much work devoted to the synthesis of such compounds is underway.^{73a}

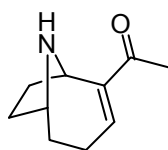


(183)

3.4 Homotropane alkaloids

The homotropanes^{72,75} are a large class of alkaloids that have attracted considerable attention from the scientific community over the past three decades. In particular, synthetic chemists have been interested in finding new methods for the formation of the homotropane nucleus, while medicinal chemists have found the powerful biological activity of the compounds very intriguing.⁷⁶

Anatoxin-a (184)⁷⁷ is a well known example of a homotropane alkaloid containing a 9-azabicyclo[4.2.1]nonane ring system. This compound was first isolated in the 1970s^{77b} from certain strains of freshwater blue green algae and is commonly referred to as “Very Fast Death Factor”, due to its extremely toxic nature. Indeed, ingestion of even the smallest amounts of this compound has proven fatal to wildlife and humans alike, resulting in rapid death.⁷⁸



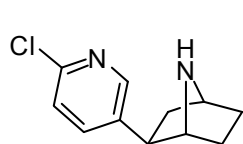
(184)

It has been deduced that anatoxin-a mimics the neurotransmitter acetylcholine, acting as a potent agonist for the nicotinic acetylcholine receptor nAChR.⁷⁹ It is this characteristic which has been attributed to the potent and highly toxic nature of this compound. Anatoxin-a lacks susceptibility to degradation by the enzyme acetylcholine esterase allowing it

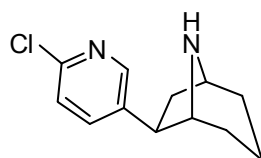
to remain available to overstimulate muscle tissue, which results in respiratory paralysis and ultimately death.^{77a}

Despite the extremely toxic nature of anatoxin-*a*, chemists have not been deterred from extensive research into this compound primarily because acetylcholine deficiency is implicated in a range of brain disorders such as Alzheimer's disease.^{77a} It is envisaged that the pursuit of analogues of anatoxin-*a* may result in the discovery of therapeutically useful compounds, which can be used as acetylcholine replacements for the treatment of brain disorders, but which are crucially far less toxic in nature than anatoxin-*a*.

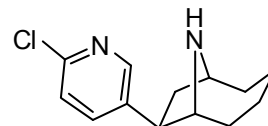
The naturally occurring alkaloid epibatidine (185) was isolated from the skin of the Ecuadorian poison frog in 1992.⁸⁰ It is the first natural product to be based on the 7-azabicyclo[2.2.1]-heptane ring system, attracting the attention of synthetic chemists due to its considerable analgesic properties, and also because it has been shown to act at the nAChR. This is in contrast to many other analgesics which function at the opioid receptor. As with anatoxin-*a*, epibatidine has been found to be extremely toxic and this has prompted the search by chemists for structurally related analogues of which compounds (186), a homoepibatidine and (187), a bis-homoepibatidine are examples. The latter is also a homotropane. It is hoped that such compounds will show increased discrimination between receptor sub-types, retaining useful pharmacological properties but showing lower toxicity.⁷⁵



(185)

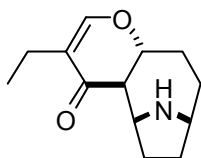


(186)



(187)

The natural product pinnamine A (188) is another example of a homotropane alkaloid and has also attracted attention as a nAChR agonist of interest in neurological research. Once more, such interest together with the scarcity of its natural supply have made the synthetic routes to this natural product of importance to the scientific community.⁸¹



(188)

Results and Discussion

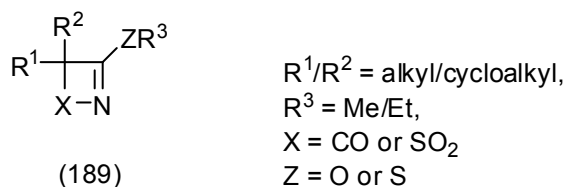
Chapter 2: Discussion

4.0 Aim of the Research

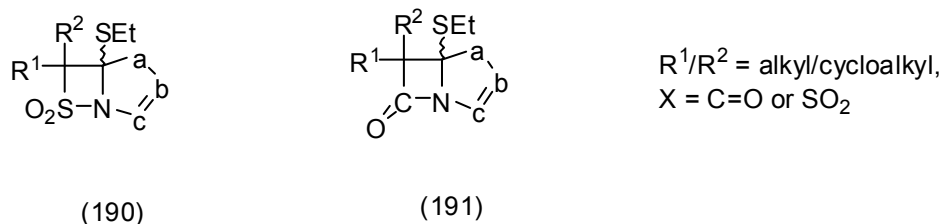
The original aim of this project was to explore the chemistry of imidate/thioimidate containing 4-membered ring heterocycles and to use them as cycloaddition precursors for the synthesis of novel bicyclic β -sultams and β -lactams as analogues of biologically relevant systems, such as penicillins.

The products have potential use as antibiotics and also as serine protease inhibitors, which are implicated in a range of diseases such as cystic fibrosis and rheumatoid arthritis.⁸² The structures targeted in this thesis are designed to function as cross-linking agents at the enzyme active site, as will be discussed below.

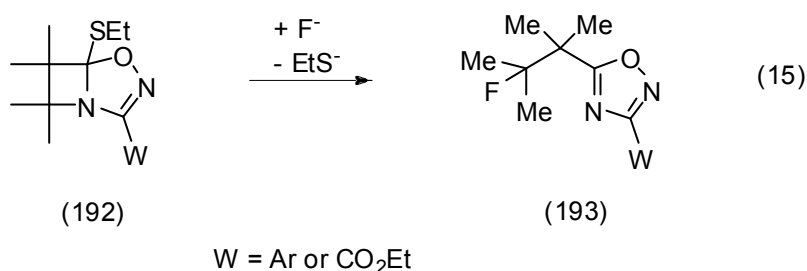
In this project the initial targets for synthesis are the monocyclic 1-azetin-4-ones and the 1,2-thiazetin-1,1-dioxides (189).⁸³



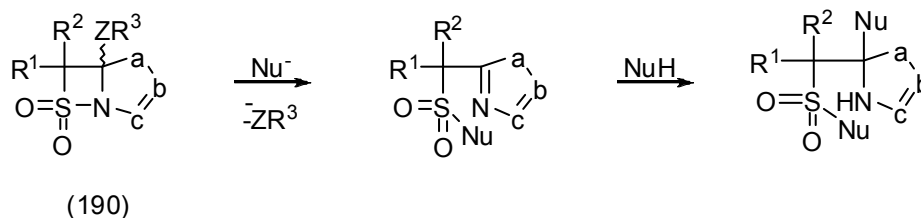
Their potential as cycloaddition precursors²⁷ for the synthesis of novel bicyclic β -sultams (190) and β -lactams (191) will then be explored. This investigation will focus particularly on their behaviour towards cyclopropenones and 1,3-dipoles. If access to the bicyclic β -sultams and β -lactams is successful, it will then be possible to investigate the reactivity of such adducts as potential serine protease enzyme inhibitors.



The literature precedent²⁶ for the latter aspect of the work is based on the known reactivity of β -lactams and β -sultams which undergo ready ring opening. It is also interesting to note that there is an example of this reaction from the literature whereby the formation of oxadiazoles (193) occurs in high yields of 71-87% from the corresponding nitrile oxide adducts (192), a reaction which does not even require the β -lactam/ β -sultam ring to be present. (equation 15).²⁶



The initial aim of this thesis was to examine adducts (190) and (191) in order to verify their reactivity with nucleophiles,^{26,27b} for example:

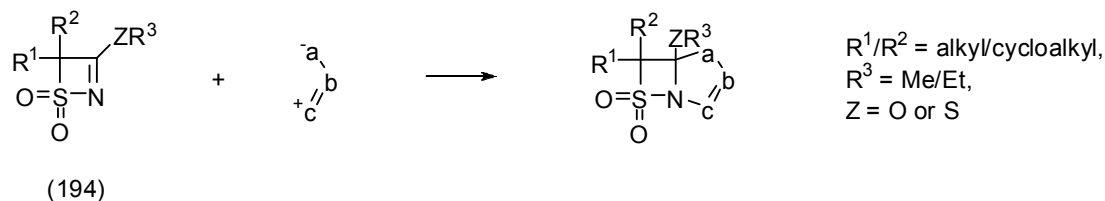


It is the possibility of the nucleophilic addition^{27b} being performed by an enzyme that offers these structures the potential to be inhibitors and, if a second nucleophilic residue attacks, cross-linking agents.

As will be explained in the discussion of this thesis, the aims of the project became subject to change from that of this original proposal, due to a failed synthesis and new work which came to light during the course of the project which resulted in the generation of a series of interesting and novel results in small ring heterocyclic chemistry.

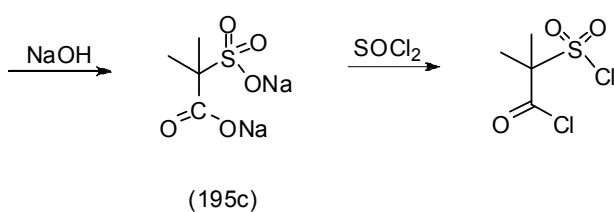
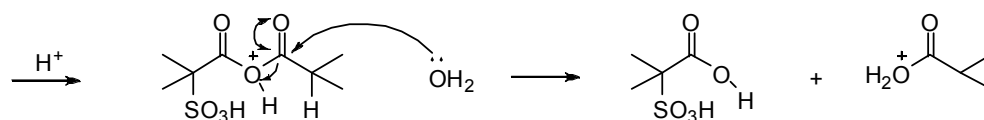
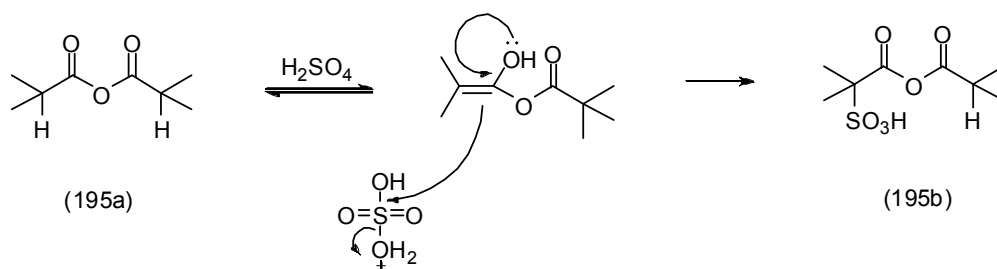
4.1 Attempted Synthesis of 1,2-thiazetidin-1,1-dioxides

In keeping with the original aims of the work (see above) the first task was to investigate the following reaction (Scheme 42).

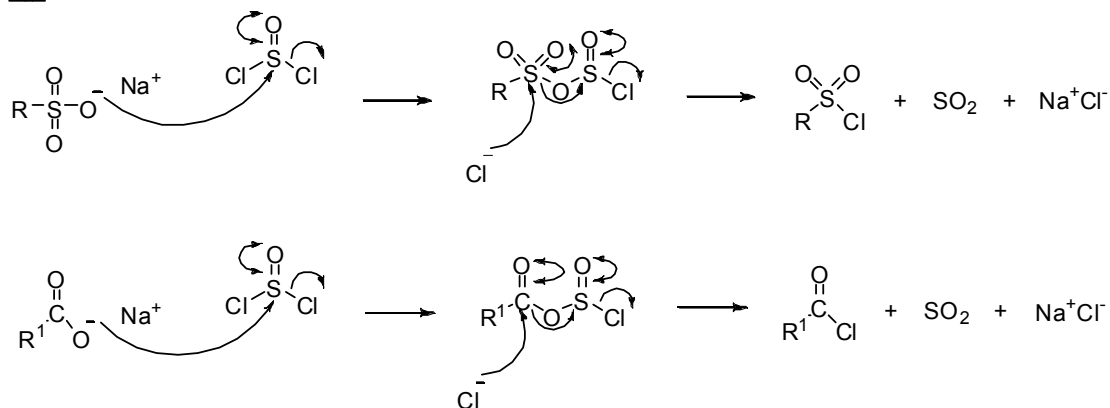


Scheme 42

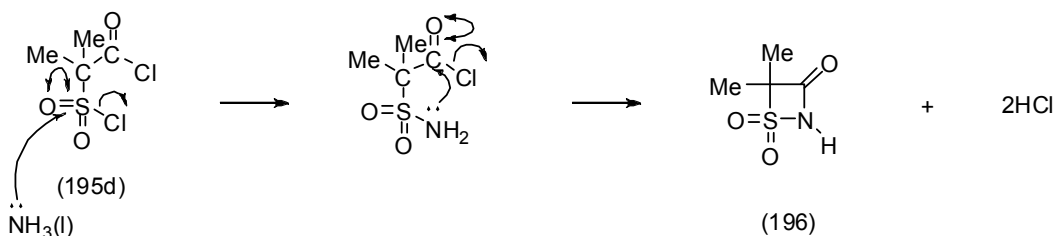
This necessitated a synthesis of molecule (194) which we hoped to make from the *O/S*-alkylation of the 1,2-thiazetidin-3-one (196). It was envisaged molecule (196) could be made as shown in Scheme 43.⁸⁴ Thus, reaction of an acid anhydride (195a) with sulfuric acid gave the sulfonic acid (195b), which formed via the formation an intermediate enol and attack of sulfuric acid. This process was followed by the hydrolysis of the other carbonyl and the formation of a disodium salt in the presence of the base, sodium hydroxide. The second part of the synthesis involved a double chlorination, using thionyl chloride, of the sulfonate and carboxylate fragments respectively, to yield the dichloride via the usual chlorination mechanism shown in Scheme 43. The third and final stage of the mechanism involves ring closure of the molecule with ammonia at -78°C , where the dichloride addition was carried out drop-wise, in order to prevent formation of either a ring opened structure or the product of double addition of ammonia, giving a non-ring closed product. This reaction successfully yielded 1,2-thiazetidin-3-one (196) in 61% yield. The final product (196) showed the expected spectroscopic characteristics.⁸⁴ These include the infrared, which showed a carbonyl at 1748 cm^{-1} typical of the carbonyl stretch of an oxo- β -sultam. The NMR also showed a ratio of 6:1 protons representative of the two-methyl groups and the N-H proton, as expected. The mass spectroscopy data also showed the main peak of 148 (ES-) at 100% indicating the loss of one proton from the molecule, also as expected.



Via



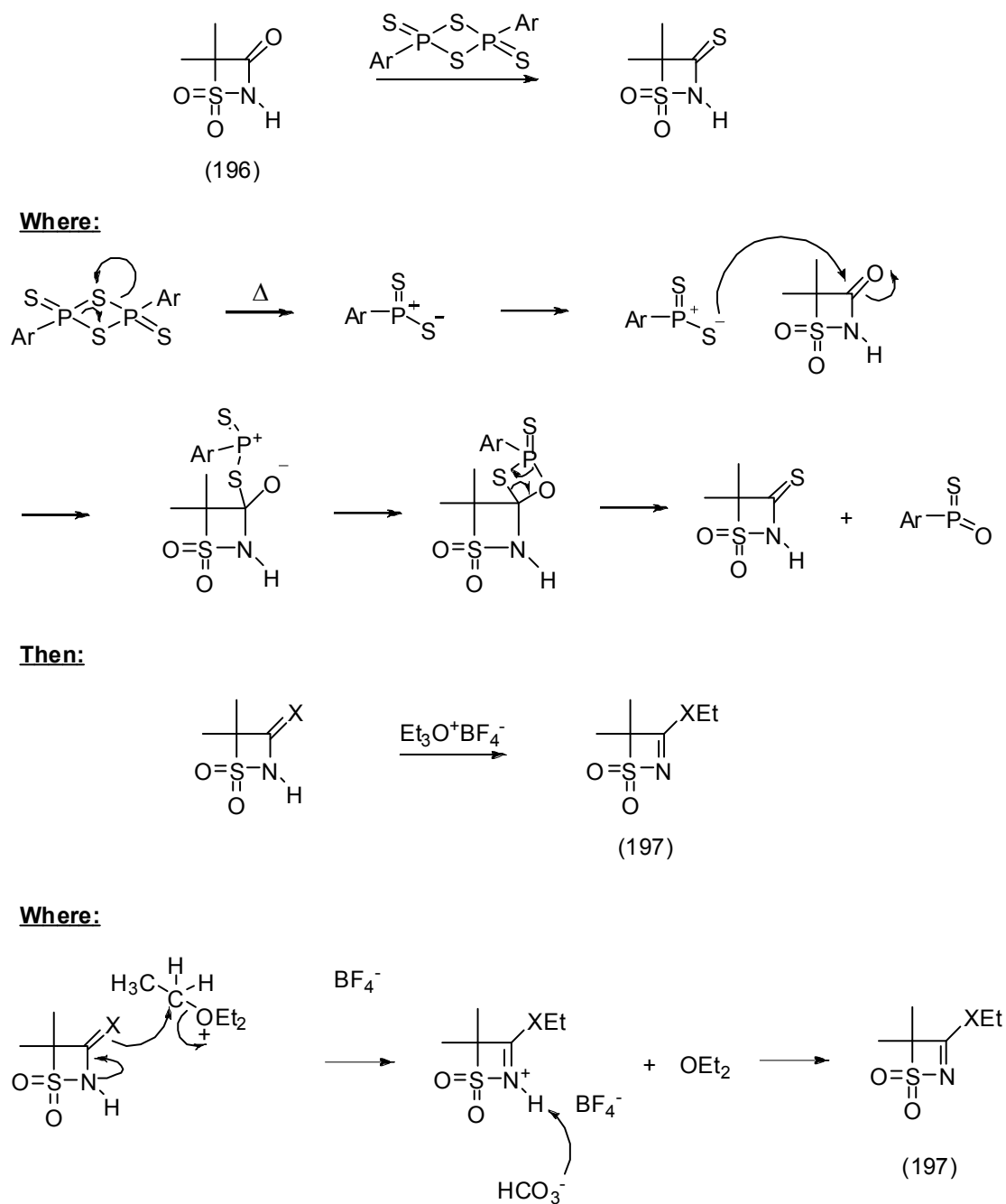
Final Step



Scheme 43

With the saturated 1,2-thiazetidin-3-one (196) successfully made, the next aim involved either thiation with Lawesson's reagent and alkylation with Meerwein's reagent, to yield the 1,2-thiazetidin-1,1-dioxide (197, X=S), or direct

O-alkylation with Meerwein's reagent, to yield the 1,2-thiazetin-1,1-dioxide (197, X=O) as shown in Scheme 44.²⁷

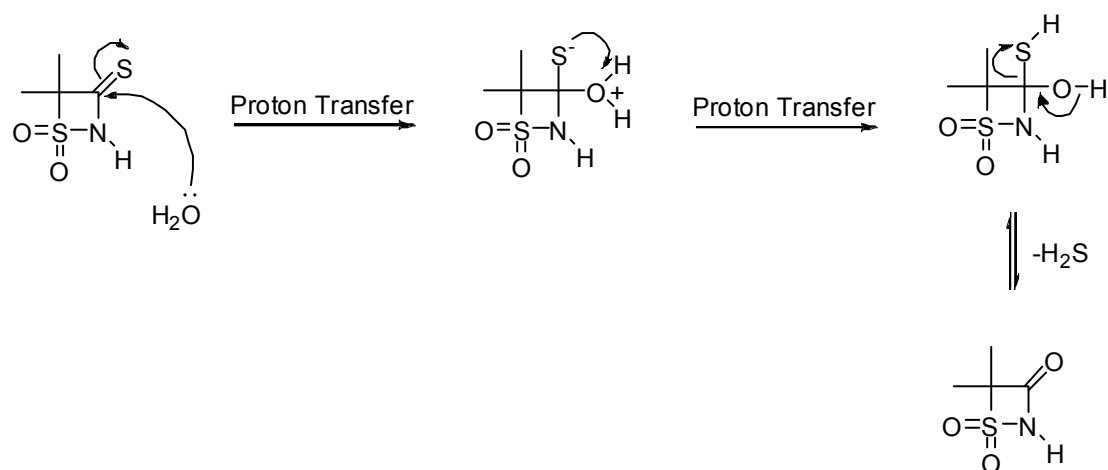


Scheme 44

In the event, compound (196) would neither alkylate nor thiate. Interestingly reaction with Lawesson's reagent appeared by TLC and infra-red spectroscopy to be successful with TLC showing a clear new product and IR showing the loss of the distinctive oxo-sultam C=O stretch. However, all

attempts towards subsequent isolation and purification of the material by column chromatography resulted only in the recovery of starting material.

One possible conclusion is that the product formed during the course of the Lawesson's reagent reaction had upon isolation and purification hydrolysed to give back 1,2-thiazetidin-3-one (196). This finding was confirmed by infrared, NMR and MS data which all showed the starting material was the only product isolated from the purification process even though it was not present prior to attempted purification. A plausible mechanism for this reaction to proceed through is shown in Scheme 45.



Scheme 45

Given the failure to form the 1,2-thiazetidin-1,1-dioxide necessary for cycloaddition via this route, it was decided next to explore the possibility of forming a 1-azetin-4-one⁸³ (198) and exploring it as a cycloaddition precursor. Before embarking upon this task, which would involve lengthy synthetic approaches (the 1-azetin-4-one is a rare heterocycle), it was decided to study the more readily available 1-azetine system (199).^{26,27a}



(198)



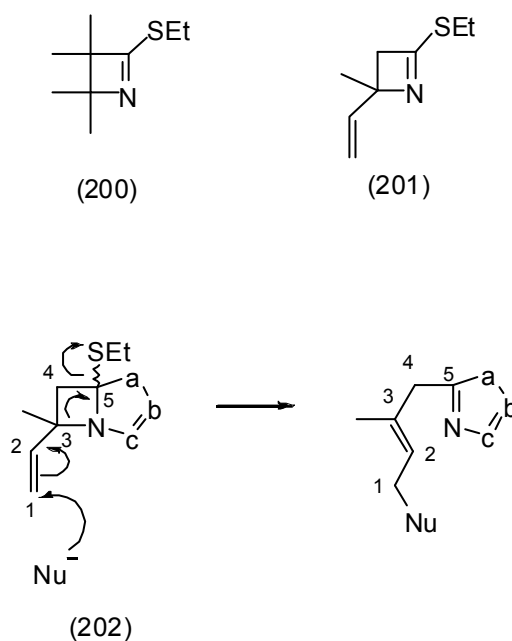
(199)

The reason for studying a model system was to verify that the Lawesson's/Meerwein's sequence discussed for the 1,2-thiazetidin-3-one (196) was indeed viable and also to explore further the chemistry of any bicyclic systems that might be formed once the 1-azetines had reacted.

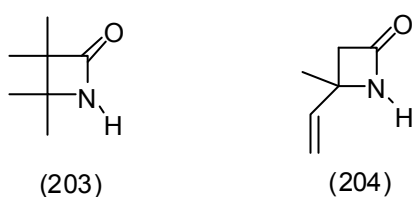
4.2 Synthesis of Model and Novel 1-Azetines and Their 1,3-Dipolar Cycloadditions

The systems selected for further study were the known 1-azetine (200) and the novel 1-azetine (201). These systems were chosen because:

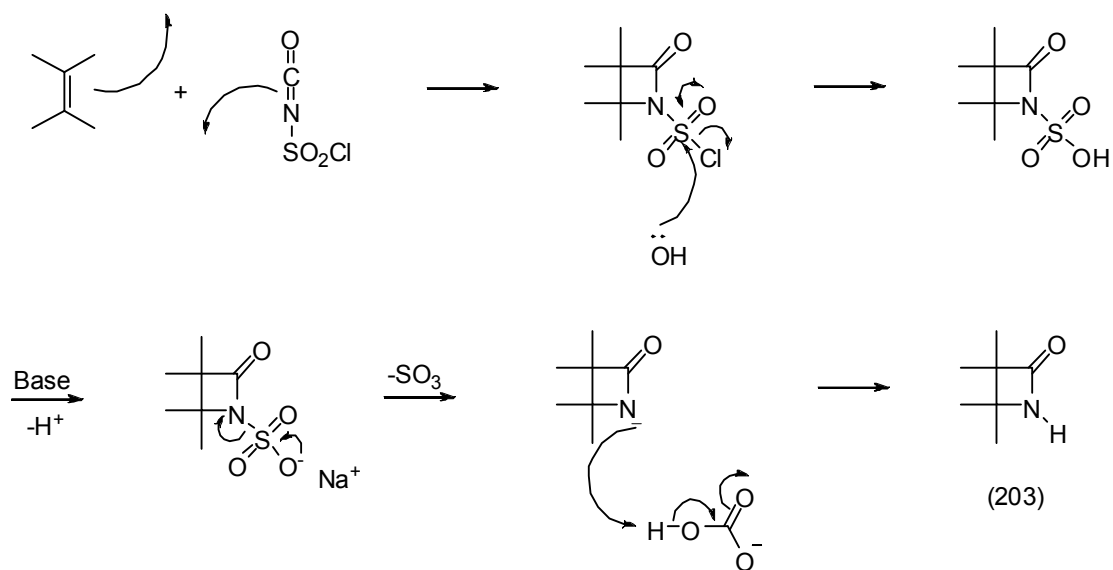
- (a) Synthesis of molecule (200) has been documented in the literature,^{26,27b} and its synthesis would therefore provide the necessary confidence that the Lawesson's and Meerwein's steps were reliable.
- (b) Compound (201) is a novel 1-azetine whose synthesis has not appeared in the literature prior to this thesis. The presence of an exocyclic double bond in this molecule was chosen as it presented some interesting potential features since the cycloadducts (202) of these systems may undergo a potentially interesting S_N2' reaction in the presence of nucleophiles offering them a unique way of ring opening.



1-Azetines (200) and (201) should be accessible from the corresponding 1-azetidiones (β -lactams) (203) and (204)⁸⁵. Such (β -lactams) are most obviously made by [2+2] cycloadditions^{27a}. This section of the thesis will describe the synthesis of compound (203) and its use as a precursor for the synthesis of the 1-azetine (200) and will move on to describe the cycloadditions of this 1-azetine. The synthesis and use of 1-azetine (201) will be described in the next section of the thesis.



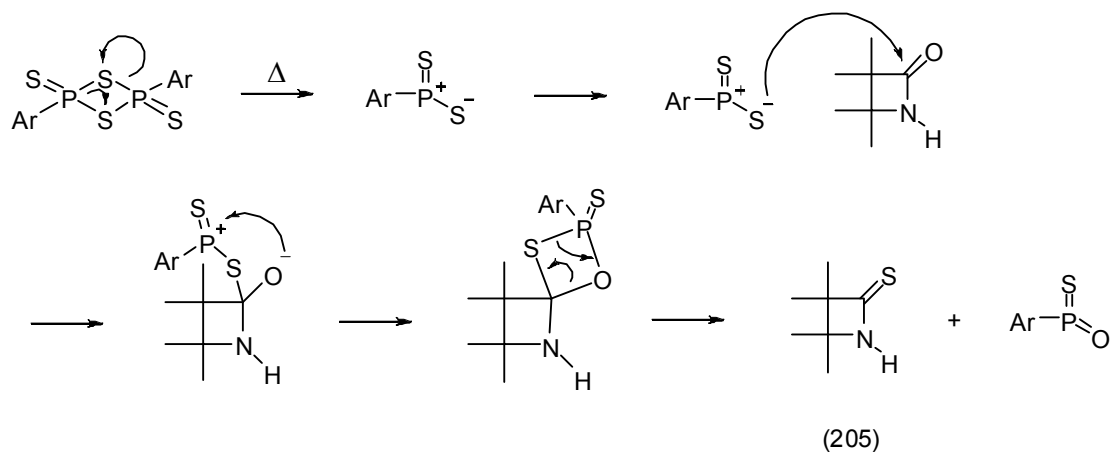
Scheme 46 shows the details for the synthesis of compound (203). The mechanism shows a [2+2] cycloaddition reaction involving concerted attack of chlorosulfonyl isocyanate by 2,3-dimethyl-2-butene. Base is then added to the reaction mixture and the chlorine of the SO_2Cl is replaced with a hydroxyl group. This facilitates the removal of SO_3 from the ring and subsequent protonation of the nitrogen to yield the desired β -lactam (203) in 96% yield as shown in Scheme 46.



Scheme 46

Compound (203) showed the expected spectroscopic characteristics²². For example the infrared spectrum showed a carbonyl at 1750 cm^{-1} typical of the carbonyl stretch of a β -lactam. The NMR also showed the four methyl groups and the N-H group in a ratio of 6:6:1, with the N-H proton in its characteristic position at $6.5\ \delta$. The mass spectroscopy data also revealed the presence of a peak at 128 (ES+) indicating the product had been formed.

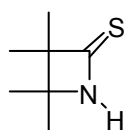
Before the cycloaddition could be performed, it was necessary to convert the β -lactam (203) in to a 1-azetine⁸⁵. Alkoxy azetines are known to be unstable and hence the thioalkyl azetines were selected as the preferred targets, since thioalkyl azetines are known²⁷ to be more stable. Therefore in keeping with the Lawesson's and Meerwein's sequence, compound (203) was thionated using Lawesson's reagent as shown in Scheme 47. Thermolysis of Lawesson's reagent breaks the sulfur-phosphorus bond and results in the formation of a ylidic intermediate. This species then acts as a nucleophile attacking the carbonyl of the beta lactam ring forming a tetrahedral intermediate which undergoes rearrangement via a four membered complex to yield thio lactam (205).



Scheme 47

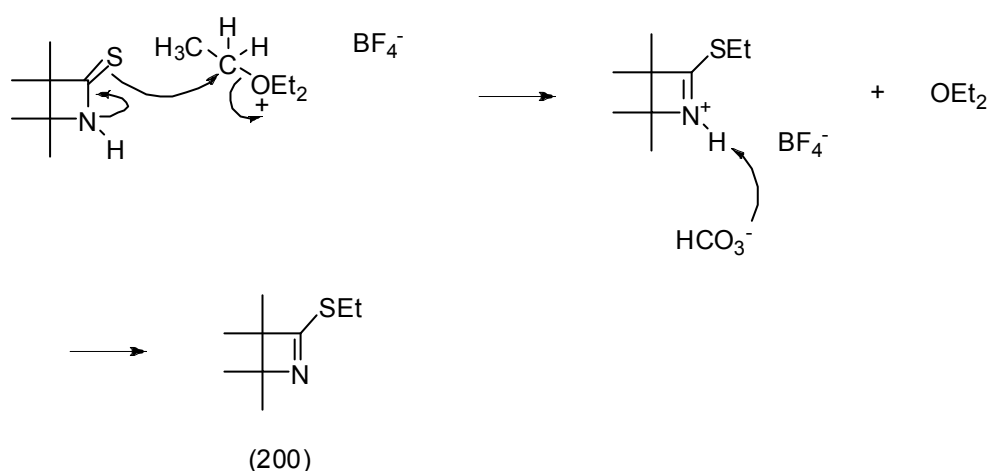
This process yielded thiolactam (205) in 90% yield and the compound showed the expected spectroscopic characteristics. The compound showed loss of the β -lactam carbonyl (IR and ^{13}C NMR) together with gain of C=S bond which showed peaks at 1498 cm^{-1} in the IR and a distinctive quaternary

carbon at 212 ppm in the ^{13}C NMR. High-resolution mass spectroscopy was also fully consistent with the assigned structure.



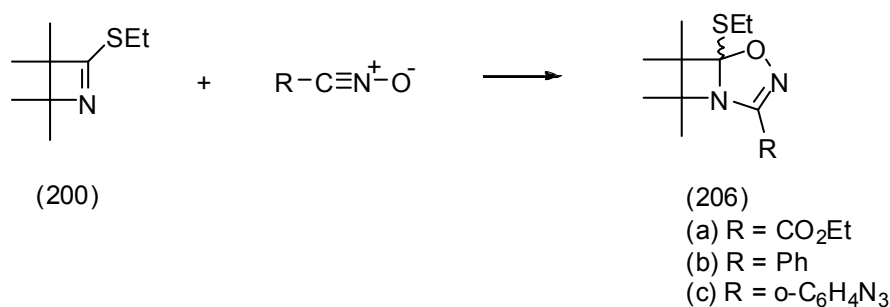
(205)

Compound (205) was converted into the thioalkyl azetine (200) using triethyloxonium tetrafluoroborate (Meerwein's reagent) in 44% yield via the mechanism shown in Scheme 48. The mechanism involves attack of triethyloxonium tetrafluoroborate by thiolactam (205), forming a C=N double bond within the four membered ring with ethylation of sulfur. This is followed by removal of the proton on nitrogen using basic work-up, resulting in the formation of thioalkyl azetine (200). The compound showed the clear presence of a new C=N bond through the IR at 1535 cm^{-1} and gain of an ethyl group (^1H NMR) and loss of N-H (^1H NMR and IR). The loss of the characteristic C=S signal in the ^{13}C NMR and the appearance of a new quaternary carbon at 187 ppm confirmed that S- and not N- alkylation had occurred. High-resolution mass spectroscopy data was also fully consistent with the assigned structure.



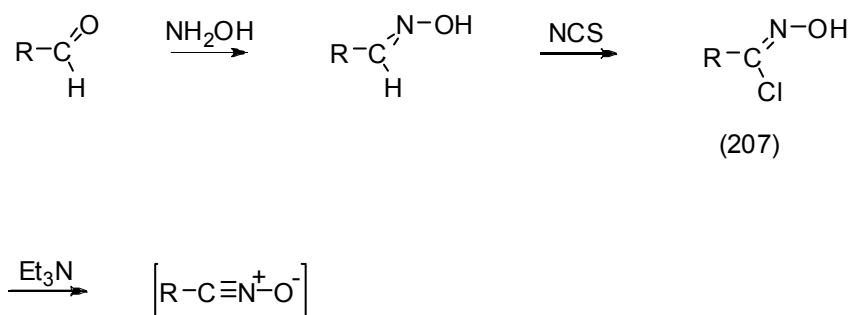
Scheme 48

With the model 1-azetine (200) successfully made using the Lawesson's/Meerwein's route, the next task was to investigate the reaction of this compound towards 1,3-dipoles. Scheme 49 shows a general equation for the synthesis of a small series of cycloadducts (206), all prepared from the 1,3-dipolar cycloaddition of nitrile oxides to 1-azetine (200) in 60-70% yield.



Scheme 49

The dipole, a nitrile oxide, was generated^{27a,86} *in situ* by reacting triethylamine with a chloroxime as shown in Scheme 50. Nitrile oxides are usually generated by dehydrochlorination of the corresponding chloroxime (207) which in turn are made by chlorination of readily available oximes with N-chlorosuccinamide (NCS), as shown in Scheme 50.

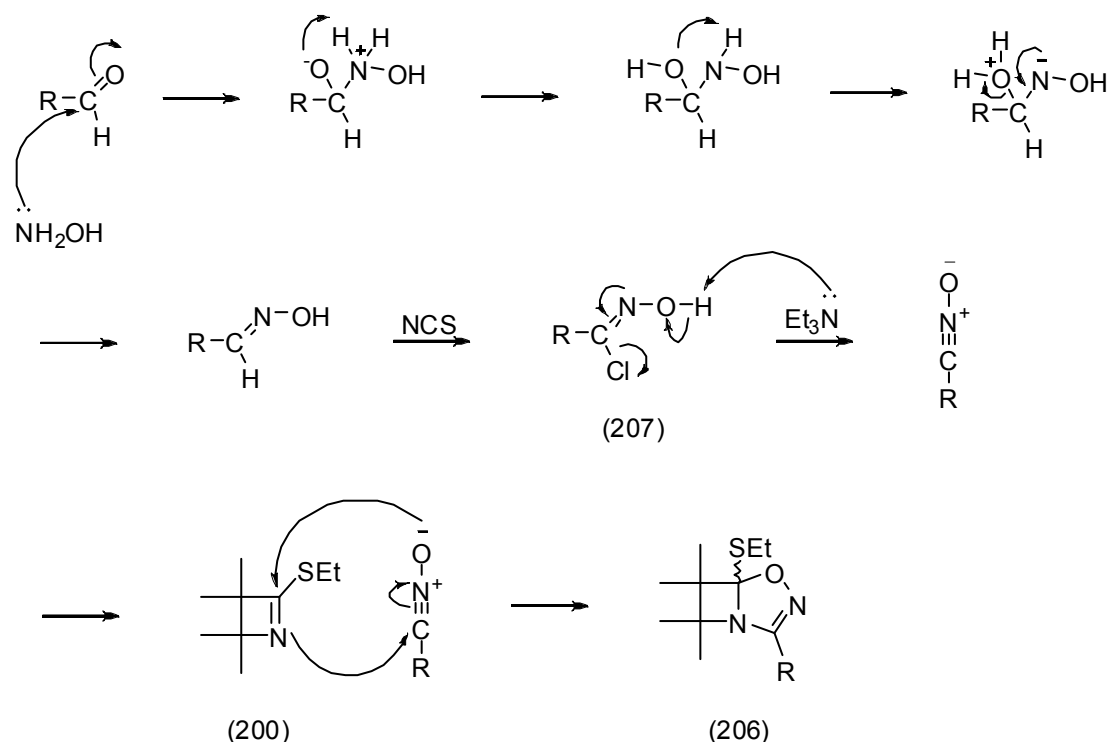


Scheme 50

The mechanisms involved during the synthesis of cycloadducts (206) and precursor (207) are shown in Scheme 51. The first step involves nucleophilic attack at the aldehyde carbonyl, by hydroxylamine (formed from the HCl salt under basic conditions of sodium acetate) in ethanol to produce the oxime.

In the second step of the reaction the oxime is treated with N-chlorosuccinimide (NCS) in dichloromethane, to yield chloroxime (207). The chloroximes were produced in good yield after purification using silica column chromatography. Subsequent spectroscopic analysis (IR and NMR) confirmed the structure of the products which showed loss of oxime C-H and confirmed the presence of the hydroxyl OH. Mass spectroscopy confirmed the take up of chlorine.

The final step of the reaction was a 1,3-dipolar cycloaddition in which the 1,3-dipole was generated *in situ*. In order to facilitate this, the reaction was carried out via slow drop-wise addition of the 1,3-dipole to the 1-azetine, allowing only a low concentration of oxime to react with the triethylamine and consequently preventing a competitive dimerisation reaction. The reaction yielded the desired cycloadducts (206) as the major product, in each of the three reactions studied.



Scheme 51

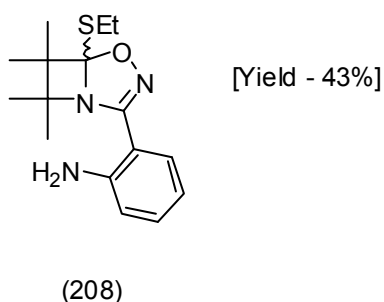
The three nitrile oxide cycloadducts (206a-c) were produced in yields of 60-70% (R = (a) CO₂Et, (b) Ph and (c) *o*-C₆H₄N₃), with each product having consistent spectroscopic data for the assigned structures. For example, for cycloadduct (206a, R = Ph) the ¹H NMR data showed the presence of the aromatic protons present on the phenyl ring in the appropriate ratio of 2:2:1. The four methyl groups appeared as four singlets and the CH₂ of the ethyl appeared as a very distinctive signal with each proton being split into a doublet of quartets (the CH₂ is diastereotopic).

For cycloadduct (206a, R = CO₂Et) the infrared showed the presence of a carbonyl at 1737cm⁻¹, typical of an ester. The ¹H NMR data showed the ethyl group of the carboxylic ester, with a characteristic splitting pattern, together with the expected diastereotopic resonances of the SEt group. The four methyl groups were again noted to be in different environments. The structure was further confirmed by high-resolution mass spectroscopy, and by ¹³C NMR spectroscopy. Compounds (206a and b) have been synthesised in the group previously,²⁶ but were not previously fully characterised, with ¹³C data, for example, being absent. A very distinctive feature in the ¹³C NMR was the bridgehead quaternary sp³ carbon, which appeared at 117 ppm.

Compound (206c) has not been synthesised previously and was accessed in order to later utilise the reactivity of the azide group. For cycloadduct (206c, R = *o*-C₆H₄N₃) the expected spectroscopic characteristics for the methyl groups and SEt in the ¹H NMR spectrum were observed together with the distinctive position of the bridgehead sp³ carbon at 117 ppm in the ¹³C NMR spectrum. Furthermore, the infrared showed the presence of the cumulated N₃ group at 2130cm⁻¹ which is typical of an azide. The high resolution mass spectroscopy data was also consistent with this being the desired product.

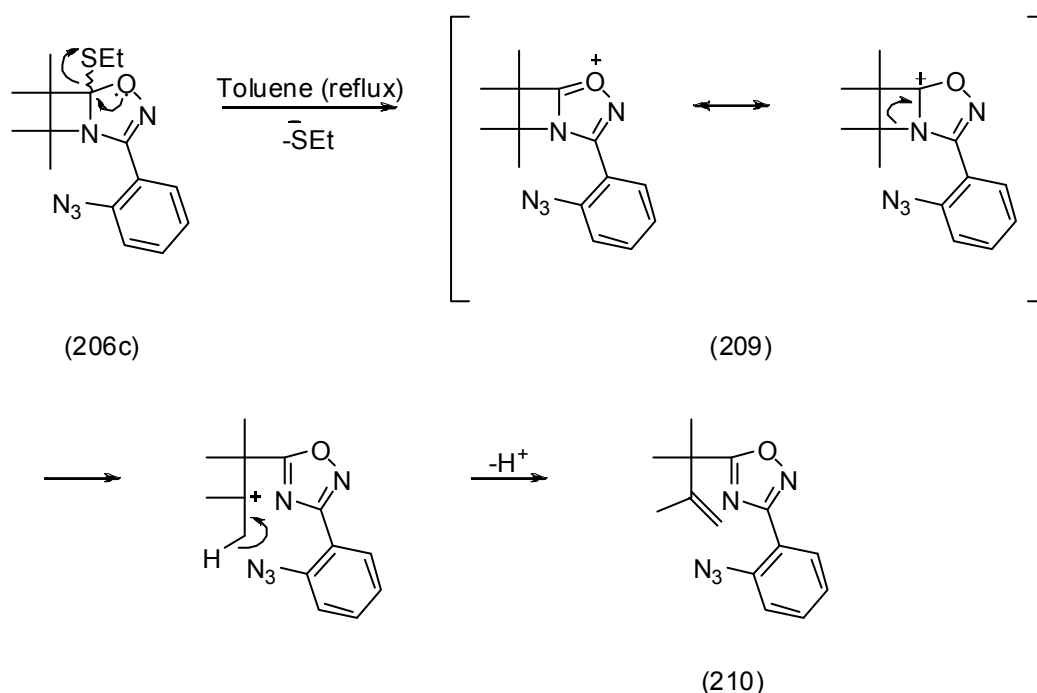
With each of the bicyclic adducts (206a-c) successfully synthesised, the next task was to investigate the potential reactivity of these compounds, something that had never been fully done in the past. Therefore, it was decided to carry out a series of thermolysis reactions, using organic solvents to determine what, if any, reactivity the respective compounds would exhibit.

Adduct (206c, R = *o*-C₆H₄N₃) was subject to thermolysis by heating at reflux in DMF. This, it was hoped, would form the nitrene, by loss of nitrogen from the azide, which might then initiate some interesting chemistry. Careful monitoring by tlc showed a clear new product had formed after 4-5 hours. In the event only the amine (208) could be isolated in 43% yield – i.e. the product of azide reduction, indicating that the nitrene had formed, but had abstracted protons from the solvent to form the amine, rather than undergoing insertion. The intact nature of the bicycle was shown by the presence of the distinctive four methyls and diastereotopic ethyl in the ¹H NMR and the quaternary sp³ bridgehead carbon at 116 ppm in the ¹³C NMR. Infra-red showed no azide absorbance together with a new absorbance at 3476 cm⁻¹ for the amine group.



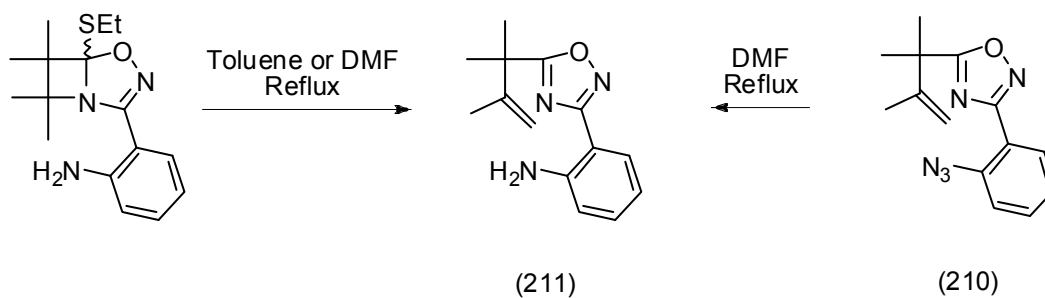
Interestingly, when compound (206c) was thermolysed in toluene, 1,2,4-oxadiazole (210) was isolated. A plausible mechanism for the formation of this product is shown in Scheme 52. This mechanism proceeds via the loss of SEt from the starting molecule to form a resonance stabilised intermediate. Ring-opening gives strain relief and forms a tertiary carbocation, together with a fully conjugated heterocyclic ring (209). This intermediate subsequently undergoes ring opening and deprotonation to form the isolated 1,2,4-oxadiazole (210). This is the first example of a 1-azetine-nitrile oxide cycloadduct undergoing thermolytic ring opening. The compound showed the expected spectroscopic characteristics, for example, the ¹H NMR showed the presence of an alkene CH₂ group at 4.89δ, in conjunction with the loss of a methyl group from the original molecule. The ¹H methyl resonances showed as two singlets in the ¹H NMR in a 2:1 ratio. The aromatic protons remained unchanged in the ¹H NMR which was an indication that the benzene ring was still present. The characteristic SEt proton resonances had disappeared in

the ^1H NMR and the distinctive sp^3 quaternary bridgehead carbon was absent in the ^{13}C NMR which also showed an extra peak at 166 ppm attributed to the new $\text{C}=\text{N}$ bond. The azide group was still present in the IR spectrum, indicating that no reaction had taken place with this group on the molecule at this lower temperature. High-resolution mass spectroscopy data also confirmed the molecular ion peak which was fully consistent with the mass of the expected product.



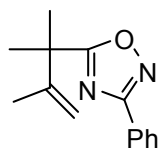
Scheme 52

Compound (208) on prolonged thermolysis in either toluene or DMF also gave a ring opened 1,2,4-oxadiazole (211) as shown in Scheme 53, via a rearrangement similar to that shown in Scheme 52. Compound (211) could also be formed by heating the azide (210) in DMF at reflux, again shown in Scheme 53. Compound (211) showed the expected spectroscopic characteristics with two methyl singlets in a 2:1 ratio, a vinylic methylene (^1H and ^{13}C). The amine appeared in the infra-red as a broad peak at 2982 cm^{-1} . The NMR confirmed the presence of the N-H protons in their typical position at 5.4 ppm. The high resolution mass spectroscopy data was fully consistent with structure (211).



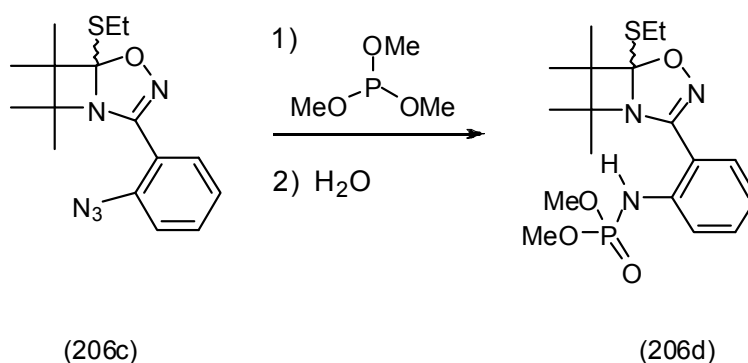
Scheme 53

Adduct (206a, R = Ph) gave 1,2,4-oxadiazole (212) in 80% yield on thermolysis in toluene, whereas adduct (206b, R = CO₂Et) was stable even to prolonged heating in boiling *o*-dichlorobenzene (182°C).

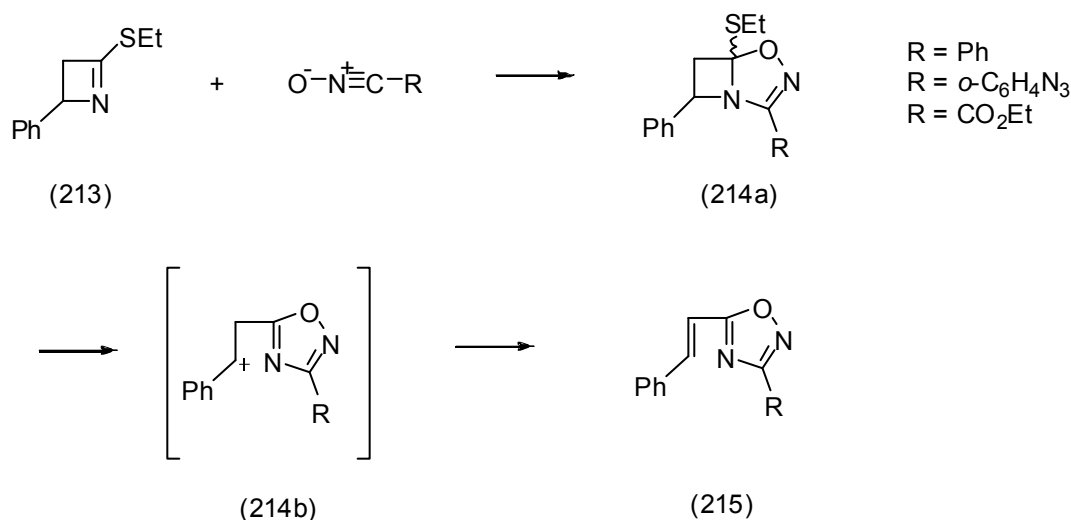


(212)

Compound (206c) was also converted into the corresponding the phosphoramidate (206d) using a Staudinger reaction shown below. Further heating in toluene over a period of 24 hours showed no change in the structure of compound (206d).

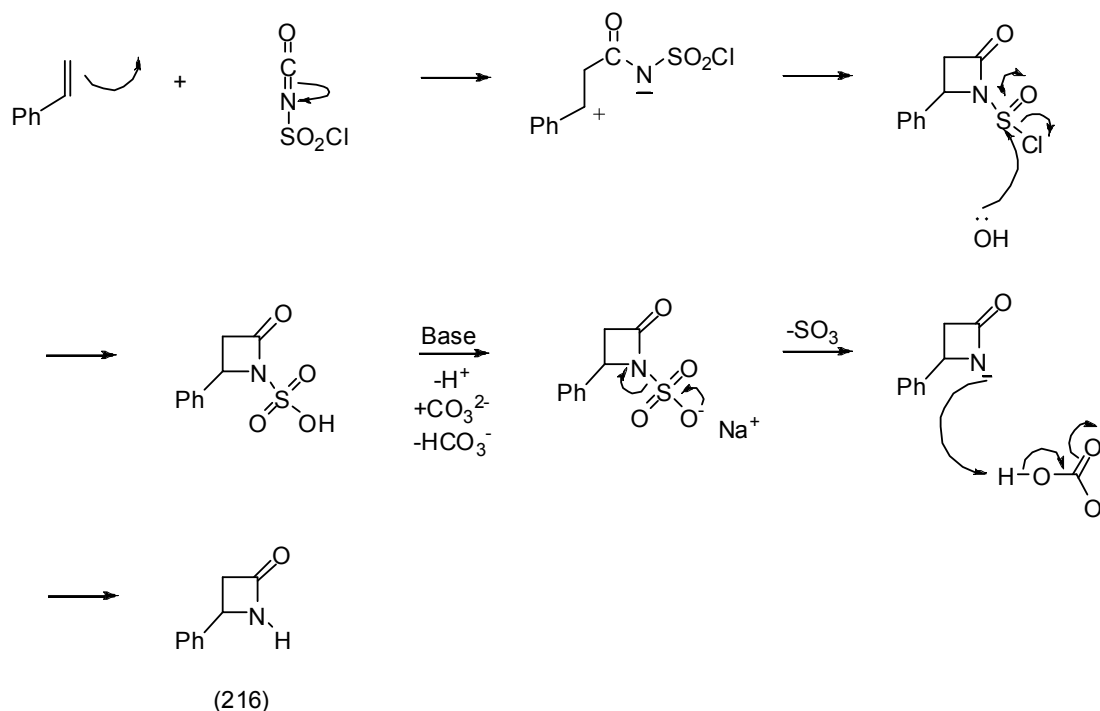


Having demonstrated that 1-azetine (200) undergoes reaction with nitrile oxides and that the adducts can also be subjected to further reaction under thermolysis, it was envisaged that other 1-azetines would also yield some interesting results. As will be discussed later, the 4-vinyl-1-azetine (201) was found to be inappropriate for such investigations due to competitive cycloaddition at the vinylic group. Therefore simple 1-azetine (213) was chosen for further study. It was anticipated that adducts of this compound would form the intermediate cation (214b) on thermolysis (in analogy to the mechanism shown in Scheme 52, above) and then go on to form the alkene (215) by proton loss. Such styrenyl 1,2,4-oxadiazoles are of great interest as Michael acceptors⁸⁷.



Scheme 54

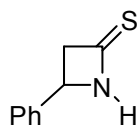
This necessitated the synthesis of molecule (213). This molecule was synthesised from the corresponding 1-azetidione (216) as shown in Scheme 55. It is useful on this occasion to consider the [2+2] reaction to be stepwise resulting in the formation of the more stable secondary benzylic carbocation, which is subsequently attacked by the nitrogen to yield the β -lactam ring. Base (carbonate) is then added to the reaction mixture and the chlorine of the SO₂Cl is replaced with a hydroxyl group. This facilitates the removal of SO₃ from the ring and subsequent protonation of the nitrogen to yield compound (216).



Scheme 55

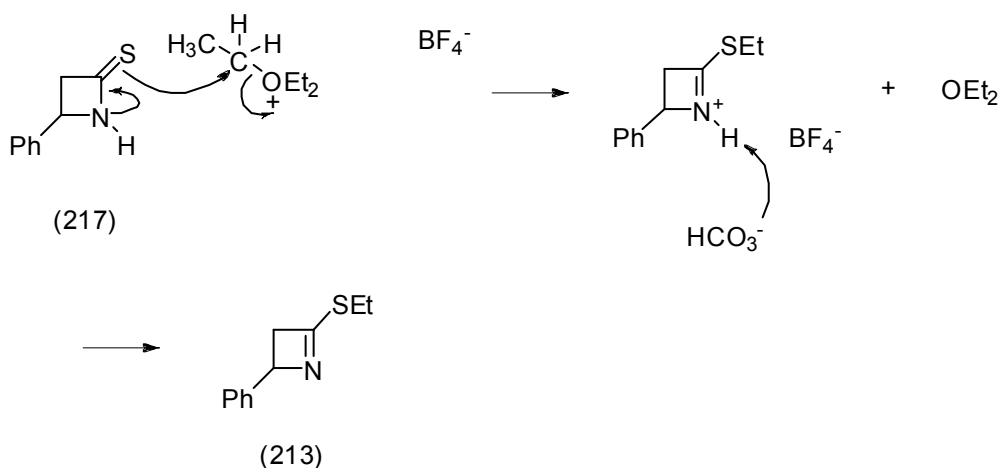
Compound (216) showed the expected spectroscopic characteristics. For example the infrared spectrum showed a carbonyl at 1758 cm^{-1} typical of the carbonyl stretch of a β -lactam. The ^1H NMR showed an N-H proton in the characteristic position of 6.7δ . The ^{13}C NMR showed the presence of four environmentally different aromatic carbons and also aliphatic methylene and methine carbons. Mass spectroscopic data revealed the presence of a peak at 148 (ES+) indicating the product had been formed.

In keeping with the Lawesson's and Meerwein's sequence, the next step of the synthesis involved the conversion of 1-azetidinone (216) into thiolactam (217) using Lawesson's reagent. The mechanism for this reaction is identical to that given in Scheme 47. This reaction successfully produced thiolactam (217) in 47% yield and the compound showed the expected spectroscopic characteristics, with loss of the β -lactam carbonyl (IR and ^{13}C NMR) together with gain of signals characteristic of the C=S group. High-resolution mass spectroscopy was also fully consistent with the assigned structure.



(217)

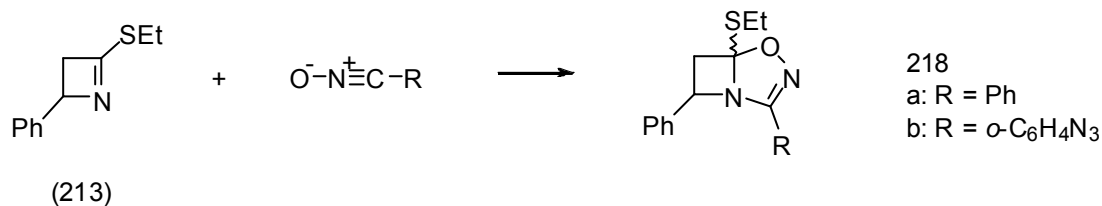
This compound was then converted into the thioalkyl azetine (213) using triethyloxonium tetrafluoroborate (Meerwein's reagent) in excellent yield, 86%, as shown in Scheme 56. The compound showed the clear presence of a new C=N bond through the IR and gain of an ethyl group (^1H NMR) and loss of N-H (^1H NMR and IR). High-resolution mass spectroscopy data was fully consistent with the assigned structure. Loss of the C=S signal in the ^{13}C NMR again confirmed the *N*-alkylation had not occurred.



Scheme 56

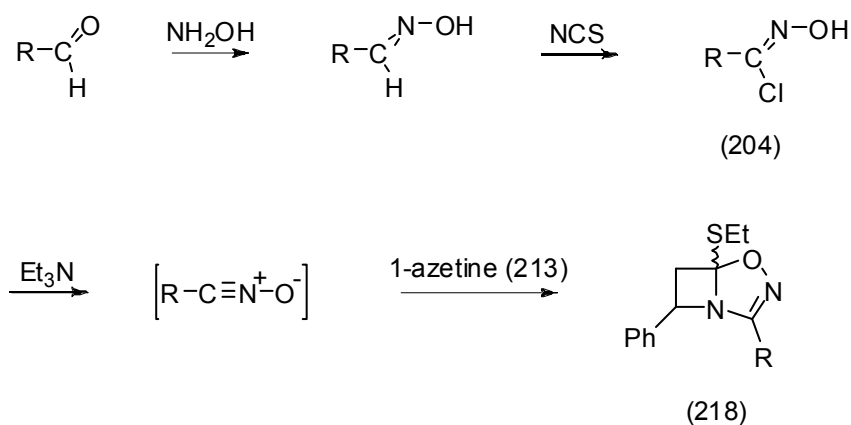
With 1-azetine (213) successfully synthesised using the Lawesson's and Meerwein's route, it was decided to investigate the reactivity of this compound towards nitrile oxides, in the same manner as the model 1-azetine (203).

Scheme 57 shows the general reaction for the synthesis of the cycloadducts prepared from the 1,3-dipolar cycloaddition of nitrile oxides to 1-azetine (213).



Scheme 57

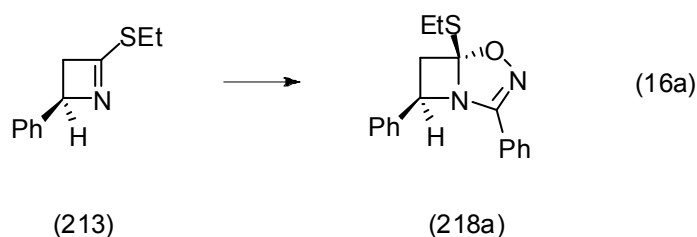
The nitrile oxide was again generated *in situ* via the reaction of triethylamine with a chloroxime as shown in Scheme 58, to yield the expected bicyclic adducts (218).



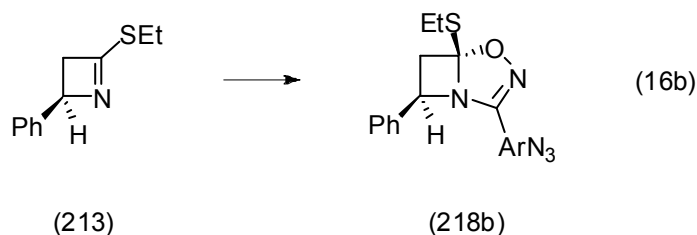
Scheme 58

The mechanism for the synthesis of cycloadducts (218) is identical to that shown in Scheme 51. Nitrile oxide cycloadducts (218a, R = Ph) and (218b, R = *o*-C₆H₄N₃) were produced in yields of 20 and 60% respectively, with each product having consistent spectroscopic data for the assigned structures. For example, for cycloadduct (218a, R = Ph) the ¹H NMR spectrum confirmed the presence of ten aromatic protons which is consistent with the expected structure containing two phenyl groups. The ¹³C NMR confirmed the presence of the two expected methylene groups and also the methyl and CH groups respectively. High resolution mass spectroscopy data was consistent and low resolution mass spectroscopy also showed the main peak of 311 (ES+) at 100% indicating the parent ion plus a proton, also as expected. ¹H and ¹³C NMR data clearly inferred a single diastereoisomer. The NOESY NMR spectrum revealed some interesting information about the

stereochemistry for the formation of the bicyclic adduct (218a). It was found that the H of the CHPh and the CH₂S groups were trans to each other: Ph-SEt interactions were seen whilst H-SEt interactions were absent. This infers that 1-azetine (213) is attacked from the face opposite to that of the existing Ph so that the incoming dipole is directed to attack the face of the molecule opposite to that of the existing Ph (equation 16a), with the consequence being that the Ph and SEt groups are *cis* to one another.

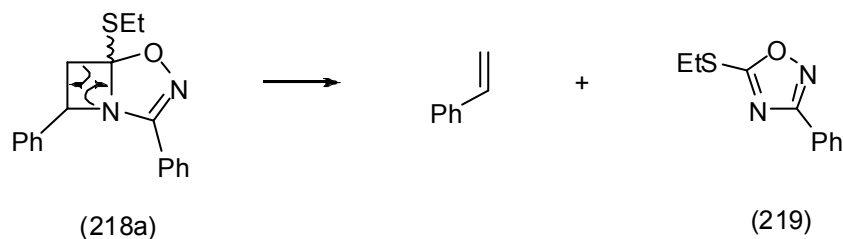


Cycloadduct (218b) also showed the expected spectroscopic characteristics, which include the infrared containing a peak at 2129 cm⁻¹ typical of an azide stretch within a molecule. The ¹H NMR spectrum confirmed the presence of nine aromatic protons together with the expected ethyl resonances and methine and methylene signals. The ¹³C NMR confirmed the presence of the two expected methylene groups and also showed the methyl and CH groups. Mass spectroscopic data also showed the main peak of 352 (ES⁺) at 100% indicating the gain of one proton to the molecule, also as expected, and accurate mass spectroscopic data was also fully consistent. Once again the NOESY spectrum confirmed that there were no methyl or CH₂S interactions with the H of CHPh which infers the 1,3-dipole (Ar-C≡N-O) is once again attacking from the face opposite to that of the existing Ph group (equation 16b), giving compound (218b) as a single diastereoisomer.



With both of the bicyclic adducts (218a and b) successfully synthesised, the next task was to investigate the potential reactivity of these compounds.

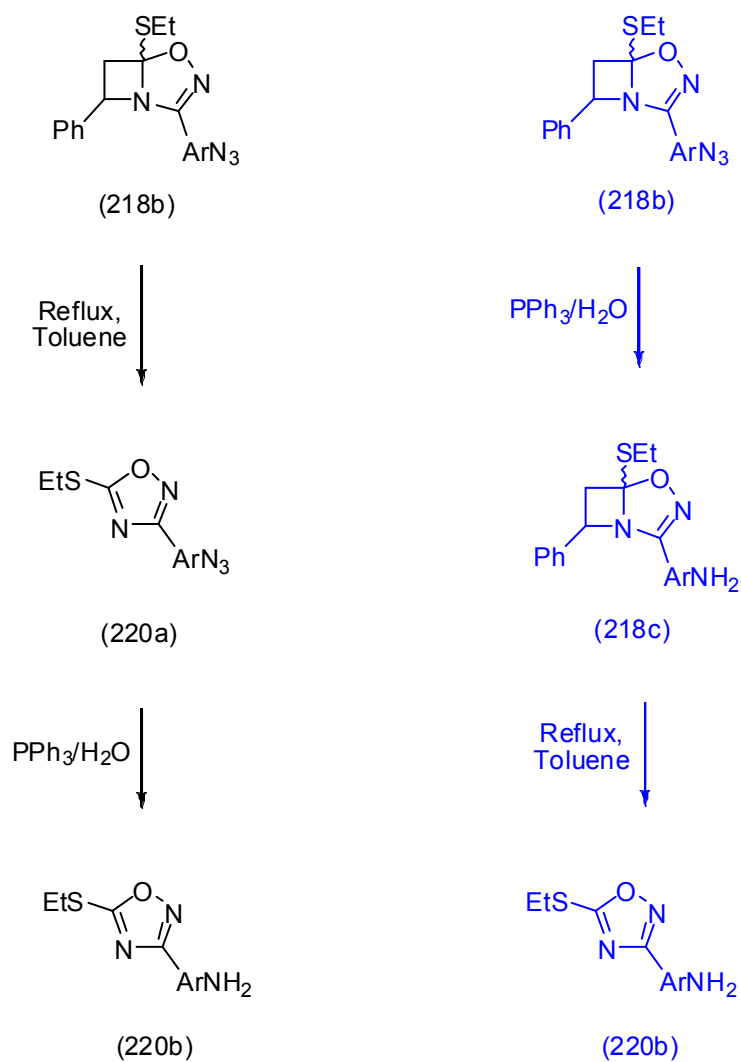
Thus, cycloadduct (218a, R = Ph) was subjected to thermolysis by heating in toluene at reflux. This resulted in the formation of compound (219) in 83% yield as shown in the mechanism in Scheme 59. The product presumably arises by virtue of a [2+2] cycloreversion with loss of styrene.



Scheme 59

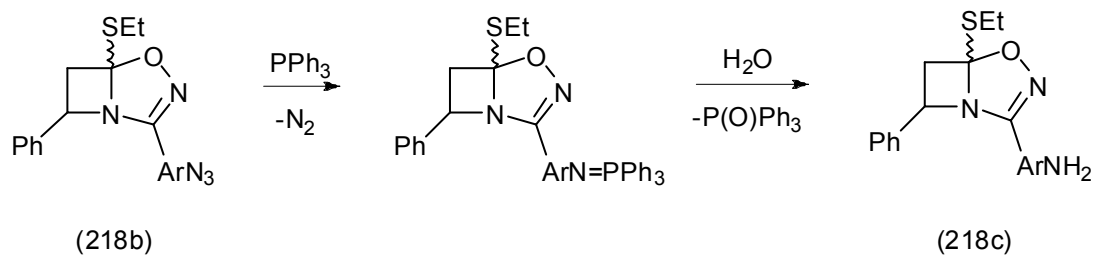
The monocyclic adduct (219) showed the expected spectroscopic characteristic. Thus the SEt group appeared as a simple triplet in the ^1H NMR spectrum, whilst the ^{13}C NMR spectrum showed the four phenyl carbon signals plus a further two quaternary carbons (at 138 and 127 ppm) for the 1,2,4-oxadiazole.

Scheme 60 shows the chemistry of adduct (218b) that was investigated. Adduct (218b, R = *o*-C₆H₄N₃) was first subject to thermolysis by heating in refluxing toluene. This resulted in the formation of a 33% yield of compound (220a), which was presumably formed by the same mechanistic route as that shown in Scheme 59.



Scheme 60

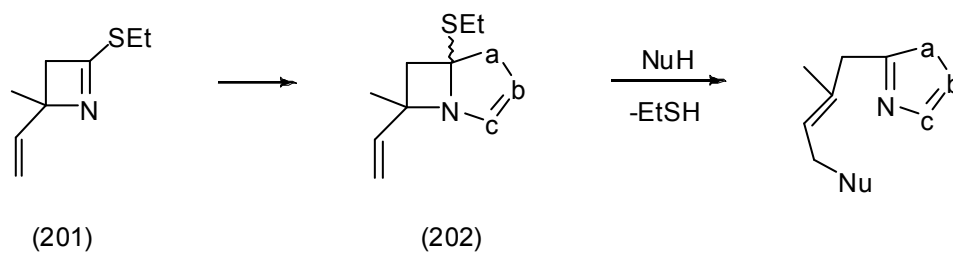
Compound (218b) was also converted into the corresponding amine (218c) using the Staudinger reaction⁸⁸, whereby the intermediate iminophosphorane (as shown in Scheme 61) was hydrolysed to the amine. Bicycle (218c) when heated in toluene (Scheme 60) underwent the same type of cycloreversion to furnish the fully conjugated 1,2,4-oxadiazole (220b). The same 1,2,4-oxadiazole could be obtained by performing the Staudinger-hydrolysis sequence upon the 1,2,4-oxadiazole (220a), also shown in Scheme 60.



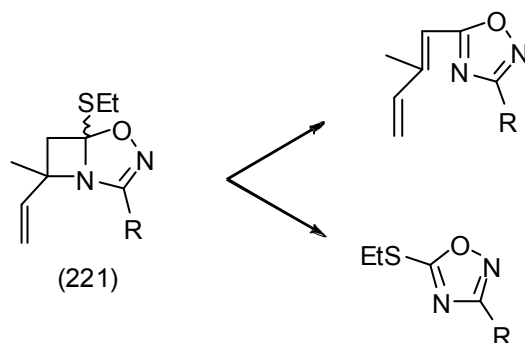
Scheme 61

4.3 Reactions of 4-Vinyl-1-azetines with 1,3-dipoles

As discussed at the beginning of section 2.3 the novel 4-vinyl-1-azetidine (201) was selected for study due to the possibility that its adducts (202) might undergo interesting reactions with nucleophilic species:

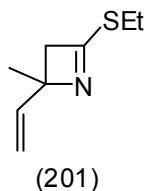


With this aim still in mind, but with processes paralleling those in Schemes 59/60 and Schemes 52/53 also now a possibility (as shown in Scheme 62) we moved on to investigate the synthesis of nitrile oxide 1,3-dipolar cycloaddition products 221.

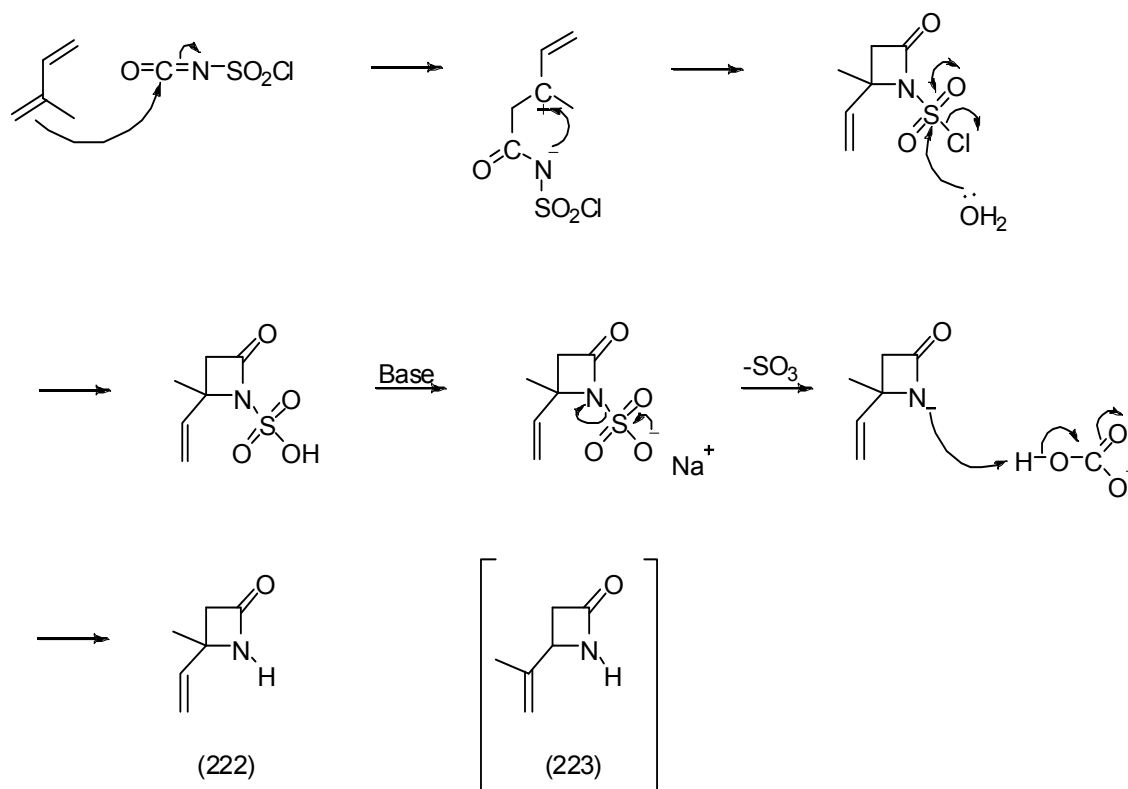


Scheme 62

In order to study such processes we needed to synthesise novel 1-azetidine (201). This was anticipated to again be available from the corresponding β -lactam which would be made as per Scheme 63^{25,89,90}.



Scheme 63 shows the mechanism for the synthesis of 4-methyl-4-vinyl-1-azetidine-2-one (222). The mechanism shows a stepwise reaction involving regioselective attack of chlorosulfonyl isocyanate by isoprene. This results in the formation of the more stable tertiary carbocation, which is subsequently attacked by the nitrogen to yield the β -lactam ring. Base is then added to the reaction mixture and the chlorine of the SO_2Cl is replaced with a hydroxyl group. This facilitates the removal of SO_3 from the ring and subsequent protonation of the nitrogen to yield compound (222) as shown in Scheme 63. The stability of the intermediate carbocation dictates the regiochemical outcome of this reaction. Compound (222) was formed in 75% yield, with no evidence for the formation of regioisomer (223).



Scheme 63

Compound (222) showed the expected spectroscopic characteristics. These include the infrared, which showed a carbonyl at 1744 cm^{-1} typical of the carbonyl stretch of a β -lactam. The ^1H NMR spectrum showed the methyl group, an aliphatic methylene group and the N-H proton, as expected. The $\text{CH}=\text{CH}_2$ unit was present in the ^1H NMR spectrum as a very characteristic set of peaks. The ^{13}C NMR spectrum showed a vinylic CH_2 together with a vinylic CH. The presence of a quaternary sp^3 carbon and the absence of a quaternary sp^2 alkene confirmed the regiochemical outcome of the reaction. The mass spectroscopic data also showed the main peak of 112 (ES-) indicating the loss of one proton from the molecule, also as expected.

When 4-methyl-4-vinyl-1-azetidin-2-one (222) was thiated using Lawesson's reagent²⁹, the reaction successfully yielded the corresponding thione (224) in excellent yield (equation 17). The compound showed the expected spectroscopic characteristics including the presence of a $\text{C}=\text{S}$ bond (IR and ^{13}C NMR) and the associated loss of the $\text{C}=\text{O}$ bond. The exocyclic alkene

CH₂ and CH protons could again clearly be seen at 5.2 and 6.1 δ (¹H NMR), with characteristic splitting as shown in Figure 1.

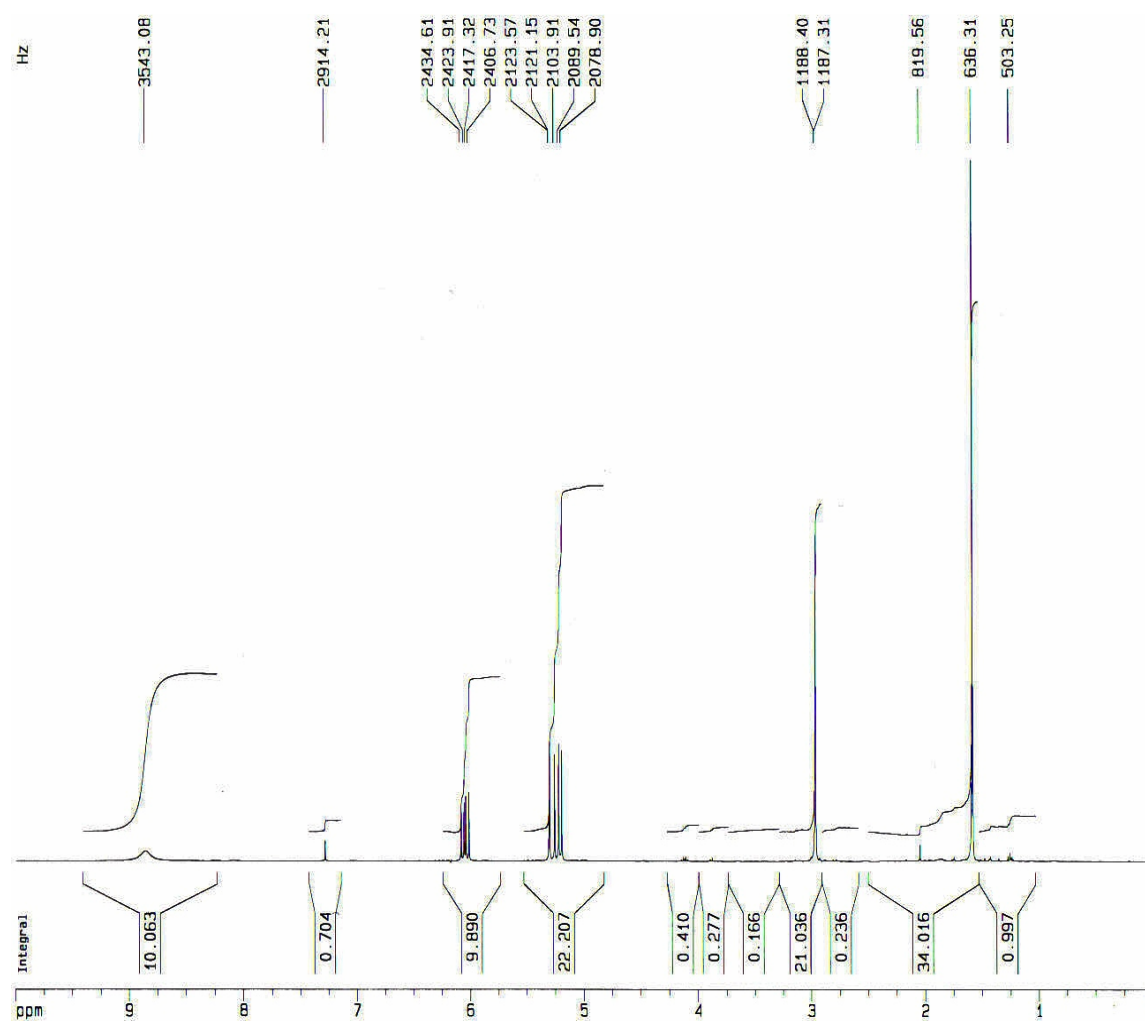
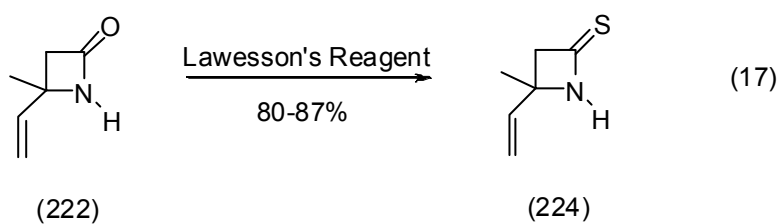
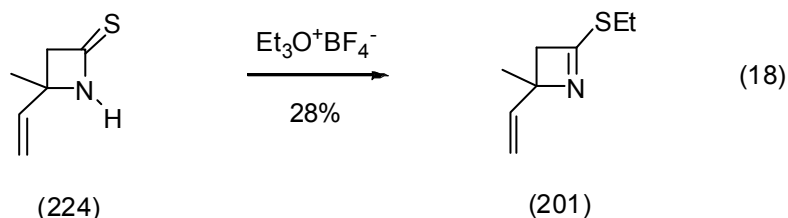


Figure 1

Mass spectroscopy confirmed the structure with the molecular ion peak at m/z 127, and with fully consistent high resolution mass spectroscopy.



Thione (224) was then converted into 1-azetine (201) using triethyloxonium tetrafluoroborate⁹¹ (Meerwein's reagent) in 28% yield as shown in equation 18.

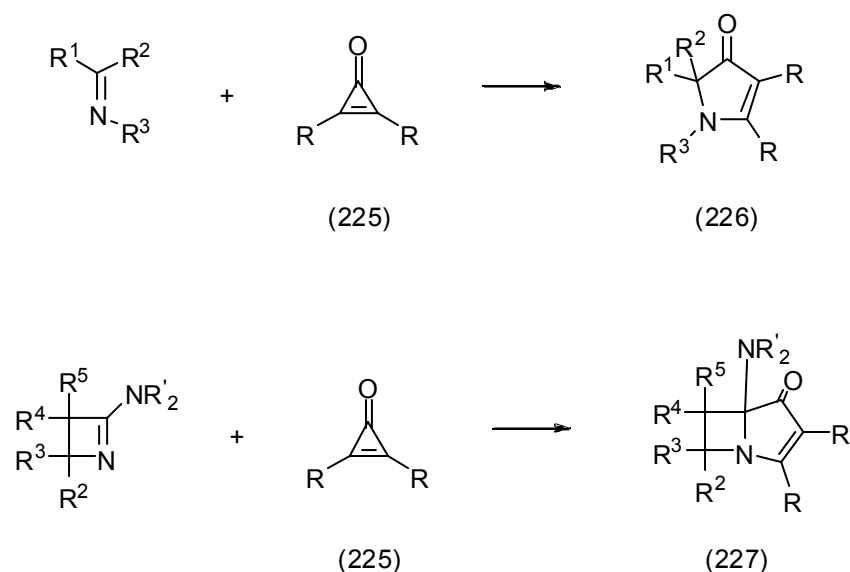


Compound (201) showed the clear presence of a new C=N bond through the IR at 1450 cm⁻¹ and gain of an ethyl group (¹H NMR) and loss of N-H (¹H NMR and IR). The loss of the characteristic C=S signal in the ¹³C NMR and the appearance of a new quaternary carbon at 181 ppm confirmed that S- and not N- alkylation had occurred. High-resolution mass spectrometry data was also fully consistent with the assigned structure.

Reactions of 1-azetine (201) with nitrile oxides proved unfruitful, resulting in multispot processes from which none of the desired adducts could be isolated. It was believed that this was due to the vinylic group competing for the nitrile oxide. In order to avoid this, a reagent was required which is known to react with electron rich imines but not with alkenes. One such reagent is diphenylcyclopropanone (DPP). This is discussed in the next section.

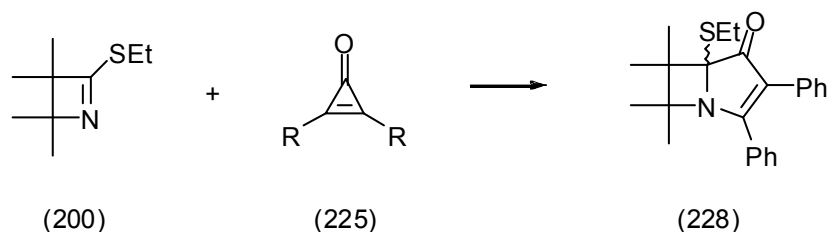
4.4 Reactions of 1-azetines with DPP

Eicher⁹² and others^{93,94} have shown that electron rich imines react with cyclopropanones (225) to form pyrrolidines (226) as shown in Scheme 64. Heimgartner went on to show that 2-amino-1-azetines also undergo this reaction to form bicyclic pyrrolidines (227).⁹³



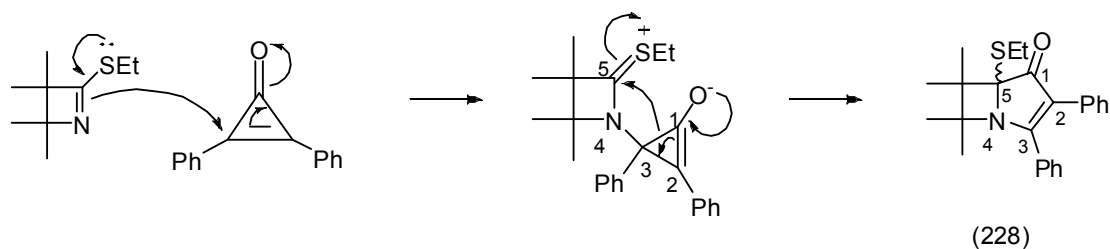
Scheme 64

Previous work²⁷ in our own group had also shown that mixing 1-azetine (200) with commercially available DPP (225, R = Ph) yielded bicyclic adduct (228) in 80-90% yield as shown in Scheme 65. Other 3,4-alkylated 1-azetines underwent a similar reaction.



Scheme 65

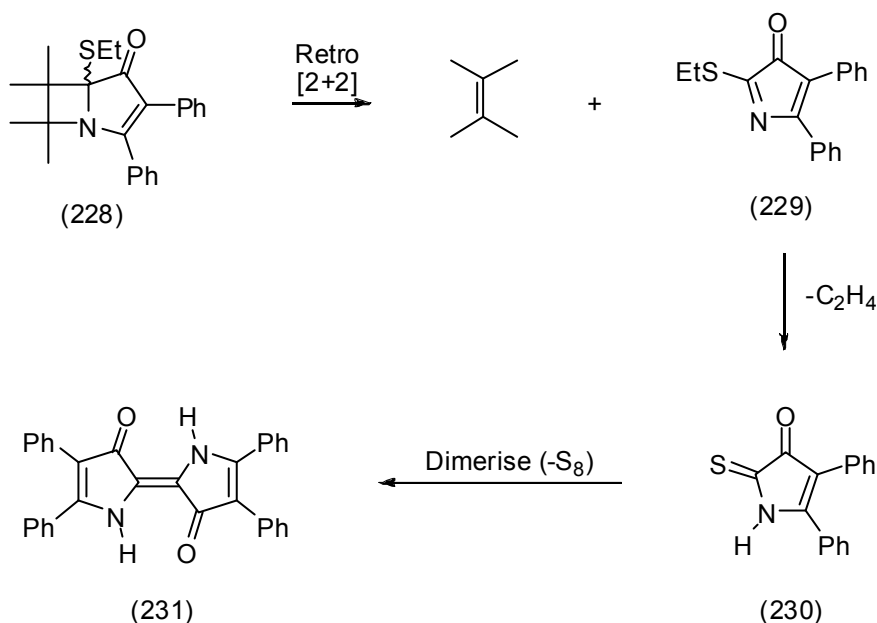
The mechanism suggested for this reaction is shown in Scheme 66 and shows attack at the alkene double bond of DPP, by 1-azetine (200). This forms an intermediate which undergoes an intramolecular reaction to produce bicyclic system (228).



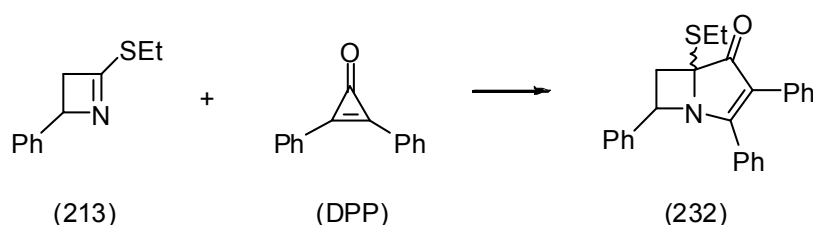
Scheme 66

Previous work had not fully characterised adduct (228) and hence its synthesis was repeated here. Compound (228) was isolated in 100% yield after reacting 1-azetine (200) and DPP (225) in acetonitrile at room temperature for 72 hours. The diagnostic ^1H NMR signals were the four distinct methyl groups and the diastereotopic SEt which showed as two sets of double quartets (dq) for the CH_2 group. The ^{13}C NMR showed the carbonyl group and the expected number of aromatic carbons for the mono substituted benzene rings. The bridgehead sp^3 carbon this time appeared at 84 ppm. IR spectroscopy confirmed the presence of a carbonyl in the molecule and high resolution mass spectroscopic data confirmed the structural assignment.

It is of interest to note²⁷ that DPP adduct (228), upon thermolysis at 200°C yielded the unexpected indigo type product (231) via the mechanism postulated below:



All attempts to isolate intermediates (229) or (230) were unsuccessful. It was thought possible that bicyclic adduct (232) might undergo similar reaction, but, due to the higher ease of formation of styrene over 2,3-dimethyl-2-butene (see Schemes 59/60) do it at lower temperature and hence allow intermediate (229) or (230) to be isolated. Compound (232) was easily synthesised by reacting 1-azetine (213) with DPP to give compound (232) in good yield as shown in Scheme 67. Compound (232) was formed as a single diastereoisomer and showed all of the expected spectroscopic characteristics, together with consistent accurate mass data. The stereochemical outcome of this process will be discussed later.

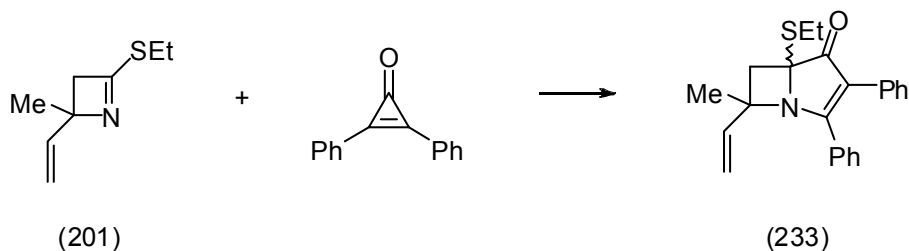


Scheme 67

In the event, compound (232) was found to be stable to thermolysis. We next looked at DPP adducts of the 4-vinyl-1-azetine (201).

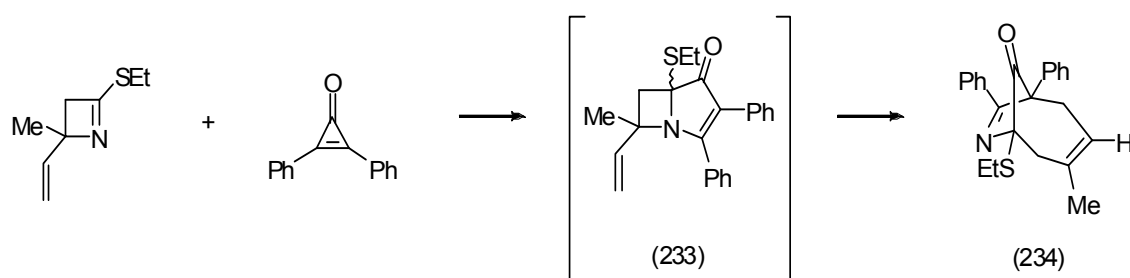
4.5 Reactions of 4-vinyl-1-azetines with DPP

As discussed above (Section 4.4) DPP is known to react with electron rich imines, but not with alkenes. With this in mind we next sought to use 1-azetine (201) as a template for cycloaddition reactions in order to produce bicyclic heterocycles in order to explore their chemical reactivities. Based on the reactivity of electron rich imines, including that of 1-azetines (200) and (213) towards DPP, we started by investigating the formal [2+3] cycloaddition of 1-azetine (201) with DPP. It was anticipated that this reaction would form cycloadduct (233) as shown in Scheme 68.



Scheme 68

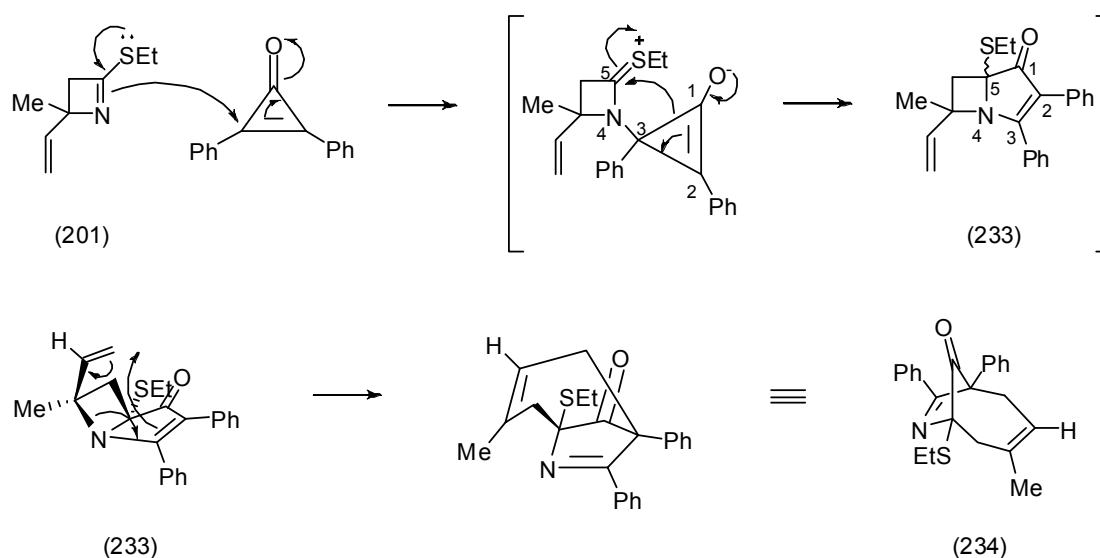
In the event, the product isolated from this reaction was not the expected cycloadduct (233) but rather a ring expanded 7-azabicyclo[4.2.1]nonane (234), as shown in Scheme 69, isolated in 48% yield. The key indicator that adduct (233) was not the product was the clear absence of the vinylic CH₂ in the ¹³C and ¹H NMR spectra.



Scheme 69

The structure of this new compound (234) was apparent from spectroscopic studies. For example, detailed ¹H NMR analysis showed the absence of the distinctive vinylic CH₂ which was expected in compound (233), the presence of the CH₂-CH=CMe=CH₂ linkage [¹H-¹H COSY] of the new ring system, an extremely distinctive quaternary sp³ carbon-phenyl linkage and a characteristic quaternary sp³ carbon-ethylthio linkage [¹H-¹³C HMBC]. The infrared showed a carbonyl at 1737 cm⁻¹ and the mass spectroscopic data was also fully consistent with the proposed structure. A mechanistic rationale for the formation of 7-azabicyclo[4.2.1]nonane (234) is shown in Scheme 70.⁹²⁻⁹⁴ This involves attack at the alkene double bond of DPP, by 1-azetine (201). This forms the expected compound (233) as an intermediate which

undergoes an intramolecular [3,3]-sigmatropic rearrangement (an aza-Cope or amino-Claisen reaction) to give the 7-azabicyclo[4.2.1]nonene (234).

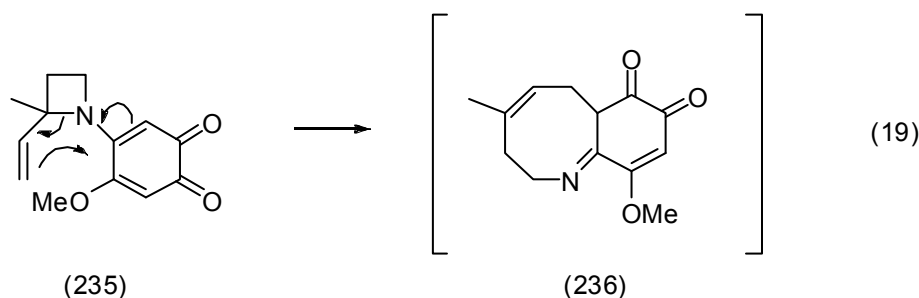


Scheme 70

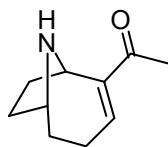
The aza-Cope rearrangement in this type of bicyclic system is unprecedented and it is thought that the rearrangement was facilitated by both strain relief and also by the fact that the azabicyclo[3.2.0]heptane ring system has an inherent “half-open” book conformation at the ring junction, as shown in Scheme 70, which allows the vinyl substituent and second alkene to overlap. This proposal necessitates that the vinylic and SEt groups in cycloadduct (233) adopt a *trans* relationship, with the larger SEt group on the less hindered convex face of the molecule.

This hypothesis is supported by the reaction of 1-azetidine (213) with DPP to yield cycloadduct (232) as shown before in Scheme 67. Adduct (232) cannot undergo [3,3]-sigmatropic rearrangement due to the absence of the exocyclic alkene, but did exhibit the expected *trans* relationship between the Ph and SEt groups as evidenced through a strong NOE enhancement between the SEt and the *cis*-H. To substantiate the aza-Cope, ring expansion hypothesis further, literature precedent⁹⁵ was sought and it was found that the monocyclic α -vinyl-azetidino systems, exemplified by compound (235) (equation 19) have been shown to undergo strain-promoted facile aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement to give azocines (236), after opening of the

four-membered ring, lending credence to the proposition of strain-relief acting as a facilitator in [3,3]-sigmatropic rearrangements.



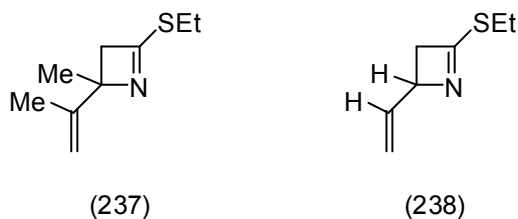
It was therefore concluded that reaction of 4-vinyl-1-azetine (201) with DPP led to the successful synthesis of 7-azabicyclo[4.2.1]nonane structure (234), via an interesting and novel rearrangement mechanism. This structure is also an interesting 7-aza analogue of the well documented 9-azabicyclo[4.2.1]nonene nucleus, which is the core component of several important alkaloid natural products of which anatoxin-a (184) is the foremost example.⁷⁵⁻⁷⁹



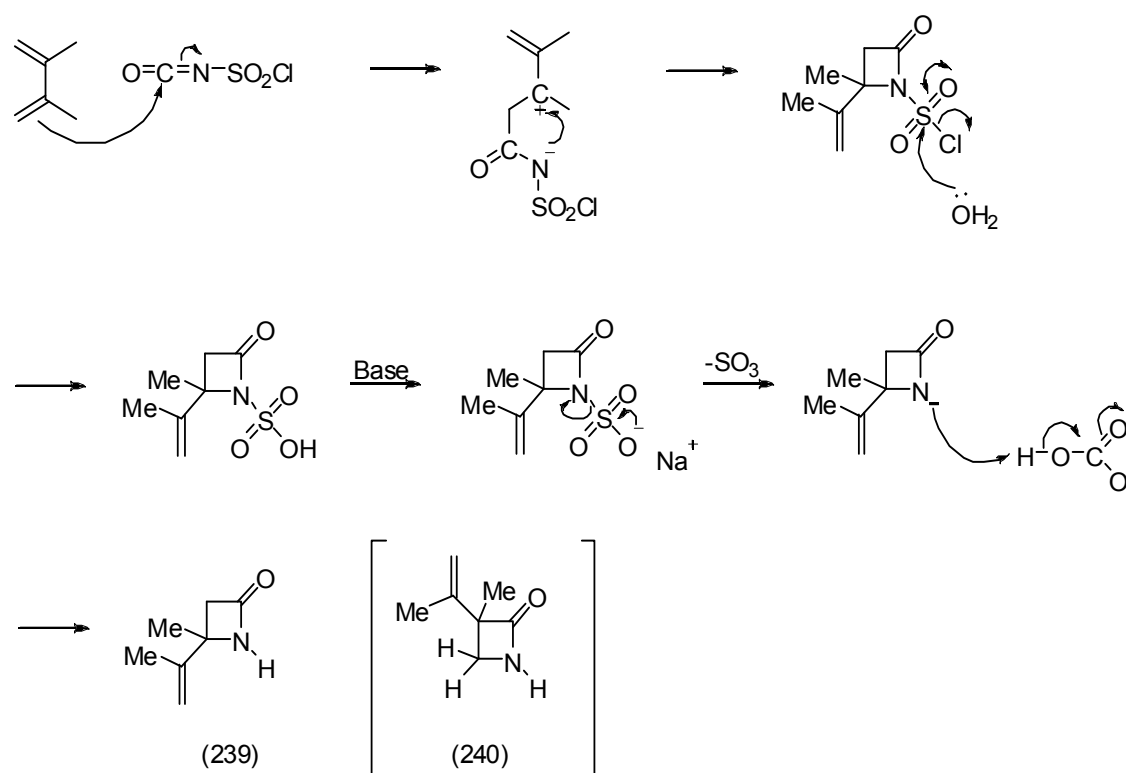
(184)

It was therefore decided to react other 4-vinyl-1-azetines with DPP in an attempt to gain access to other examples of this interesting and novel rearrangement.

In order to study such processes we needed to synthesise 1-azetines with similar structural characteristics to that of compound (201), with the most important structural feature being the presence of an exocyclic double bond. Therefore, 1-azetines (237) and (238) were selected for study. These were easily available from the corresponding β -lactams as discussed below.



Scheme 71 shows the mechanism for the synthesis of the 4-methyl-4-vinyl-1-azetidin-2-one (239). The mechanism shows a stepwise reaction involving attack of chlorosulfonyl isocyanate by 2,3-dimethyl-1,3-butadiene. This results in the regioselective formation of the more stable tertiary carbocation, which is subsequently attacked by the nitrogen lone pair to yield the β -lactam ring. Treatment with aqueous base results in desulfonation as discussed previously. The regioisomer (240) was not formed.

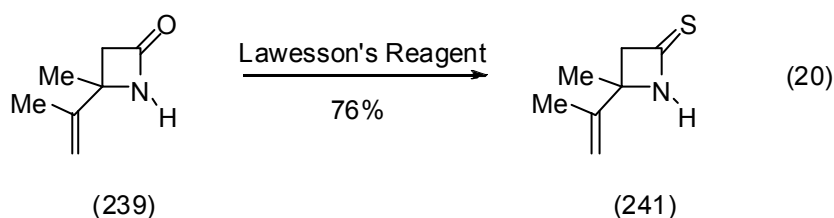


Scheme 71

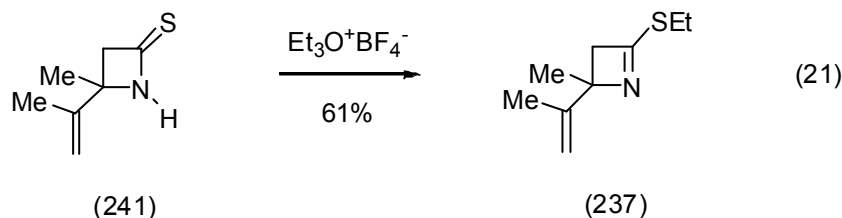
Compound (239) showed the expected spectroscopic characteristics. These include the infrared, which showed a carbonyl at 1762 cm^{-1} typical of the carbonyl stretch of a β -lactam. The ^1H NMR spectrum showed peaks in a

ratio of 3:3:2:2:1 representative of the two-methyl groups, two methylene groups and the N-H proton, as expected. The lack of coupling between the aliphatic CH₂ and the NH verified the regiochemical assignment. ¹³C NMR data was also consistent with the assigned structure. Mass spectroscopy showed the expected main peak of 126 (ES positive), which was confirmed by accurate mass measurement.

When the 4-methyl-4-vinyl-1-azetidin-2-one (239) was thiated using Lawesson's reagent, the reaction successfully yielded the corresponding thione (241) in good yield (equation 20). The compound showed the expected spectroscopic characteristics including the presence of a C=S bond (IR and ¹³C NMR). The exocyclic alkene CH₂ and the ring CH₂ could be seen at 4.9 and 2.8δ (¹H NMR). High resolution mass spectroscopy confirmed the structural assignment.



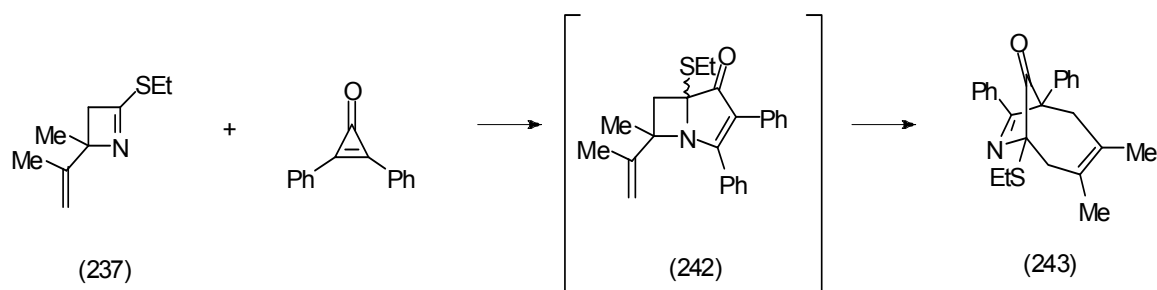
Thione (241) was then converted into 1-azetine (237) using triethyloxonium tetrafluoroborate (Meerwein's reagent) in 61% yield as shown in equation 21.



1-azetine (237) showed the expected spectroscopic characteristics. For example, the presence of a C=N bond at 148 ppm (¹³C NMR) and loss of N-H (¹H NMR and IR). The loss of the characteristic C=S signal in the ¹³C NMR and the appearance of a new quaternary carbon at 171 ppm confirmed that

S-alkylation had occurred. High-resolution mass spectroscopy data was also fully consistent with the assigned structure.

With the synthesis of a second 4-vinyl-1-azetine successfully achieved it was next subjected to cycloaddition reaction with DPP, in order to access a further example of the rearranged 9-azabicyclo[4.2.1]nonane system. This was undertaken using the same conditions as that of 1-azetine (201) shown in Scheme 69 above. The product isolated from this reaction was indeed the ring expanded 7-azabicyclo[4.2.1]nonane (243), as shown in Scheme 72, isolated in 51% yield.

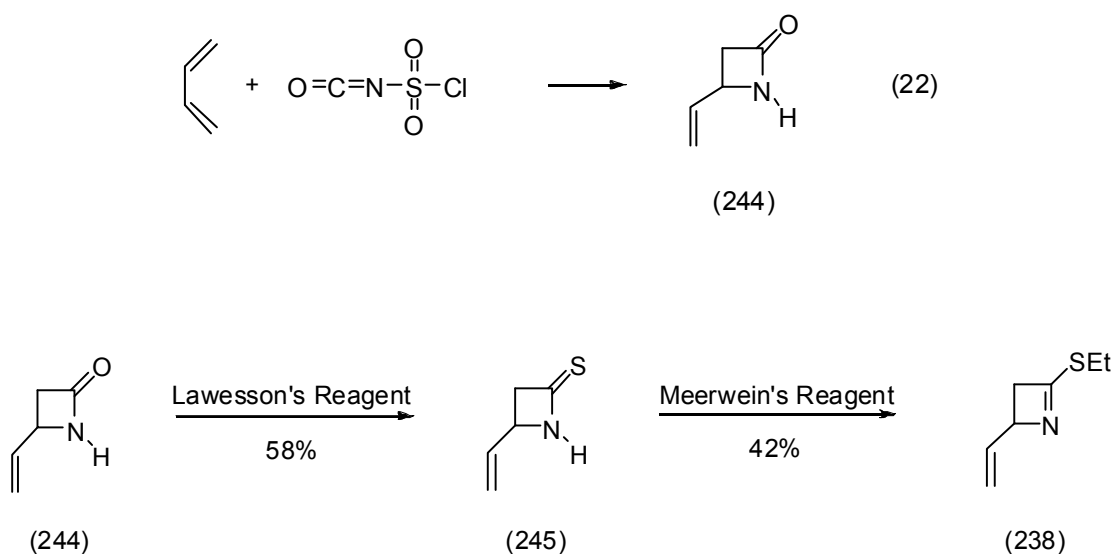


Scheme 72

The structure of the new compound (243) was confirmed from spectroscopic studies. For example, the NMR showed the absence of a distinctive vinylic CH_2 , fully consistent with that of the rearranged 9-azabicyclo[4.2.1]nonane system and discounting cycloadduct (242) as the product of the reaction. The 2D NMR data also showed the presence of the extremely distinctive quaternary sp^3 carbon-phenyl linkage and a characteristic quaternary sp^3 carbon-ethylthio linkage. The infrared showed a carbonyl at 1768 cm^{-1} and the mass spectroscopic data was also fully consistent with the proposed structure.

The mechanistic rationale for the formation of 7-azabicyclo[4.2.1]nonane (243) is identical to that shown in Scheme 70, proceeding via the aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement.

With the successful synthesis of 9-azabicyclo[4.2.1]nonane (243) a further example of this novel rearrangement process was sought, using the reaction of 1-azetine (238) with DPP. The known 4-vinyl-1-azetidin-2-one (244) was synthesised by standard chlorosulfonyl isocyanate to alkene cycloaddition, as shown in equation 22. Thiation with Lawesson's reagent (58%) and alkylation with Meerwein's reagent (42%) gave the desired 4-vinyl-1-azetine (238) via the thione (245), as shown in Scheme 73.

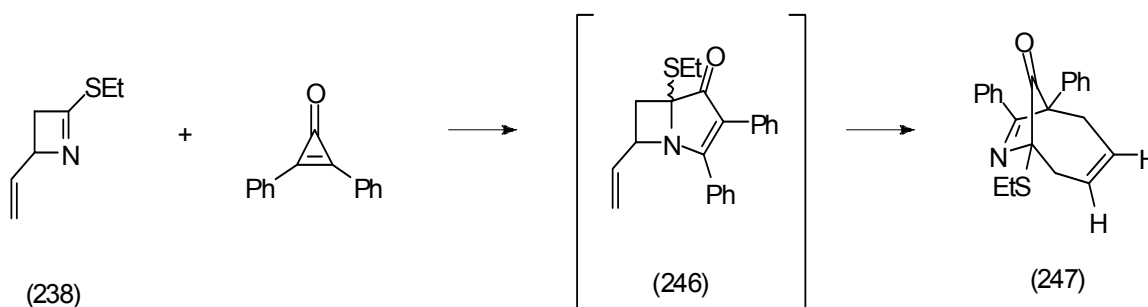


Scheme 73

Compounds (244), (245) and (238) showed the expected spectroscopic characteristics. These include, for compound (238) the presence of a C=N bond at 183 ppm (¹³C NMR) and loss of N-H (¹H NMR and IR). The loss of the characteristic C=S signal in the ¹³C NMR and the appearance of a new quaternary carbon confirmed that S- and not N-alkylation had occurred. High-resolution mass spectroscopy data was also fully consistent with the assigned structure.

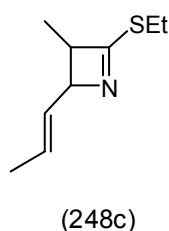
4-vinyl-1-azetine (238) could now be used as a template for the cycloaddition reaction with DPP in order to produce bicyclic heterocycle (247) as shown in Scheme 74. Continual monitoring of the reaction (tlc) indicated when the reaction had gone to completion. This reaction successfully yielded 7-azabicyclo[4.2.1]nonane (247) in 62% yield. The final product showed the expected spectroscopic characteristic. These include the absence of a

distinctive vinylic CH₂ (NMR), fully consistent with that of the rearranged 9-azabicyclo[4.2.1]nonane system and discounting cycloadduct (246) as the product of the reaction. The NMR spectra (COSY, HMBC and HSQC) also showed the presence of the extremely distinctive quaternary sp³ carbon-phenyl linkage and a characteristic quaternary sp³ carbon-ethylthio linkage together with a very clear [¹H-¹H COSY] CH₂CH=CHCH₂ chain. The infrared showed a carbonyl at 1755 cm⁻¹, and accurate mass measurement was also consistent. The mechanistic rationale for the formation of 7-azabicyclo[4.2.1]nonane (247) is once again identical to that shown in Scheme 70, proceeding via the aza-Cope (amino-Claisen) [3,3]-sigmatropic rearrangement.



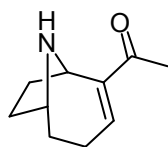
Scheme 74

The 3-methyl-4-vinyl system (248c) shown below, synthesised from 2,4-hexadiene in the usual way, failed to react with DPP.

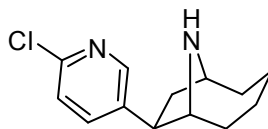


In conclusion the reaction of 4-vinyl-1-azetines with diphenylcyclopropanone, has successfully provided access to the 7-azabicyclo[4.2.1]nonane nucleus, which is an interesting analogue of the 9-azabicyclo[4.2.1]nonane system. This latter structure is present in the important alkaloids anatoxin-a (184)^{76,77a,96}, bis-homoepibatidine (187)⁷⁵ and pinnamine (188).^{81,97} Anatoxin-a together with its synthetic analogues, have been shown to have a high

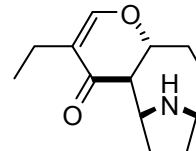
affinity for the nicotinic acetylcholine receptor (nAChR), important in a range of neurotransmission diseases and hence guaranteeing the interest of the synthetic community for some time to come.



(184)



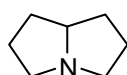
(187)



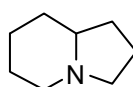
(188)

4.6 Reactions of 5,6 and 7-membered cyclic imidates with DPP

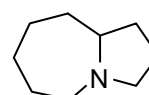
In keeping with the established theme of reacting DPP with cyclic electron rich imines,⁹²⁻⁹⁴ it was decided to investigate the reactions of other cyclic imines with DPP, in an attempt to access further examples of analogues of alkaloid natural products. The systems selected for study were the pyrrolizidines (172), indolizidines (164), and pyrroloazepines (180), which, as with their homotropane counterparts are known to exhibit significant pharmacological properties and are of interest in the search for leads relevant to the treatment of a wide range of diseases, discussed in the introduction.



(172)

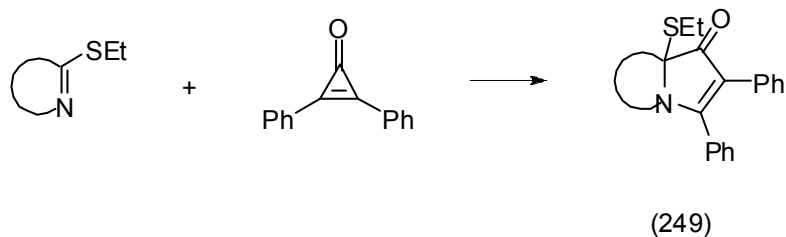


(164)



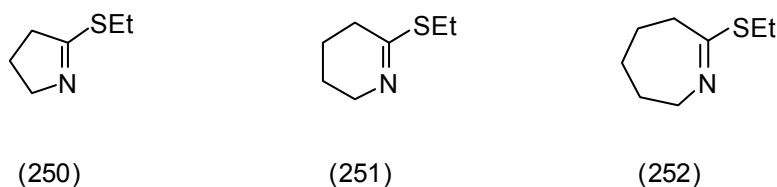
(180)

Based on the reactivity of 1-azetines with DPP, it was anticipated that our approach would provide compounds of general structure (249) (Scheme 75).

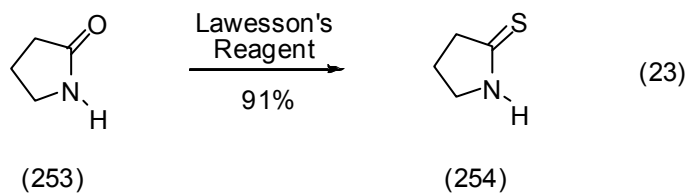


Scheme 75

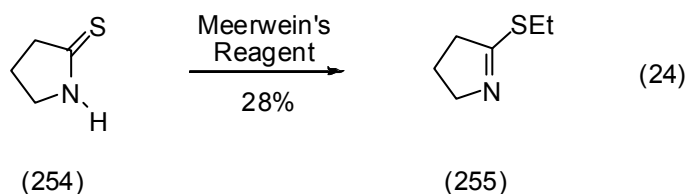
This necessitated the synthesis of cyclic imines (250), (251) and (252). It was anticipated that these systems should be accessible from the corresponding and readily available lactams.



When 2-pyrrolidinone (253) was thiated using Lawesson's reagent, the reaction successfully yielded the corresponding thione (254) in 91% yield as shown in equation (23). The product showed the expected spectroscopic characteristics for example, loss of the lactam carbonyl (IR and ^{13}C NMR) together with gain of C=S bond which showed peaks at 1568 cm^{-1} in the IR and a distinctive quaternary carbon at 205 ppm in the ^{13}C NMR. The ^1H NMR also showed the expected ratio of 2:2:2:1 protons representative of the three-methylene groups and the N-H proton, as expected. The mass spectroscopy data was also fully consistent with the expected structure, showing the main peak $[\text{M}+1]$ at 102 (ES+) at 100%.



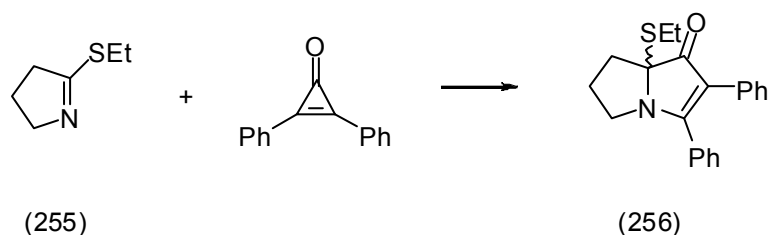
2-Pyrolidinethione (254) was then converted into thioimino ether (255) using triethyloxonium tetrafluoroborate (Meerwein's reagent) in 28% yield (equation 24). Attempts were made to improve the yield of this reaction, but were unsuccessful due to the high volatility of the compound.



Thioimino ether (255) showed the expected spectroscopic characteristic. For example, the presence of a new C=N bond at 172 ppm and loss of the characteristic C=S signal (^{13}C NMR). The ^1H NMR confirmed the addition of an ethyl group to the molecule, with peaks at 1.9 and 1.3 δ respectively. The IR also confirmed the loss of a C=S stretch within the molecule. High-resolution mass spectroscopic data was fully consistent with the expected structure.

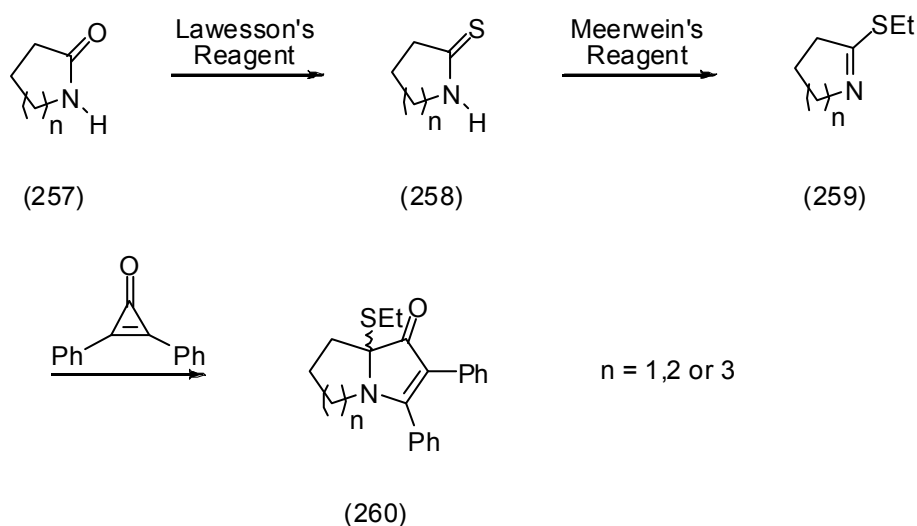
Having successfully synthesised thioimino ether (255), the next task was to use this compound to carry out a cycloaddition reaction with DPP in order to access the desired bicyclic adduct (256) (Scheme 73).

Compound (256) was isolated in 26% yield after reacting thioimino ether (255) and DPP in acetonitrile at room temperature for 24 hours (Scheme 76). The ^1H NMR confirmed the presence of the diastereotopic SEt which showed as two distinguishable doublet of quartets (dq) for the CH_2 group. The ^{13}C NMR showed the carbonyl group and the expected number of aromatic carbons in the appropriate ratios for mono substituted benzene rings. The bridgehead sp^3 carbon appeared at 80 ppm. IR spectroscopy confirmed the presence of a carbonyl in the molecule at 1678 cm^{-1} and high resolution mass spectroscopic data confirmed the structural assignment.



Scheme 76

Having successfully applied this synthetic approach to the synthesis of compound (256), an example of the pyrrolizidine alkaloid system, we next sought to use identical methodology to access examples of the indolizidine and pyrroloazepine ring systems, represented by general structure (260) in Scheme 77.



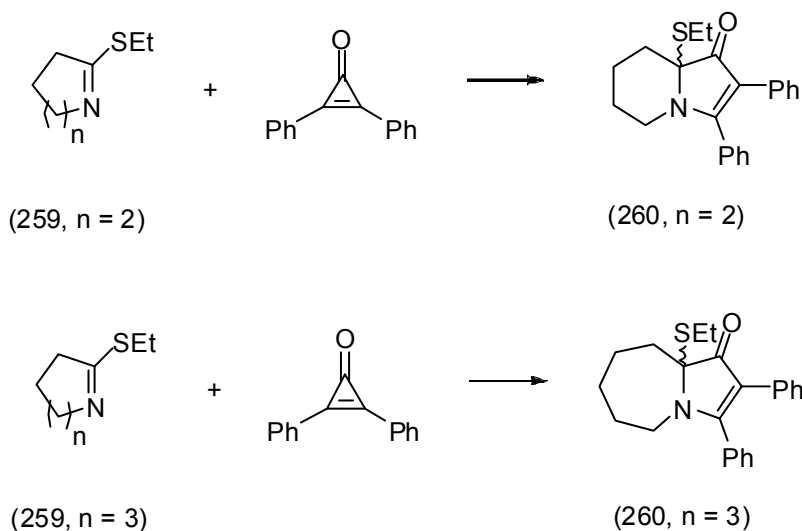
Scheme 77

Valerolactam (257, $n = 2$) and ϵ -caprolactam (257, $n = 3$) were both thiated using Lawesson's reagent to yield the corresponding thiolactams (258, $n = 2$) and (258, $n = 3$) in 88% and 98% yields respectively. As with their 5-membered ring counterpart, both compounds showed the expected spectroscopic characteristics. The characteristic difference was the presence of further methylene signals in both the ^1H and ^{13}C NMRs respectively. The 6-membered thiolactam (258, $n = 2$) contained a further methylene group to that of its 5-membered ring counterpart (^1H and ^{13}C NMR). The 7-membered

thiolactam (258, $n = 3$) showed two extra methylene groups (^1H and ^{13}C NMR) to that of its 5-membered ring counterpart.

Valerothiolactam (258, $n = 2$) and ϵ -caprothiolactam (258, $n = 3$) were subsequently both converted into their corresponding thioimino ethers (259, $n = 2$) and (259, $n = 3$) with Meerwein's reagent in 28 and 65% yields respectively. As with the 5-membered thioimino ether, attempts to improve the yields of the reactions were largely unsuccessful, again, due to the high volatility of the compounds. As with the 5-membered system the 6 and 7-membered thioimino ethers showed the expected spectroscopic characteristics. The loss of the characteristic C=S signal (IR and ^{13}C NMR) and gain of the ethyl groups is particularly noteworthy, together with the presence of a new C=N bond in both systems.

Thioimino ethers (259, $n = 2$) and (259, $n = 3$) could now be used as templates for the cycloaddition reaction to produce bicyclic heterocycles (260, $n = 2$) and (260, $n = 3$) as shown in Scheme 78.

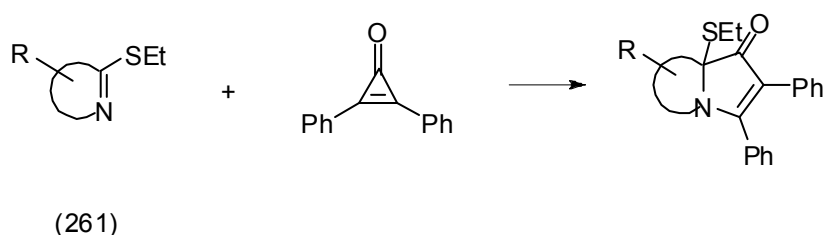


Scheme 78

Compounds (260, $n = 2$) and (260, $n = 3$) were respectively isolated in 54 and 18% yield after reacting thioimino ether (259, $n = 2$) and (259, $n = 3$) with DPP, in acetonitrile at room temperature for 24 hours. Both products showed consistent spectroscopic data for the assigned structures. For example, for

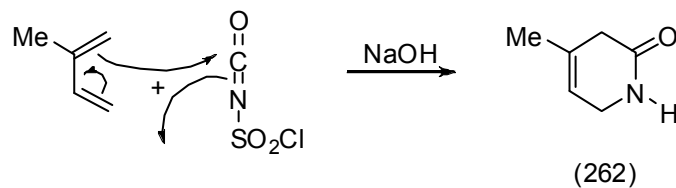
cycloadduct (260, $n = 2$) the ^1H NMR data showed the presence of the diastereotopic SEt as two doublets of quartets (dq) for the CH_2 group. The ^{13}C NMR showed the carbonyl group and the expected number of aromatic carbons, which were present also in the appropriate ratios in the ^1H NMR spectrum. The bridgehead sp^3 carbon appeared at 73 ppm in the ^{13}C NMR spectrum. IR spectroscopy confirmed the presence of a carbonyl in the molecule at 1760 cm^{-1} . High resolution mass spectroscopic data confirmed the assignment.

Having gained access to examples of the pyrrolizidine, indolizidine, and pyrroloazepine alkaloid natural products, it was next decided to investigate the reaction of a substituted cyclic imine ring system (261) towards DPP (Scheme 79). This it was hoped would demonstrate greater flexibility in the reaction of thioimino ethers with DPP and also verify the viability of this reaction pathway in accessing analogues of alkaloid natural products.



Scheme 79

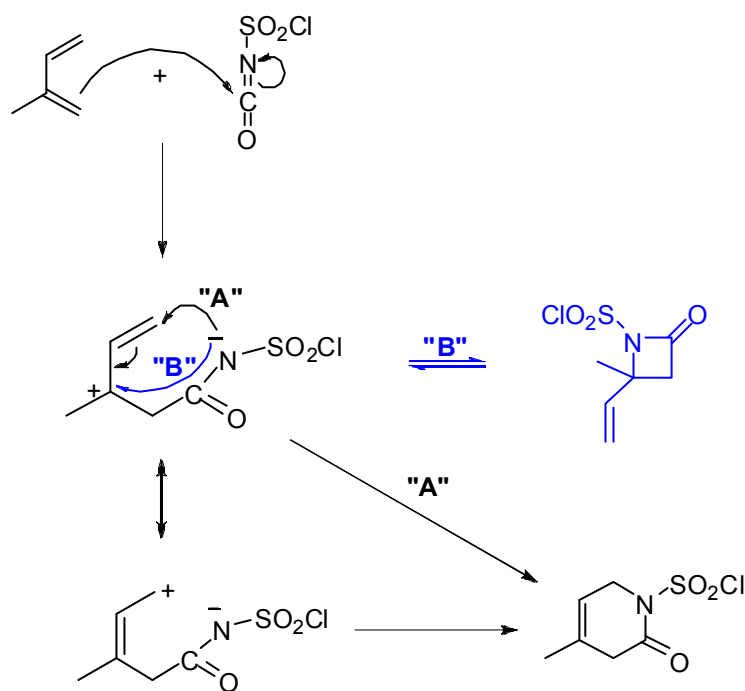
This necessitated the synthesis of a β -lactam ring that could undergo thiation with Lawesson's reagent and alkylation with Meerwein's reagent, in order to access the desired thioimino ether required for the cycloaddition with DPP. The substituted 6-membered β -lactam ring (262) (Scheme 80) could be synthesised using a [4+2] cycloaddition pathway. This is in contrast to the way in which the β -lactam rings were synthesised previously via the [2+2] cycloaddition pathway, as discussed in section 2.3 above.



Scheme 80

Thus, reaction of isoprene with chlorosulfonyl isocyanate at -10°C (rather than the -60°C required for a formal [2+2] cycloaddition reaction), followed by addition of aqueous base to facilitate the removal of SO_2Cl from the ring and subsequent protonation of the nitrogen, yielded the desired lactam (262) in 26% yield. Compound (262) showed the expected spectroscopic characteristics, confirming the formation of the 6-membered ring product in preference to the formation of the 4-membered ring described in section 2.3. For example, the infrared spectrum showed the presence of a carbonyl group at 1665 cm^{-1} , rather than the 1744 cm^{-1} typical of a β -lactam.

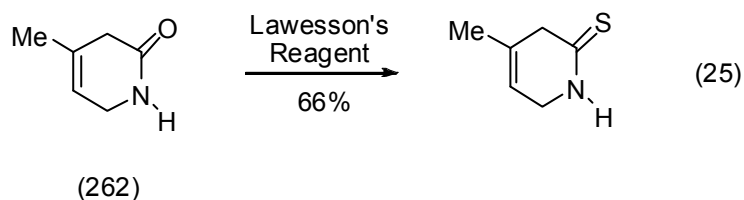
The ^1H NMR confirmed the presence of the methyl, methylene and methine protons in a ratio of 3:2:2:1, together with the absence of the characteristic alkene peaks and appropriate splitting patterns present in the equivalent 4-membered ring product (222 - see page 71, Scheme 63).



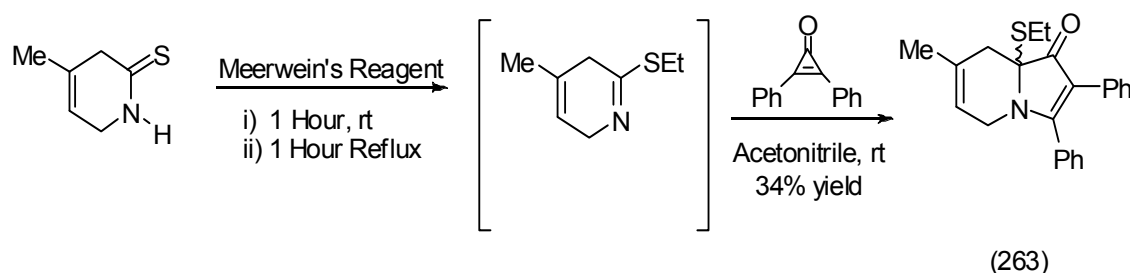
Scheme 81

The formation of the six membered ring at the higher temperature (and longer reaction time – overnight compared to 4 hours) is indicative of the greater stability of the 6-membered ring over the 4-membered ring. Formation of the 4-membered ring at lower temperature may imply that ring closure to the 4-membered ring (ring closure B in Scheme 81) is irreversible at low temperature, enabling isolation of the β -lactam. Higher temperature favours reversal of the reaction leading to the β -lactam (route B) and hence leads to preferential formation of the thermodynamically more stable 6-membered ring (route A).

Lactam (262) was next thiated using Lawesson's reagent, and the reaction successfully yielded the corresponding thione in 66% yield (equation 25). The compound showed the expected spectroscopic characteristics including the presence of a C=S bond (IR and ¹³C NMR) and N-H bond (IR and ¹H NMR).



The thione was then converted into the corresponding thioimino ether (Scheme 82) using triethyloxonium tetrafluoroborate (Meerwein's reagent). This compound was found to be highly volatile in nature and was subject to rapid decomposition. This is possibly due to the addition of a second double bond to the system. Fortunately, *in-situ* reaction with DPP resulted in the successful synthesis of bicyclic compound (263), after reaction in acetonitrile at room temperature for one week (Scheme 82).



Scheme 82

The final product (263) showed the expected spectroscopic characteristics. These include the presence of a carbonyl at 1766 cm^{-1} (IR). The diagnostic ^1H NMR signals were two methyl groups, three methylene groups, one of which was the diastereotopic SEt methylene which showed as a complex multiplet at $3.6\ \delta$ and also one vinylic CH group. All the protons were present in the appropriate ratios. The ^{13}C NMR also confirmed the presence of a carbonyl group at 195 ppm together with the expected number of aromatic carbons with the appropriate quaternary:CH ratios for the two mono substituted benzene rings. High resolution mass spectroscopic data confirmed the structural assignment.

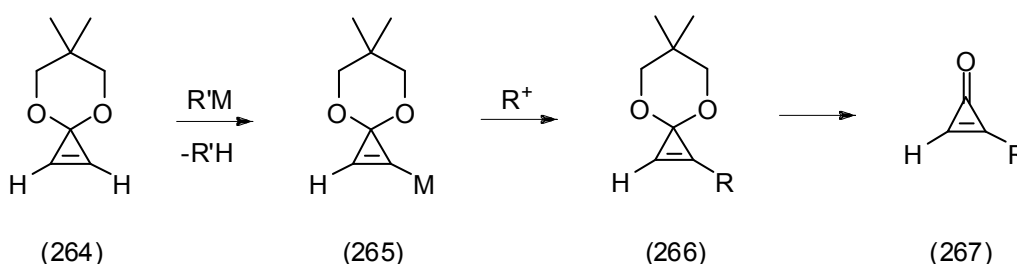
4.7 Synthesis of other cyclopropenones

With access to examples of analogues of the pyrrolizidines, indolizidines and pyrroloazepines now developed, it was necessary to develop this area further. We had already shown that the imine ring system can be varied in terms of size and substitution of the ring and so the next task was to investigate the possibility of using other cyclopropenone rings, in an attempt to demonstrate a

greater degree of flexibility in the overall reaction and in the molecules that could be subsequently synthesised.

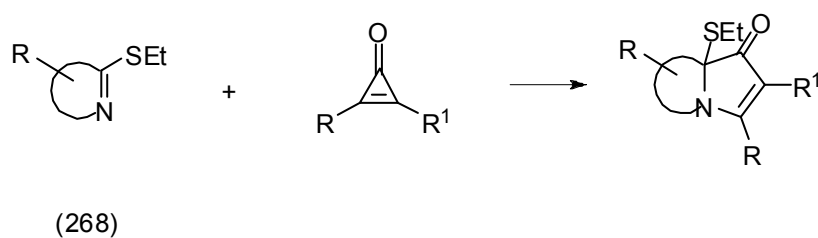
This presented us with a key issue of the lack of commercially available cyclopropenones, with DPP found to be the only known example. With this in mind, it was therefore decided to look at routes for the synthesis of cyclopropenones,⁹⁸ which could potentially be used in cycloaddition reactions with the cyclic thioimidates synthesised above. Synthetic routes to cyclopropenones are still relatively unexplored and a significant number^{99a} are neither acceptably flexible or versatile in their approach to be considered as general.

Nakamura,⁹⁹ however, has developed a general synthesis of cyclopropenones, which utilises the chemistry of metalated cyclopropenone acetals. This approach allows the insertion of a variety of groups, including alkyl, into cyclopropenone acetal (264), via the metalated compound (265). The corresponding disubstituted adduct can be procured by simple repetition of the process on molecule (266). Hydrolysis of the substituted acetal (266) results in the formation of corresponding cyclopropenone (267) (Scheme 83).



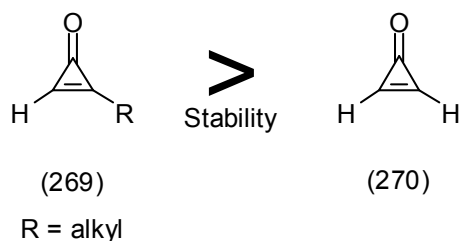
Scheme 83

Following this approach it was decided to embark upon the synthesis of a cyclopropenone to use as an alternative to that of DPP. This compound would serve as a template for the subsequent cycloaddition reactions with the previously synthesised cyclic thioimidates (268) (Scheme 84). This approach would demonstrate both the desired degree of flexibility and also produce further examples of analogues of the pyrrolizidines, indolizidines and pyrroloazepines.

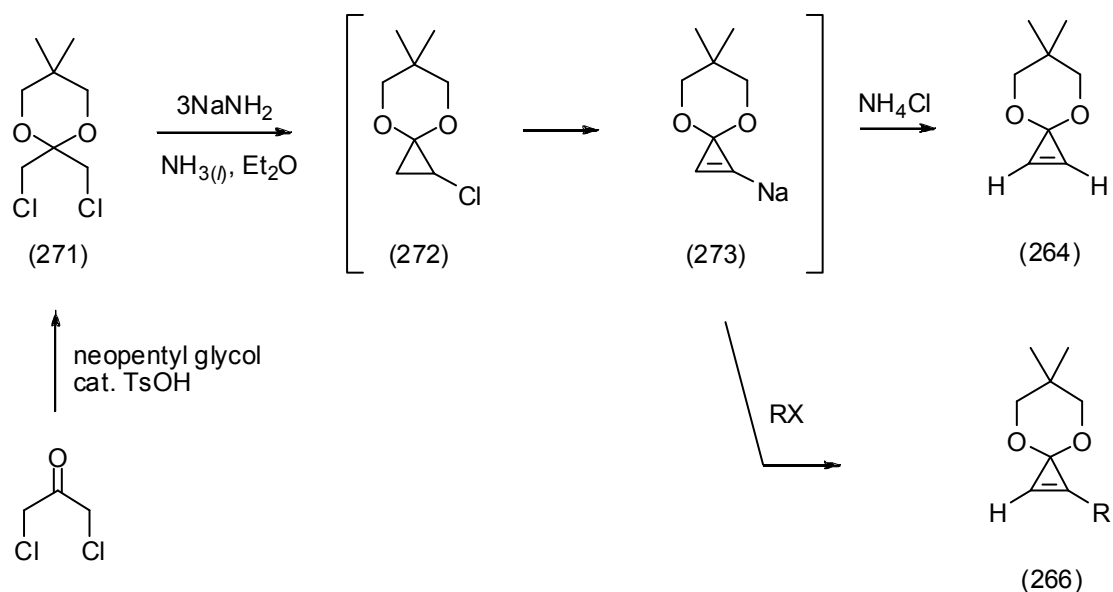


Scheme 84

An alkyl-substituted cyclopropanone (269) was chosen as the initial target for synthesis, as it was thought that this would offer a greater degree of stability compared with that of its unsubstituted counterpart (270).

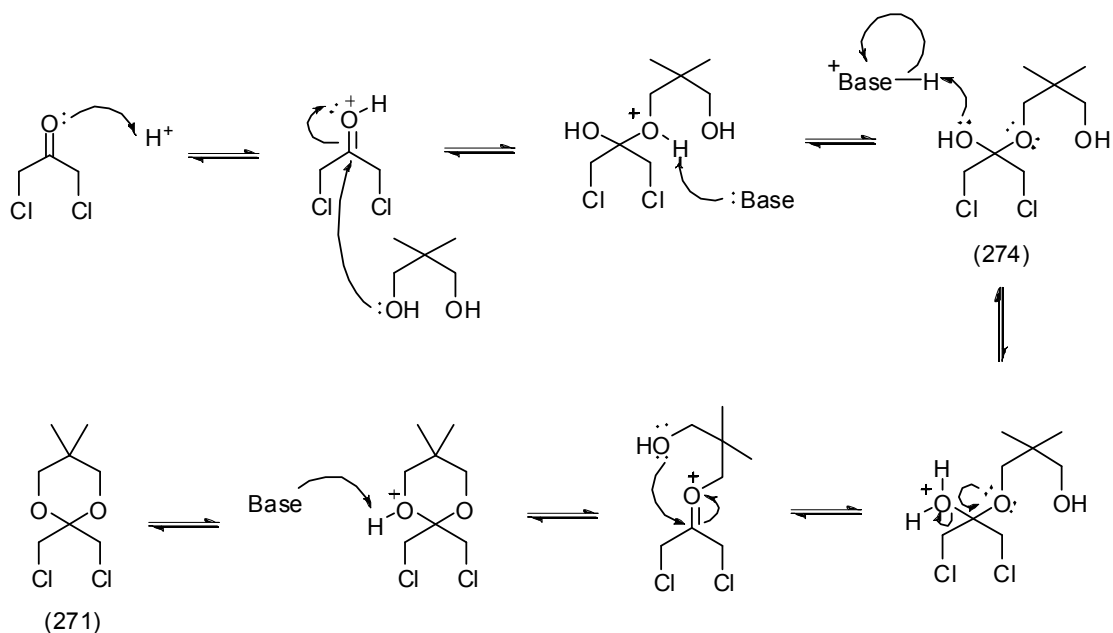


This necessitated the synthesis of cyclopropanone acetal (266), which we anticipated could be obtained from the corresponding 1,3-dichloroacetone acetal (271) via the pathway shown in Scheme 85 and described previously by Nakamura.⁹⁹



Scheme 85

The first task was to synthesise 1,3-dichloroacetone acetal (271). Thus, reaction of 1,3-dichloroacetone with neopentyl glycol in the presence of *p*-toluenesulfonic acid, at reflux, yielded 1,3-dichloroacetone acetal (271) in 72% yield. The mechanism for this reaction (Scheme 86) involves the protonation of the carbonyl oxygen, which activates the molecule for nucleophilic attack by the oxygen lone pair from the alcohol. Loss of a proton then yields the neutral hemiacetal intermediate (274). Protonation of the hemiacetal hydroxyl group converts this into a good leaving group which yields an intermediate oxonium ion. Intramolecular addition of the second alcohol group gives a protonated acetal, which subsequently loses a proton to yield acetal (271).

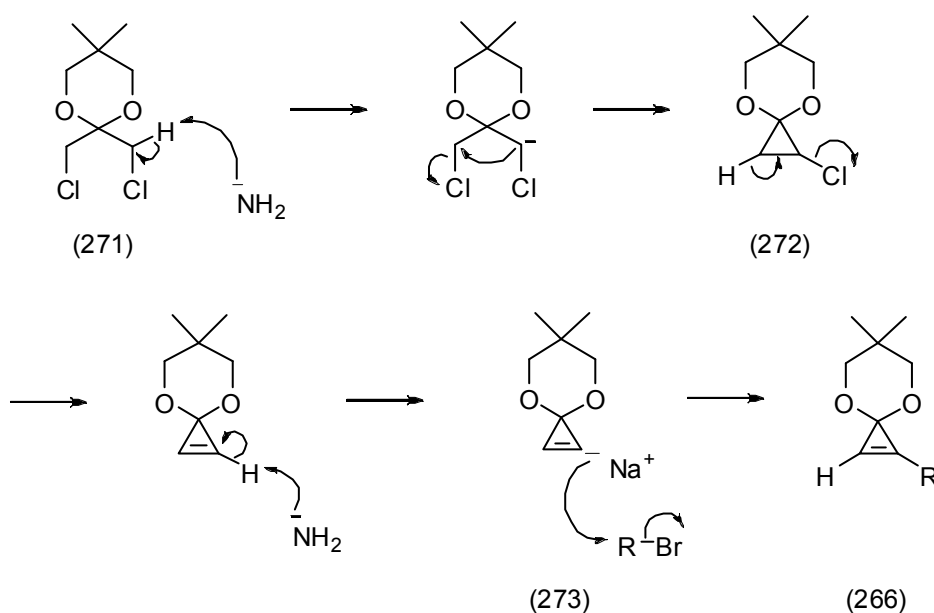


Scheme 86

The acetalised product showed the expected spectroscopic characteristics. For example, the 1H NMR spectrum showed a ratio of 6:4:4 protons representative of the two-methyl groups and two sets of methylene protons, as expected. The IR spectrum was also fully consistent with the expected structure of the product.

Having successfully synthesised 1,3-dichloroacetone acetal (271) the next task was to convert this compound into the substituted cyclopropenone acetal (266) using a one pot cyclisation/alkylation reaction. With reference to Scheme 85, this reaction required a minimum of 3 equivalents of sodium amide in liquid ammonia, in order to favour the formation of the sodium salt (273), rather than chlorocyclopropane (272). The formation of the sodium salt (273) was essential in order to facilitate the formation of the alkyl-substituted cyclopropenone product, rather than its unsubstituted counterpart (264). The next stage of the reaction saw a slow and controlled addition of bromoethane at $-70^\circ C$ to the reaction mixture, which was necessary to avoid the formation of the 2,3-dialkylated product. This was followed by an equally steady and controlled warming period to yield the desired cyclopropenone acetal (266). The mechanism for this process is given in Scheme 87. The first step involves the removal of a proton from 1,3-dichloroacetone acetal (271), using

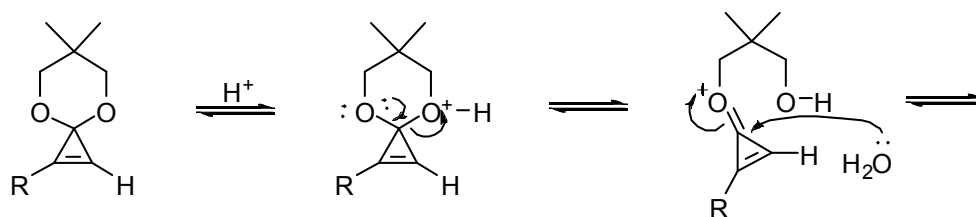
sodium amide at -70°C . This is followed by an intramolecular cyclisation to form chlorocyclopropane (272), which through the subsequent attack of a further mole of sodium amide results in the formation of sodium salt (273). The final step is the attack of a primary alkyl halide, which serves as an electrophile to yield the desired monosubstituted cyclopropenone acetal (266).



Scheme 87

The cyclised product (266, $\text{R} = \text{Et}$) showed the expected spectroscopic characteristics. For example, the ^1H NMR showed the presence of the alkene proton at 7.3δ . The NMR also showed a ratio of 6:4:3:2:1 protons representative of the five proton environments as expected. The ^{13}C NMR also showed the presence of the characteristic alkene double bond.

With access to cyclised product (266) successfully achieved, the final step was to hydrolyse compound (266) into the desired cyclopropenone (269). Therefore a solution of cyclopropenone acetal (266) in wet THF was hydrolysed using Amberlyst 15 catalyst, to give mono ethylated cyclopropenone (269). The mechanism for this reaction is shown in Scheme 88. This involves protonation, followed by oxonium formation and attack of water.

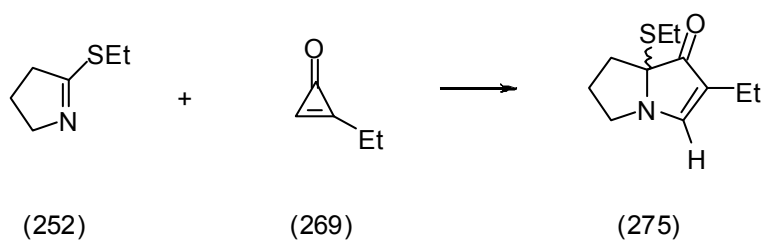


Scheme 88

The final product (269) showed the expected spectroscopic characteristics. These include the infrared, which showed a carbonyl at 1831 cm^{-1} typical of cyclopropenones.^{99a,100} The ^1H NMR spectrum also showed the presence of the ethyl group and also the characteristic alkene hydrogen. In the ^{13}C NMR the alkene was present as a quaternary carbon (158 ppm) and a CH (147 ppm), together with a C=O at 170 ppm.

With a viable route to cyclopropenone (269) now established, this compound could be used in the cycloaddition reactions with the cyclic thioimides previously synthesised.

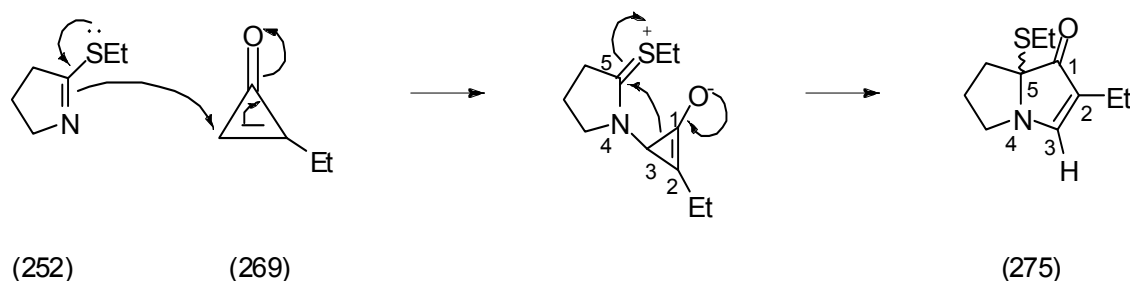
In the first of three reactions cyclic thioimide (252) was reacted with monoethylated cyclopropenone (269) in acetonitrile, at room temperature for 72 hours. This reaction successfully yielded cycloadduct (275) in 50% yield (Scheme 89).



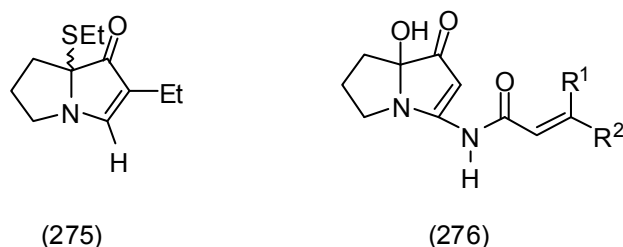
Scheme 89

A plausible mechanism for this reaction is given in Scheme 90 and shows attack at the alkene double bond of monoethylated cyclopropenone (269) by thioimino ether (252) as previously discussed for DPP in Scheme 66. This reaction is interesting because of the regiochemical outcome which is

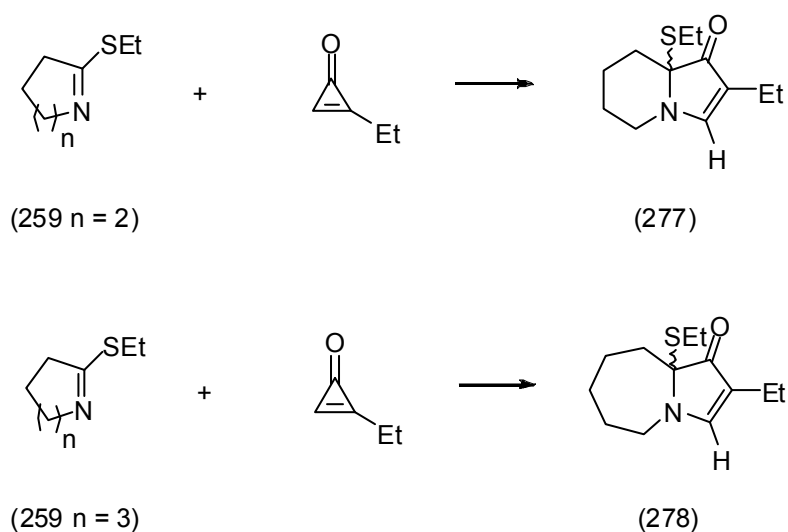
exhibited in the bicyclic product. HMBC NMR studies confirmed that the ethyl group is present at position 2 of the product, showing a strong CH_2 to $\text{C}=\text{O}$ coupling for the ethyl group. The regiochemical outcome may be as a result of the thioimide selectively attacking the mono ethylated cyclopropenone at the sterically least hindered carbon. The outcome is a single regioisomer, which is orientated as shown in structure (275). The product showed the expected spectroscopic characteristics, which included the presence of the diastereotopic SEt as two doublet of quartets (dq) for the CH_2 group (^1H NMR). The ^1H and ^{13}C NMR also confirmed the presence of the alkene proton present in the molecule. The ^{13}C NMR showed the presence of the bridgehead sp^3 carbon at 80 ppm and also a carbonyl group which was shown at 204 ppm. IR spectroscopy also confirmed the presence of a carbonyl in the molecule at 1681 cm^{-1} much lower than the cyclopropenone $\text{C}=\text{O}$ at 1831 cm^{-1} . High resolution mass spectroscopy data also showed the main peak of 212 (ES+) at 100% indicating the gain of one proton $[\text{M}+\text{H}]$ for the molecule, which along with the expected HRMS, confirmed the structure.



Scheme 90



Pyrrolizidines, such as the jenamidines (276)⁷⁰, are biologically active natural products of much interest in synthesis, and it is hoped future work will allow a route to the jenamidines to be developed. In the current work, we next looked at the synthesis of the indolizidine (277) and pyrroloazepine (278).



Scheme 91

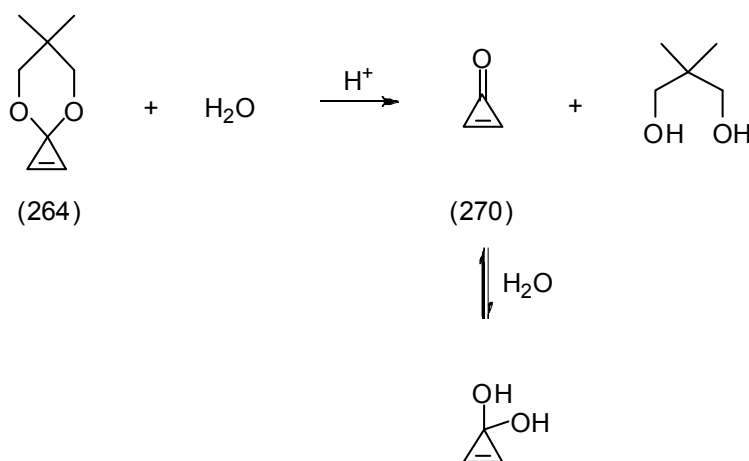
Cycloadducts (277) and (278) were isolated in 45 and 63% yield after reacting thioimidates (259, $n = 2$) and (259, $n = 3$) with the monoethylated cyclopropenone (269), in acetonitrile at room temperature. It was found that the six membered ring compound reacted more rapidly (24 hours), than its seven membered ring counterpart, which required 72 hours to go to completion on tlc. Both products showed consistent spectroscopic data for the assigned structures. For example, cycloadduct (277) showed the presence of the diastereotopic SEt as a multiplet ($2 \times dq$) for the CH_2 group (^1H NMR). The ^1H and ^{13}C NMR also confirmed the presence of the alkene proton present in the molecule. As with cycloadduct (275) HMBC studies carried out on the molecule confirmed that the regiochemistry present within this compound was as shown in structure (277). The ^{13}C NMR showed the presence of the bridgehead sp^3 carbon at 72 ppm and also a carbonyl group which was at 203 ppm. IR spectroscopy also confirmed the presence of a carbonyl in the molecule at 1647 cm^{-1} . Mass spectroscopic data showed the main peak of 226 (ES+) at 100% indicating the gain of one proton $[\text{M}+\text{H}]$ for the expected molecule, which along with a consistent accurate mass measurement confirmed the assignment.

The diethylated cyclopropenone was also synthesised in parallel to this work. It has been shown by other members of our research group to react with

thioimidates of structure (256) in the same manner as DPP and its monoethylated counterpart. It was next decided to explore the synthesis of the unsubstituted cyclopropenone (270). This system was chosen as it was anticipated that the resultant pyrrolizidines, indolizidines and pyrroloazepines would be excellent for further transformations.

This process required the use of cyclopropenone acetal (264) as shown in Scheme 85 above. Acetal (264) was isolated upon the treatment of intermediate (273) (see Scheme 85, above) with ammonium chloride.

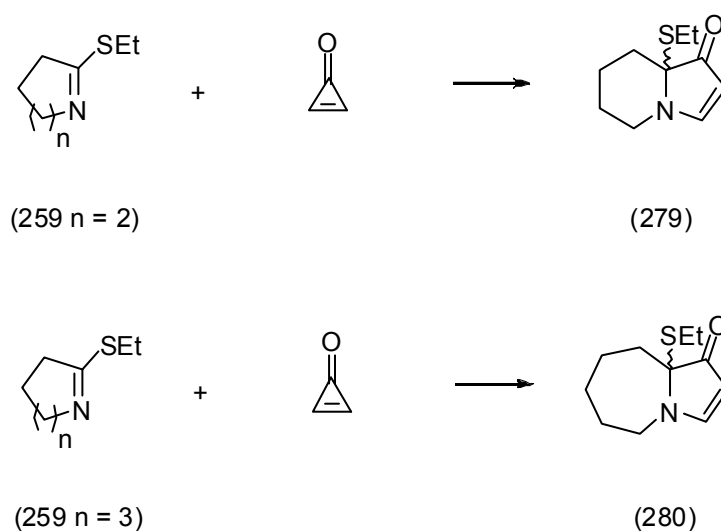
It was anticipated that crude cyclopropenone acetal (264) would undergo deprotection to yield crude cyclopropenone (270), which could then be purified by column chromatography. Therefore Amberlyst 15 catalyst was added to a solution of crude cyclopropenone acetal (264) in THF in an attempt to access the desired cyclopropenone (270). Careful monitoring by TLC and IR showed that the reaction had gone to completion after three hours. Thus, the sample was evaporated to dryness and purification was attempted using silica column chromatography. In the event the cyclopropenone proved troublesome to purify by this method, which may be as a direct result of the highly volatile nature of the compound (literature b.p. 26°C).¹⁰¹ Other cyclopropenones used and synthesised in this thesis are far less volatile. Another possibility is that the cyclopropenone was picking up water, as shown in Scheme 92, making it difficult to recover from the column.



Scheme 92

Due to the challenging nature of the column purification process, the crude cyclopropenone acetal (264) was deprotected using Amberlyst 15 catalyst and the residue was distilled, which resulted in a larger amount of the desired pure cyclopropenone (270) being obtained. The compound showed consistent spectroscopic data for the assigned structure. For example, the IR showed the presence of a carbonyl stretch at 1837 cm^{-1} .

With pure cyclopropenone (270) in hand, the next step was to carry out cycloaddition reactions with cyclic thioimidates. Cyclic thioimidates (256, $n = 2$) and (256, $n = 3$) were selected to exemplify the cycloaddition process, in order to produce bicyclic heterocycles (279) and (280) as shown in Scheme 93.



Scheme 93

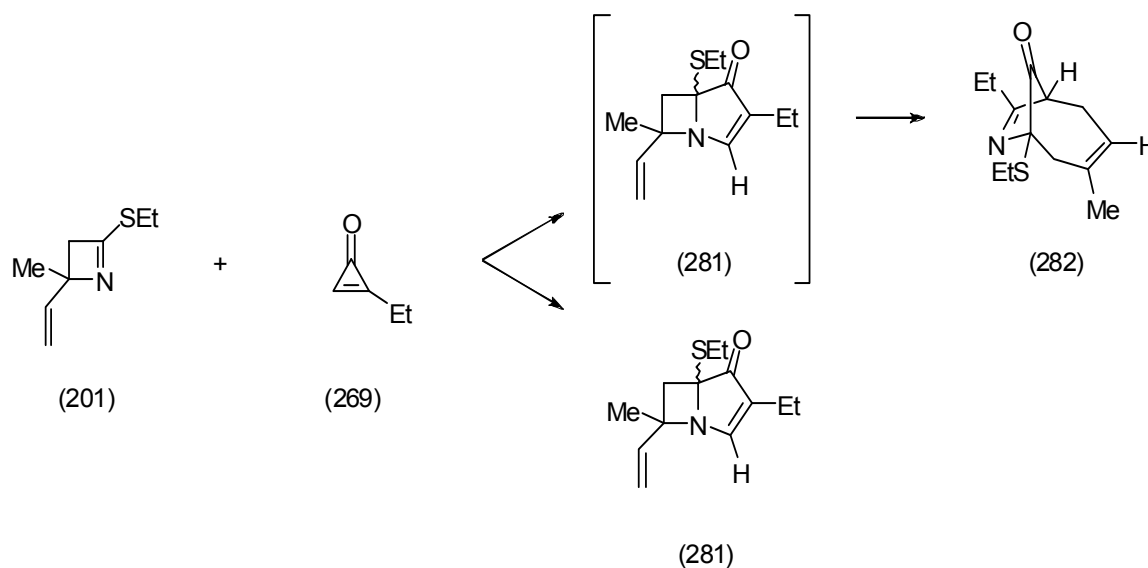
Cycloadducts (279) and (280) were isolated in moderate yields after reacting thioimidates (259, $n = 2$) and (259, $n = 3$) with cyclopropenone (270), in acetonitrile at room temperature. The proposed mechanism for this reaction is identical to that given in Scheme 90 above. As with its monoethylated counterpart, it was found that the six membered ring compound reacted more rapidly (24 hours), than its seven membered ring counterpart, which required 72 hours to go to completion on tlc.

Cycloadduct (279) showed the presence of the alkene hydrogen atoms at 7.4 and 4.6 δ as doublets (^1H NMR) and also the diastereotopic SEt as two sets of double quartets. The ^{13}C NMR showed the presence of 5 CH_2 groups together with the presence of the bridgehead sp^3 carbon at 37 ppm, two alkene CH's and also a carbonyl group, which was present at 171 ppm. IR spectroscopy also confirmed the presence of a carbonyl in the molecule at 1663 cm^{-1} .

Cycloadduct (280) also showed the presence of the diastereotopic SEt as a multiplet for the CH_2 group (^1H NMR). The ^1H and ^{13}C NMR also confirmed that 6 CH_2 groups and the alkene protons were also present in the molecule. IR spectroscopy showed the presence of a carbonyl in the molecule at 1662 cm^{-1} , a feature confirmed in the ^{13}C NMR spectrum. Compounds (279) and (280) also gave fully consistent mass spectroscopic and HRMS data.

This work has resulted in the synthesis of examples of compounds which contain the main framework present in simple alkaloid natural products in the indolizidine, pyrrolizidine and pyrroloazepine classes. This offers huge potential for future work.

It has already been demonstrated in this thesis that 4-vinyl-1-azetines undergo a novel reaction with DPP to form a ring expanded 9-azabicyclo[4.2.1]nonane system (Scheme 72). With access to cyclopropenones other than DPP available through the synthesis shown above, it was decided to investigate if this reaction would be emulated with a different cyclopropenone (Scheme 94).

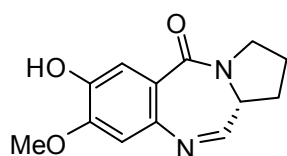


Scheme 94

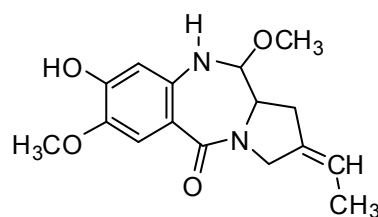
When 1-azetine (201) was reacted with cyclopropenone (269) in acetonitrile at room temperature, the reaction successfully yielded bicyclic adduct (281) in good yield (Scheme 95). Compound (281) did not expand to form the 9-azabicyclo[4.2.1]nonane system (282). The compound showed the expected spectroscopic characteristics including the presence of the exocyclic double bond protons at 5.4 and 5.1 δ (^1H NMR). The diastereotopic SEt appeared as a multiplet for the CH_2 group in the ^1H NMR along with the diagnostic 5-membered ring C-H alkene proton at 7.6 δ . The IR and ^{13}C NMR confirmed the presence of the $\text{C}=\text{O}$ in the molecule, together with the presence of the alkene carbons, with the vinylic CH_2 group resonating at 132ppm.

4.8 The Use of 4-Vinyl- β -lactams in the Synthesis of Pyrrolobenzodiazepine Analogues

Due to their antitumour antibiotic activity pyrrolobenzodiazepines (PBDs) are a naturally occurring class of compound which have attracted significant interest in the literature.¹⁰² DC-81 (283) and tomaymycin (284) are typical examples of these naturally occurring compounds and synthetic dimeric analogues have been studied for their potential biological activity and are currently in clinical development.¹⁰³⁻¹⁰⁶

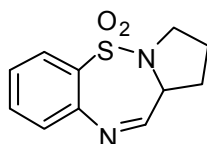


(283)



(284)

The corresponding pyrrolobenzothiadiazepines (PBTDs) (285), although coming under far less scrutiny than their PBD counterparts, have been shown¹⁰⁴ to have, amongst others, activity in the treatment of CNS disorders activity as antiarrhythmic agents and activity as non-nucleosidic reverse transcriptase inhibitors.

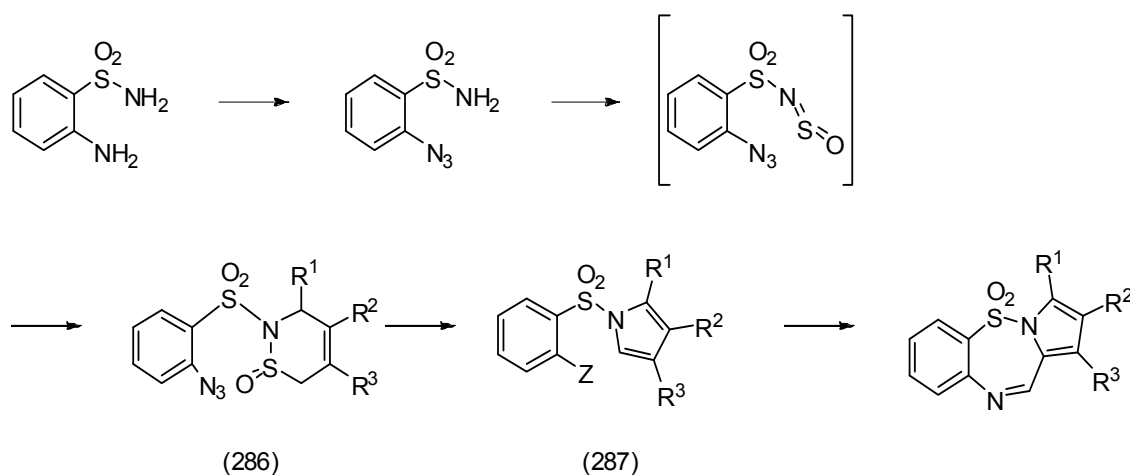


(285)

PBDs and PBTDs both have activity as antitumour antibiotics.¹⁰⁵ These compounds bind covalently to the C2-NH₂ position of guanine within the minor groove of DNA. PBD monomers can cover three DNA base pairs showing a particular affinity for the Pur-G-Pur sequences and block transcription taking place by inhibiting RNA polymerase activity. The potency of PBDs has been improved significantly by linking two PBD units through their aryl ether linkages, forming a dimer that can cross-link appropriately separated guanines on opposite DNA strands.¹⁰⁶

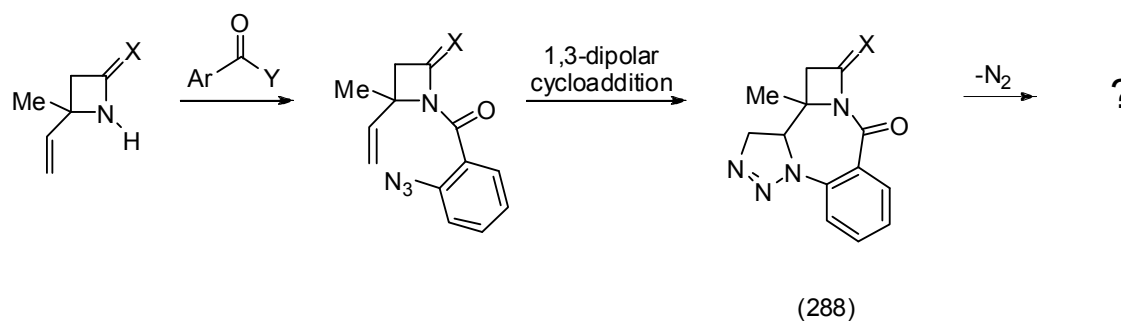
These compounds are highly successful as antibiotics because they fit into the minor groove of the DNA strand, such that little of the PBD unit remains exposed. The complexes are resistant to repair enzymes that are reliant on tracing distortion in DNA, as the PBDs bind in a manner that leaves little of the molecule exposed. The failure of the repair enzymes to detect sites of cross-linking also accounts for the bactericidal nature of these molecules as interstrand cross links if not repaired will interfere with the process of DNA replication and result in cell death.¹⁰⁶

Our interest in this area came about following a comprehensive programme of study^{107,108} undertaken by our research group into the synthesis of PBDs, which are sulfonamide analogues of the PBDs. The PBD analogues synthesised by our research group use the pyrrole (287) as the source of the five membered ring (Scheme 95), where compound (287) was obtained by a ring-contraction process of the 1,2-thiazine-1-oxide (286).^{102a}



Scheme 95

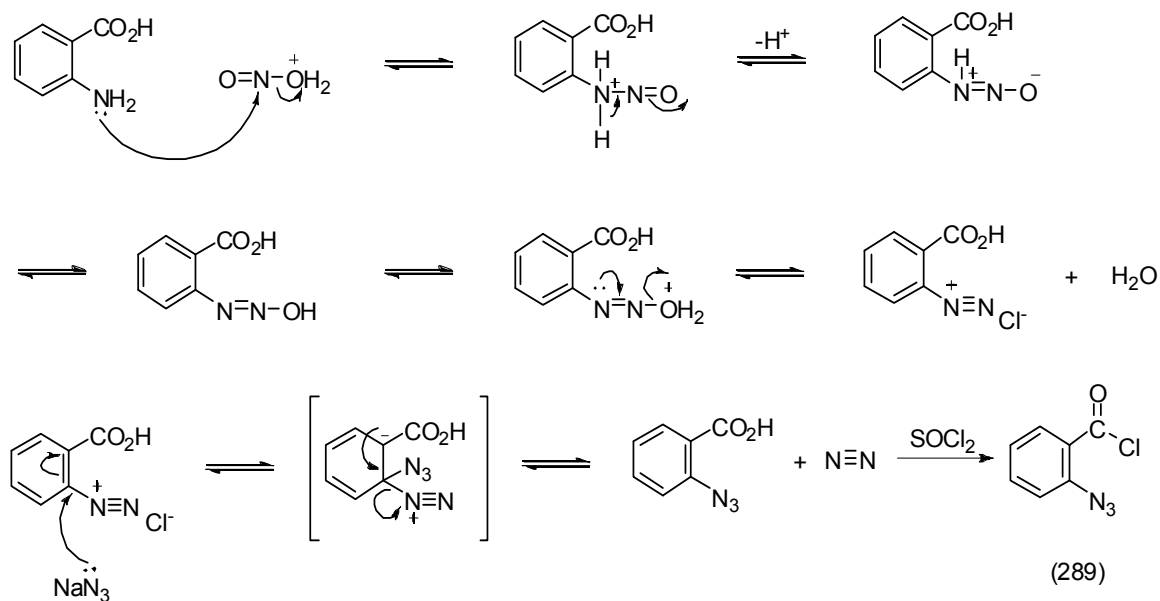
It was on this basis that it was decided to explore the possibility of using 4-vinyl beta lactams, which vary only by a single carbon atom to that of their pyrrole counterparts, in an attempt to access azetidino analogues of PBDs. It was anticipated that the beta lactam would be used as a template for coupling with an acid chloride and that the resulting compound would subsequently undergo a 1,3-dipolar cycloaddition reaction, to form a PBD analogue (288) (Scheme 96), which could then lose nitrogen to form new heterocyclic products.



Scheme 96

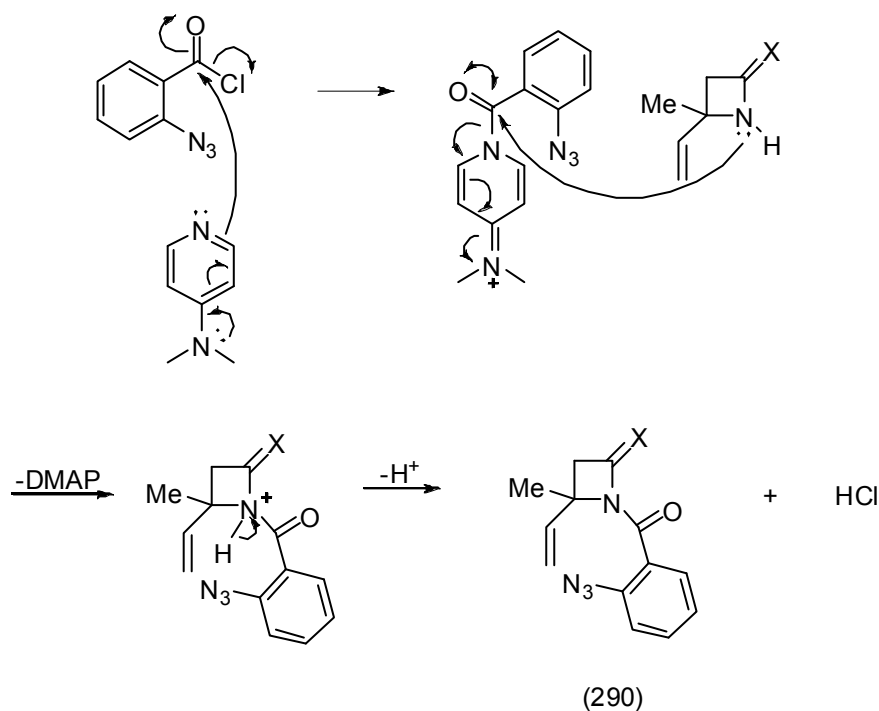
Beta lactam (222) (see section 2.3) was selected for the attempted synthesis of an initial PBD analogue. This was due to the molecule containing an exocyclic C=C double bond, which would be required for the 1,3-dipolar cycloaddition reaction to yield the desired PBD analogue.

O-azidobenzoyl chloride (289) has previously been shown by our research group to couple successfully with pyrrolidines.¹⁰⁹ Therefore, *o*-azidobenzoyl chloride (289) was synthesised from anthranilamide in two steps as shown by the mechanisms in Scheme 97. The first step involves formation of the azide and begins with nucleophilic attack of nitrous acid by anthranilamide, with simultaneously loss of water. This intermediate is then deprotonated and subsequent proton transfer then takes place resulting in the formation of a *N*-hydroxylated species. The hydroxyl group undergoes further protonation and eliminates water to yield a diazonium salt. The diazonium salt undergoes aromatic nucleophilic substitution by sodium azide, which attacks the aromatic ring forming a resonance-stabilised carbanion intermediate. The carbanion intermediate then undergoes elimination of nitrogen, which is the driving force for this reaction to occur, to yield *o*-azidobenzoic acid in 65% yield. Subsequent spectroscopic analysis (IR and NMR) confirmed the structure of *o*-azidobenzoic acid which showed the clear presence of an azide in the IR and also an OH stretch for the carboxylic acid hydroxyl group. The ¹H NMR also confirmed the presence of the OH group from the carboxylic acid and the ¹H and ¹³C NMR showed the presence of four aromatic protons and seven carbons. The *o*-azidobenzoic acid was converted into the acid chloride (289) by treatment with thionyl chloride.¹¹⁰



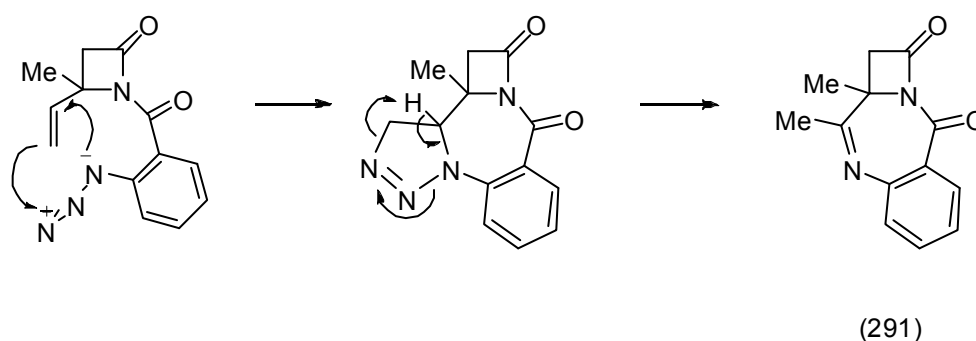
Scheme 97

With access to the acid chloride (289) successfully achieved, the next task was to investigate the reactivity of this compound towards beta lactam (222). The two reactants were successfully coupled using triethylamine and dimethylaminopyridine in dichloromethane to give the desired product (290). Scheme 98 shows the mechanism for the reaction of beta lactam (222) with *o*-azidobenzoyl chloride (289). The first step of the reaction involves the nucleophilic attack of DMAP with *o*-azidobenzoyl chloride. DMAP acts as a hypernucleophilic acylation agent and in its presence the acylation occurs much more rapidly. The second step of the reaction involves attack of the DMAP-coupled reagent by the nitrogen of the beta lactam. This is accompanied by subsequent loss of the DMAP which is regenerated. The final stage of the reaction involves loss of a proton to form coupled product (290).



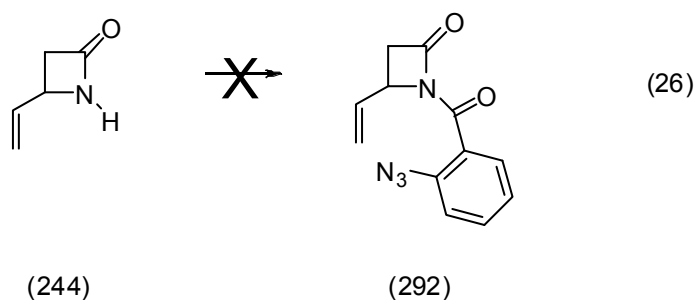
Scheme 98

Compound (290) was thermolysed by heating in toluene to yield a new product, which was identified as the methyl imine (291) in 91% yield (Scheme 99). The mechanism for this reaction involves a 1,3-dipolar cycloaddition between the azide and alkene. Loss of nitrogen from the resulting triazolone and proton transfer, then gives the product (291) (Scheme 99). Compound (291) showed the expected spectroscopic characteristics. These include the infrared, which showed two carbonyl stretches at 1685 and 1655 cm^{-1} . The NMR also showed a ratio of 3:3:2 protons representative of the two methyl groups and the methylene group. The mass spectroscopy data also showed the main peak of 229 (ES⁺) consistent with M+1 for the proposed structure, a feature confirmed by accurate mass measurement.



Scheme 99

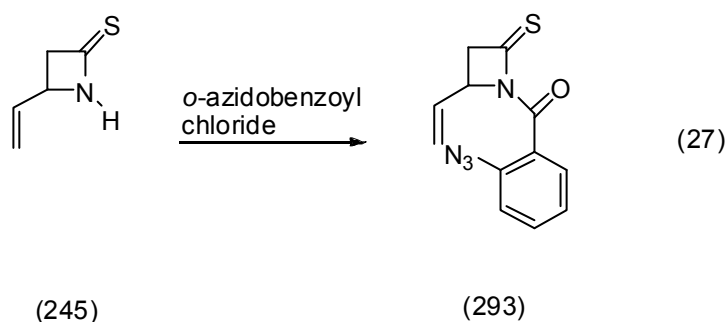
Following the successful synthesis of azetidino-benzodiazepine (291) a further example of this reaction was sought. Therefore, β -lactam (244) was selected for the attempted coupling with *o*-azidobenzoyl chloride (289) (equation 26). It was hoped compound (292) could then be thermolysed to yield another azetidino analogue of the PBDs.



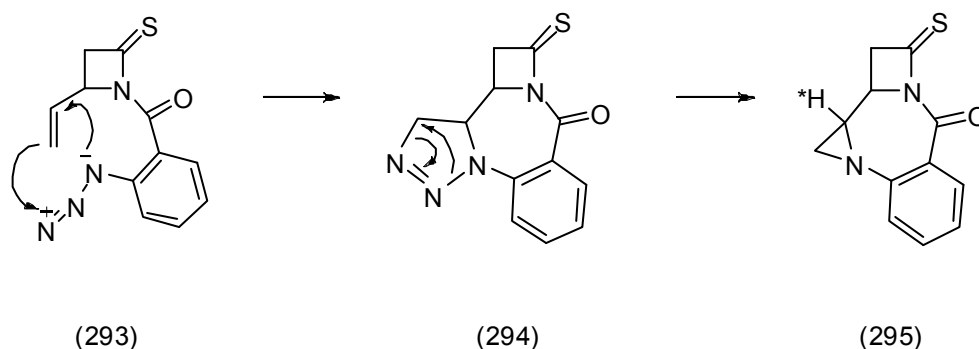
In the event, β -lactam (244) did not undergo the initial coupling step, even after prolonged and repeated attempts. In an attempt to synthesise a further example of a PBD analogue, it was decided to explore the possibility of thionating beta lactam (244) prior to attempting the coupling process. This was based on the hypothesis that the increased availability of the nitrogen lone pair might give an increased chance of coupling.

On reaction of thione (245) with *o*-azidobenzoyl chloride (289), compound (293) was synthesised in 71% yield (equation 27). The proposed mechanism for this reaction is identical to that shown in Scheme 98. Compound (293) showed the expected spectroscopic characteristics. These include the infrared, which showed a carbonyl stretch at 1687 cm^{-1} , a C=S stretch at 1463 cm^{-1} , and peak at 2128 cm^{-1} , which is typical of an azide group. The NMR

showed the appropriate ratio of protons and also the absence of an N-H proton, which provided further confirmation that the coupling process had taken place successfully. Mass spectroscopy also confirmed the correct mass of the product with the main peak [M+1] of 259 (ES+) at 100%, together with a fully consistent high resolution mass measurement.

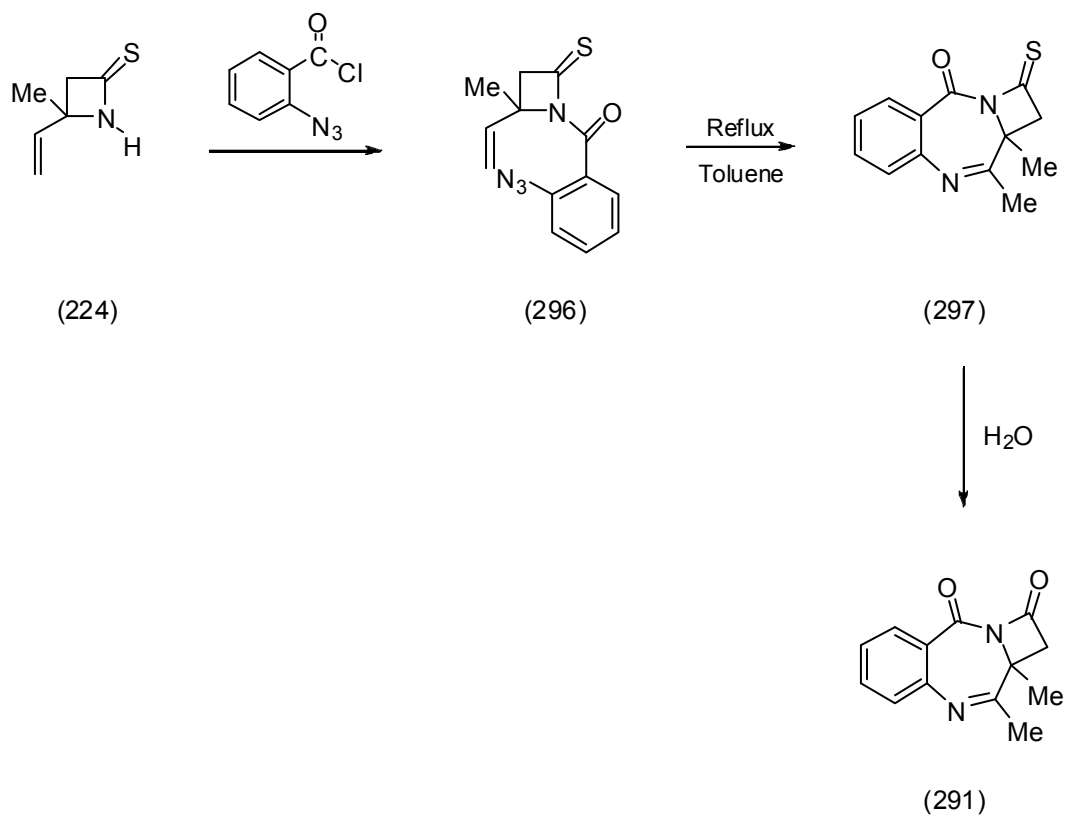


Having successfully synthesised coupled compound (293) the next step was to thermolyse this compound in order to obtain the desired PBD analogue. This time, thermolysis in toluene gave the aziridino compound (295) in 48% yield, as shown in the mechanism in Scheme 100. The first step again involves a 1,3-dipolar cycloaddition reaction between the alkene of the lactam and the azide group in order to form compound (294). This compound spontaneously loses nitrogen to form aziridine (295) (Scheme 100). Compound (295) showed the expected spectroscopic characteristics. These include the infrared, which shows peaks at 1698 and 1454 cm^{-1} representative of the lactam and thiolactam moieties within the molecule. There were no methyl peaks present in either the ^1H or ^{13}C NMR spectra which precluded the possibility of the product being the methyl imine akin to that formed in Scheme 99. There is also a distinct splitting pattern present in the ^1H NMR spectrum of compound (295). The two geminal protons on the aziridine couple only to the proton H^* and not to each other. Mass spectral analysis confirmed loss of N_2 and confirmed that the product was not triazoline (294). The formation of aziridines in this way is well documented.¹¹¹



Scheme 100

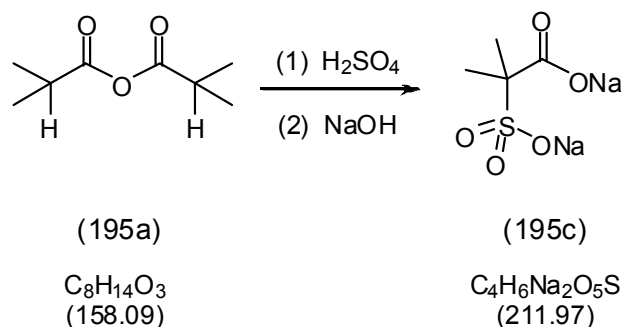
The final synthesis in the coupling reaction series was that of methyl thiolactam (224). Reaction of thiolactam (224) with *o*-azidobenzoyl chloride resulted in the formation of coupled compound (296). The structure of this product was confirmed by spectroscopic analysis. For example, the IR showed the presence of an azide at 2128 cm^{-1} , a C=O stretch at 1687 cm^{-1} and also a C=S stretch at 1463 cm^{-1} . The ^1H NMR showed the appropriate ratio of protons and the IR and ^1H NMR showed the loss of N-H from the molecule, which provided further confirmation that the coupling process had taken place successfully. High resolution mass spectroscopy was also fully consistent with the structure of the product. Having successfully completed the coupling step, the final stage of the reaction was to thermolyse compound (296) in order to obtain the desired PBD analogue. Thermolysis in toluene surprisingly resulted in the production of compound (291) in 91% yield. The first step involves a 1,3-dipolar cycloaddition reaction between the alkene of the lactam and the azide group, extraction of nitrogen to form the methyl imine (as per Scheme 99), and subsequent hydrolysis as shown in Scheme 101. The final product of the reaction was confirmed by spectroscopic analysis to be identical to that of compound (291), the product shown in Scheme 99. Compound (291) was present prior to chromatography and it is probable therefore that the toluene was wet or that compound (297) underwent atmospheric hydrolysis.



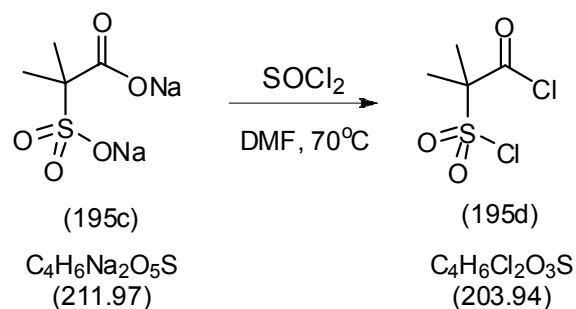
Scheme 101

In conclusion, 4-vinyl-azetidinones were found to be excellent substrates for the synthesis of azetidinobenzodiazepines via the use of intramolecular azide to alkene 1,3-dipolar cycloadditions.

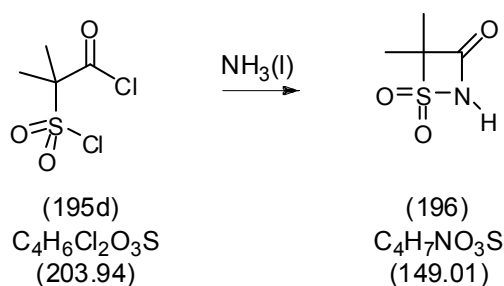
Experimental

Chapter 3: Experimental**5.0 Synthesis of 3-oxo- β -sultam****Synthesis of disodium-2-methyl-2-sulfonatopropionate**

A solution of isobutyric anhydride and concentrated sulphuric acid was stirred at ambient temperature for 30 minutes before being heated to 90°C until no precipitate remained. (In order to ascertain that sulfonation was complete an aliquot was removed and a few drops of BaCl₂ were added. If no precipitate was formed then the reaction was complete). The reaction mixture was poured into ice-cold water and extracted with ether (3×200 mL) to remove the isobutyric anhydride from the sulfonation process. A solution of sodium hydroxide (30.8 g) and water (100 mL) was added to the aqueous phase adjusting the pH to 8 and the resulting solution was concentrated by rotary evaporation. The crude residue was dissolved in hot water (100 mL) (charcoaling where necessary) and ethanol (260 mL). The product was filtered and ethanol added to the mother liquor to yield a second batch of product. **Disodium-2-methyl-2-sulfonatopropionate (195c)** was obtained in 46% yield as a white solid.

Synthesis of 2-(chlorosulfonyl)-2-methylpropionyl chloride

To a stirring solution of disodium-2-methyl-2-sulfonatopropionate (21.14 g, 99.7 mmol) in thionyl chloride (79 mL) at 0°C, was added dimethylformamide (1.6 mL). The reaction mixture was heated at 70°C until gas production was complete and then for an additional 5 hours. The solution was cooled to room temperature and additional thionyl chloride was removed on the rotary evaporator. The crude residue was dissolved in ether, filtered and again evaporated to dryness under vacuum to give **2-(chlorosulfonyl)-2-methylpropionyl chloride** in 50% yield as a clear, yellow oil.

Synthesis of 4,4-dimethyl-1,2-thiazetid-3-one-1,1-dioxide

2-(Chlorosulfonyl)-2-methylpropionyl chloride (10.21 g, 50.1 mmol) dissolved in dry ether (24 mL) was added dropwise (VERY SLOWLY) over 3 hours, at -78°C to liquid ammonia (50 mL) in dry ether (25 mL). After the addition was complete, the mixture was warmed to room temperature and the solvent allowed to evaporate. The residue was dissolved in chloroform (25 mL) and water (25 mL) at 0°C. The pH was adjusted to 1 using cold hydrochloric acid (1M) and the resulting solution was extracted using chloroform (3 × 50 mL). The organic layers were combined, dried over sodium sulfate, filtered and

evaporated to dryness under vacuum to give **4,4-dimethyl-1,2-thiazetid-3-one-1,1-dioxide (196)**; 4.58 g, 61% yield) as a white solid.

The sample was also able to be purified by silica column chromatography using 3:1 petroleum ether:EtOAc solvent system.

Compound data

IR: ν_{\max} (cm⁻¹) thin film in chloroform: 3145.0 (m), 1752.7 (s), 1464.1 (w), 1387.7 (w), 1331.3 (s), 1271.0 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.35 (1H, s, NH), 1.86 (6H, s, 2 × CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 163.78 (C=O), 82.33 (q), 18.56 (2 × CH₃).

(ESMS-): 64.2, 100.2, 105.1, 148.1.

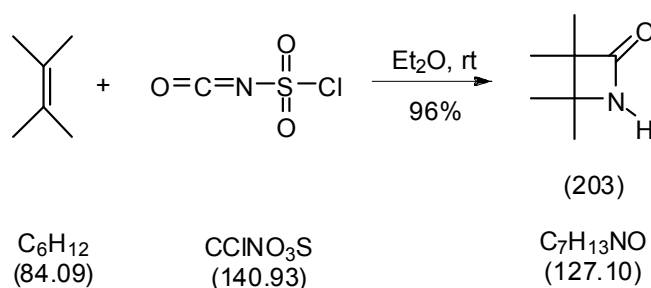
High Resolution Mass Spectroscopy: Electrospray (negative), calc. = 148.0074, measured = 148.0073.

Attempts to thionate 4,4-dimethyl-1,2-thiazetid-3-one-1,1-dioxide (**196**) using Lawesson's reagent, resulted in the suspected hydrolysis of the sulfur compound back to its oxygen analogue.

Similarly attempts to O-alkylate 4,4-dimethyl-1,2-thiazetid-3-one-1,1-dioxide (**196**) were also unsuccessful and the compound decomposed.

5.1 Synthesis of model and novel 1-azetines and their 1,3-dipolar cycloadditions

Synthesis of 3,3,4,4-Tetramethylazetid-2-one



To 2,3-dimethyl-2-butene (4.3 mL, 35.7 mmol) dissolved in anhydrous ether (10 mL), was added a solution of chlorosulfonylisocyanate (4.0 mL, 46.0 mmol) in dry ether (5 mL), dropwise over five minutes. The reaction was carried out under an inert atmosphere of nitrogen at ambient temperature. The resulting clear and colourless solution was left to stir at room temperature for 24 hours.

Ether was removed by rotary evaporation to produce a bright yellow solid, which was subsequently redissolved in fresh ether (20 mL) to yield a bright yellow solution. The liquid was added to a vigorously stirred solution of water (30 mL), ice (20 g), sodium hydrogen carbonate (9 g) and sodium sulfite (6 g) which was stirred at 0°C for four hours.

The resulting solution was extracted with ether (5x20 mL), the organic layers combined, dried over magnesium sulfate and concentrated under vacuum, to yield **3,3,4,4-tetramethylazetid-2-one (203)**; 4.41 g, 96% yield) as a white solid.

Compound data

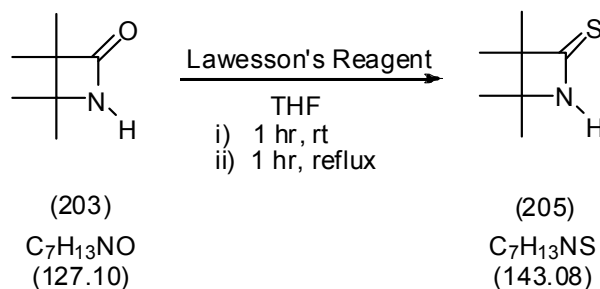
IR: ν_{\max} (cm⁻¹) nujol mull: 3185.5 (s), 2922.7 (s), 1704.2 (s), 1459.6 (m), 1397.3 (m), 1376.8 (m), 1313.7 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.49 (1H, s, NH), 1.26 (6H, s, CH₃), 1.23 (6H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 175.02 (C=O), 54.06 (q), 57.98 (q), 24.87 (CH₃), 19.34 (CH₃).

(ESMS+): 58.3, 85.3, 128.1.

Synthesis of 3,3,4,4-Tetramethylazetididin-2-thione

3,3,4,4-Tetramethylazetididin-2-one (2.0 g, 15.7 mmol) was dissolved in dry tetrahydrofuran (30 mL) at room temperature under an inert atmosphere of nitrogen. To this solution Lawesson's reagent (3.18 g, 7.9 mmol) was added in one portion and the sample was stirred for one hour. The resulting clear, yellow solution was heated at reflux for a further hour and monitored for completion by tlc. The sample was concentrated under vacuum and purified by flash silica column chromatography, (eluent: petroleum ether:ethyl acetate/3:1) to yield **3,3,4,4-tetramethylazetididin-2-thione (205)**; 2.03 g, 90% yield) as a white solid.

Compound data

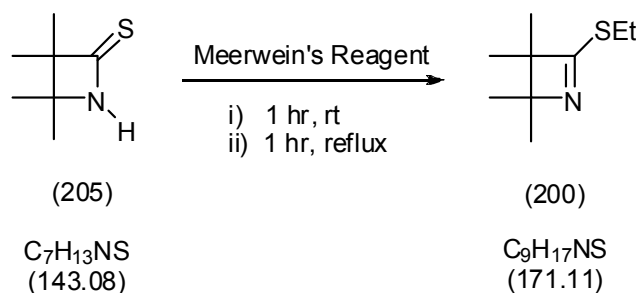
IR: ν_{max} (cm^{-1}) thin film in chloroform: 3379.7 (w), 3134.5 (m), 2989.9 (m), 1498.4 (s), 1373.9 (m), 1216.2 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 8.60 (1H, s, NH), 1.25 (6H, s, CH_3), 1.41 (6H, s, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 212.10 (C=S), 68.52 (q), 56.76 (q), 23.47 (CH_3), 20.82 (CH_3).

(ESMS+): 58.3, 85.2, 110.1, 144.2.

Synthesis of 2-(ethylthio)-3,3,4,4-tetramethyl-1-azetine

To 3,3,4,4-tetramethylazetidion-2-thione (0.68 g, 4.76 mmol) under an inert atmosphere of nitrogen, at room temperature, was added Meerwein's reagent (1M solution in methylene chloride, 7.16 mL, 7.13 mmol) dropwise over five minutes. The mixture was stirred for one hour at room temperature, before being heated at reflux for an additional hour. The sample was cooled to room temperature and added dropwise over 30 minutes to an ice cold aqueous solution of potassium carbonate (50%) at -10°C and stirred for one hour, before being filtered through celite. The resulting clear, yellow solution was extracted using dichloromethane (3×20 mL), the organic layers combined, dried over magnesium sulfate, filtered and rotary evaporated to dryness. The crude sample was subsequently purified using silica column chromatography, (eluent: petroleum ether:ethyl acetate/3:1, to yield **2-(ethylthio)-3,3,4,4-tetramethyl-1-azetine (200)**; 0.36 g, 44% yield) as a clear orange oil.

Compound data

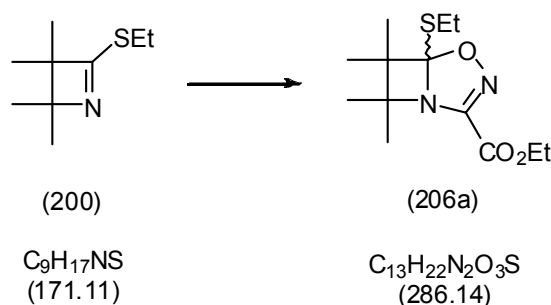
IR: ν_{\max} (cm⁻¹): 2963.3 (m), 2876.8 (w), 1535.1 (m), 1448.6 (m), 1372.1 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 2.98 (2H, q, J 7.4, CH₂), 1.34 (3H, t, J 7.4, CH₃), 1.27 (6H, s, CH₃), 1.14 (6H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 187.08 (C=N), 69.95 (q), 51.32 (q), 23.79 (CH₃), 21.82 (CH₂), 20.62 (CH₃), 14.87 (CH₃).

Synthesis of 2-Ethoxycarbonyl-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene



To ethylchloroximidoacetate (0.22 g, 1.46 mmol) was added 2-(ethylthio)-3,3,4,4-tetramethyl-1-azetidine (0.25 g, 1.46 mmol) in THF (10 ml) in one portion forming a clear, pale yellow solution. A solution of triethylamine (0.28 mL, 1.61 mmol) in THF (5 mL) was added drop-wise over 5 hours. The mixture was left to stir overnight at ambient temperature under an inert atmosphere of nitrogen. The resulting solution was evaporated to dryness and purified using silica column chromatography (eluent: Petroleum ether:Ethyl acetate/5:1), to yield **2-ethoxycarbonyl-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (206a; 0.24 g, 61% yield)** as a white solid.

Compound data

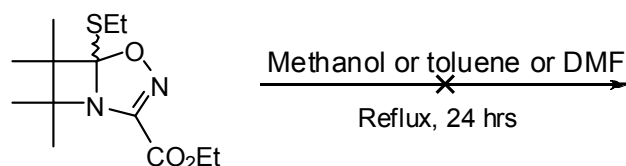
IR: ν_{max} (cm^{-1}): 2971.3 (m), 2930.6 (m), 1737.0 (s), 1548.8 (s), 1448.4 (m), 1374.6 (m), 1194.7 (s).

NMR

1H : δ_H (400 MHz, $CDCl_3$): 4.35 (2H, dq, J 7.1, 3.6 CH_2), 2.63 (2H, 2 \times dq, J 7.5, 3.0, CH_2), 1.53 (3H, s, CH_3), 1.36 (3H, t, J 7.1, CH_3), 1.26 (3H, s, CH_3), 1.24 (3H, t, J 7.5, CH_3), 1.21 (3H, s, CH_3), 1.20 (3H, s, CH_3).

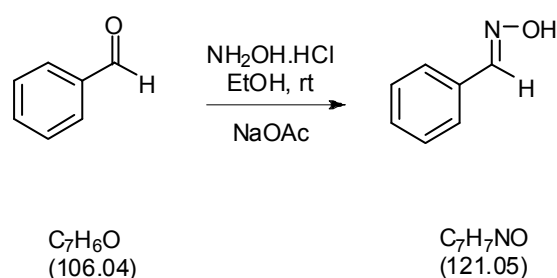
^{13}C : δ_C (100 MHz, $CDCl_3$): 158.38 (C=O), 153.12 (C=N), 121.15 (C-O), 73.69 (q), 62.50 (CH_2), 54.29 (q), 26.20 (CH_3), 21.66 (CH_2), 20.49 (CH_3), 20.08 (CH_3), 20.49 (CH_3), 14.21 (CH_3), 14.00 (CH_3).

The attempted thermolysis of 2-ethoxycarbonyl-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene



A sample of 2-ethoxycarbonyl-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.18g) was dissolved in dry methanol (10 mL) and heated at reflux, under an inert atmosphere of nitrogen, for 24 hours. TLC confirmed no reaction had taken place and 50% of the sample was removed, the solvent replaced with toluene and heated simultaneously with the sample in methanol, for a further period of 24 hours. The reactions were continually monitored by tlc throughout the heating period. TLC showed no further reaction had taken place and the samples were subsequently combined and heated at reflux in anhydrous dimethylformamide (5 mL) for one week. The tlc showed no reaction and eventual decomposition of the sample to a multi-spot inseparable mixture.

Synthesis of benzaldehyde nitrile oxide



To a mixture of hydroxylamine hydrochloride (10.5 g, 150.9 mmol) and sodium acetate (15 g) in ethanol (150 mL) was added at room temperature under an inert atmosphere of nitrogen, with vigorous stirring, benzaldehyde (8 g, 75.5 mmol). The reaction was left to stir for five hours at room temperature. The solution was filtered to remove precipitates and the resulting mother liquor was evaporated to dryness under vacuum. The solid was dissolved in dichloromethane, the aqueous layer removed and extracted with

dichloromethane (2×10 mL), and the combined organics dried over sodium sulfate, filtered and rotary evaporated to dryness to yield **benzaldoxime** (10.43 g, 87%) as a clear, yellow oil.

Compound data

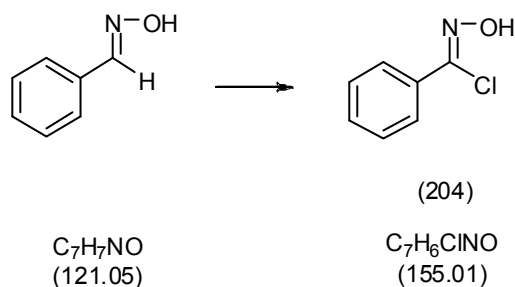
IR: ν_{\max} (cm^{-1}): 3388.4 (m, broad), 3085.8 (m), 3064.0 (m), 3030.4 (m), 2819.8 (m), 2737.6 (m), 1703.1 (vs), 1597.4 (s), 1584.1 (s), 1455.8 (s), 1390.9 (m), 1311.1 (s).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 9.45 (1H, s, CH), 7.59 (2H, m, 2 × Ar-H), 7.42 (3H, m, 3 × Ar-H), 2.18 (1H, s, OH).

^{13}C : δ_{C} (100 MHz, CDCl_3): 150.05 (CH), 131.78 (q), 130.35 (CH), 128.80 (CH), 127.01 (CH).

Synthesis of benzaldoxime chloride



To a solution of N-chlorosuccinimide (5.5 g, 41.3 mmol) in anhydrous dichloromethane (50 mL) was added dry pyridine (0.5 mL) in one portion with continual stirring. This process was undertaken at room temperature, under an inert atmosphere of nitrogen and the resulting clear and colourless solution was stirred for ten minutes. Upon subsequent addition of benzaldoxime (5.0 g, 41.3 mmol) in one portion, the solution turned a clear orange colour and was left to stir overnight at ambient temperature. The sample was concentrated under vacuum and purified using column chromatography (eluent: petroleum ether:ethyl acetate/5:1), to yield **benzaldoxime chloride** (**204**; 4.34 g, 68% yield) as a clear, yellow oil.

Compound data

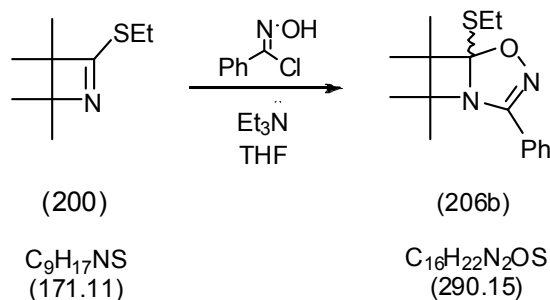
IR: ν_{\max} (cm⁻¹): 3330.9 (s, broad), 3063.0 (s), 1702.2 (s), 1600.1 (s), 1578.1 (m), 1447.7 (m), 1376.1 (m), 1235.6 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 9.02 (1H, s, broad, OH), 7.85 (2H, m, 2 × Ar-H), 7.43 (3H, m, 3 × Ar-H).

¹³C: δ_{C} (100 MHz, CDCl₃): 147.50 (q), 139.85 (q), 130.61 (CH), 128.68 (CH), 127.15 (CH).

Synthesis of 5-(ethylthio)-6,6,7,7-tetramethyl-2-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene



To benzaldoxime chloride (0.22 g, 1.46 mmol) was added 2-(ethylthio)-3,3,4,4-tetramethyl-1-azetidine (0.25 g, 1.46 mmol) in THF (10 mL) in one portion. To this, a solution of triethylamine (0.22 mL, 1.61 mmol) in THF (5 mL) was added dropwise over 6 hours. The mixture was left to stir for 24 hours at ambient temperature under an inert atmosphere of nitrogen. The resulting solution was evaporated to dryness and the product purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/9:1) to yield **the title compound (206b)**; 0.31 g, 71% yield) as a white solid.

Compound data

IR: ν_{\max} (cm⁻¹): 2970.1 (m), 2927.8 (w), 1552.9 (w), 1447.6 (m), 1361.1 (m), 1160.4 (m).

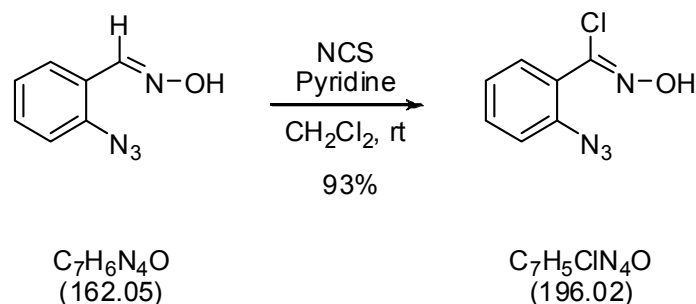
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.73 (2H, d, J 6.7, Ph), 7.41. (3H, m, Ph), 2.68 (2H, 2 × dq, J 7.5, 4.9, CH₂), 1.61 (3H, s, CH₃), 1.26 - 1.28 (9H, 2 × s, 3 × CH₃), 1.00 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 159.57 (C=N), 130.73 (CH), 128.65 (CH), 127.71 (q), 127.09 (CH), 118.12 (q), 71.58 (q), 52.71 (q), 26.82 (CH₃), 21.73 (CH₂), 21.32 (CH₃), 20.85 (CH₃), 19.83 (CH₃), 14.66 (CH₃).

MS(Cl(NH₃)): 52.2, 128.1, 145.1, 231.1, 291.2.

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 291.1526, measured = 291.1523.

Synthesis of o-azidobenzohydroximoyl chloride

To a solution of N-chlorosuccinimide (2.28 g, 17.1 mmol) and pyridine (0.15 mL, d= 0.978) dissolved in dry dichloromethane (15 mL) was added o-azidobenzaldoxime (2.77 g, 17.1 mmol), in one portion at room temperature under an inert atmosphere of nitrogen. The resulting bright orange solution was stirred overnight before removing the solvent by rotary evaporation to produce a brown solid. This was subsequently purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/7:3) to yield **o-azidobenzohydroximoyl chloride** (3.11 g, 93% yield) as a brown solid. Melting point: 79-82°C (literature melting point: 80-82°C).¹¹²

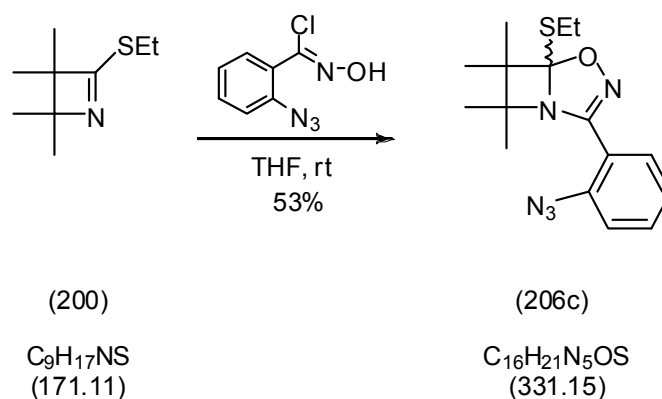
Compound data

IR: ν_{\max} (cm^{-1}): 3237.1 (vs, broad), 3058.9 (s), 2131.4 (vs), 1772.2 (s), 1708.1 (vs), 1489.9 (s), 1445.8 (m), 1351.7 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 9.60 (1H, s, OH), 7.59-7.48 (2H, m, Ar-H), 7.24 (2H, m, Ar-H).

^{13}C : δ_{C} (100 MHz, CDCl_3): 138.33 (q, C=N), 136.20 (q), 131.54 (CH), 131.13 (CH), 124.74 (CH), 119.01 (CH), 60.62 (q).

Synthesis of 2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene

To a stirring solution of o-azidobenzohydroximoyl chloride (0.68 g, 3.46 mmol) in anhydrous tetrahydrofuran (10 mL) was added 2-(ethylthio)-3,3,4,4-tetramethyl-1-azetidine (0.59 g, 3.46 mmol) in one portion, under an inert nitrogen atmosphere. The sample was stirred for 10 minutes before triethylamine (0.53 mL, 3.80 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise over 5 hours and the reaction left to stir overnight. When the reaction was complete the sample was reduced in volume using rotary evaporation and the sample purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/7:1), to yield **2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (206c; 0.61 g, 53% yield)** as a yellow solid, melting point: 167-171°C.

Compound data

IR: ν_{\max} (cm⁻¹): 3053.3 (w), 2974.3 (w), 2129.6 (m), 1582.1 (w), 1492.1 (w), 1265.6 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.66 (1H, dd, J 6.3, 1.5, Ar-H), 7.47. (1H, td, J 8.0, 1.7, Ar-H), 7.24 (3H, m, 3 × Ar-H), 2.70 (2H, 2 × dq, J 7.5, 2.6, CH₂ (SEt)), 1.51 (3H, s, CH₃), 1.31 (3H, s, CH₃) 1.30 (3H, t, J 7.5, CH₃(SEt)), 1.27 (3H, s, CH₃), 0.97 (3H, s, CH₃).

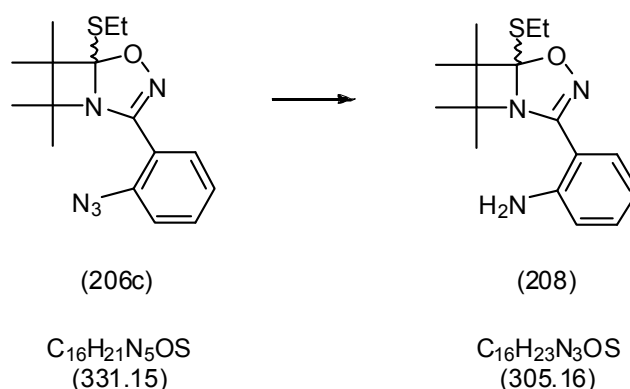
¹³C: δ_{C} (100 MHz, CDCl₃): 157.10 (q), 138.37 (q), 131.46 (CH), 130.77 (CH), 124.64 (CH), 119.57 (CH), 119.22 (q), 117.34 (q), 71.87 (q), 53.18 (q), 26.60 (CH₃), 21.80 (CH₂), 21.10 (CH₃), 20.62 (CH₃), 19.98 (CH₃), 14.77 (CH₃).

MSES+: 159.0, 332.1, 685.1.

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 332.1540, measured = 332.1544.

5.2 Thermolysis reactions of 2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene.

Synthesis of 2-(2'-aminoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene



2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.15 g) was dissolved in dry dimethylformamide (10 mL) under an inert nitrogen atmosphere. The mixture was heated at reflux for 2 hours and monitored by tlc. The sample was concentrated by rotary evaporation and

purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/7:1), to yield **2-(2'-aminoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (208)**; 0.059 g, 43%) yield as an orange oil.

Compound data

IR: ν_{\max} (cm⁻¹): 3475.5 (w), 3356.7 (w), 2966.7 (m), 2927.6 (m), 1618.9 (s), 1492.0 (m), 1359.8 (m), 1261.8 (m).

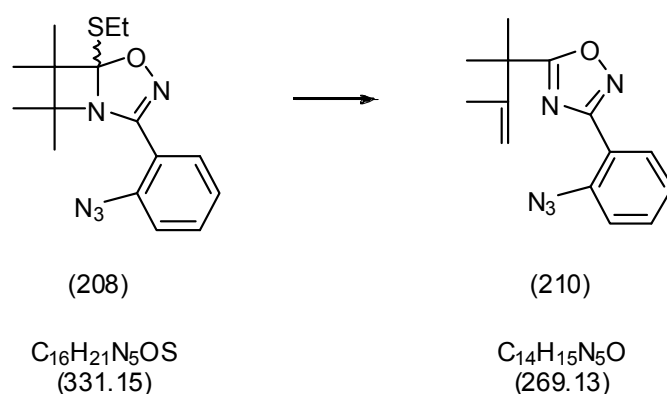
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.30 (2H, m, 2 × Ar-H), 6.71 (2H, m, 2 × Ar-H), 2.65 (2H, m, CH₂ (SEt)), 1.56 (3H, s, CH₃), 1.32 (3H, s, CH₃), 1.29 (3H, t, J 7.2, CH₃), 1.26 (3H, s, CH₃), 0.99 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 159.81 (q), 146.35 (q), 131.25 (CH), 129.76 (CH), 117.06 (CH), 116.45 (q), 116.06 (CH), 111.78 (q), 71.86 (q), 51.83 (q), 29.64 (CH₂), 26.53 (CH₃), 25.73 (CH₃), 21.28 (CH₃), 19.57 (CH₃), 14.66 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 306.1635, measured = 306.1635.

Synthesis of 3-(2'-azidoaryl)-5-(2,3-dimethyl-1-buten-3-yl)-1,2,4-oxadiazole



2-(2'-aminoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.15 g) was dissolved in dry toluene (10 mL) under an inert nitrogen atmosphere. The reaction was heated at reflux for 44

hours and monitored by tlc. The sample was concentrated by rotary evaporation and purified using silica gel column chromatography (eluent: petroleum ether:ethyl acetate/7:1), to yield **the title compound (210)**; 0.077 g, 63% yield) as an orange oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2982.4 (w), 2129.5 (s), 2099.7 (m), 1557.7 (w), 1484.6 (m), 1348.4 (m).

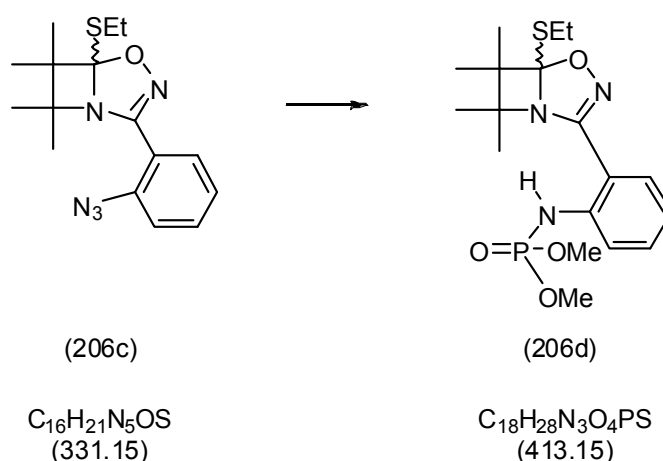
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.01 (1H, m, Ar-H), 7.53 (1H, m, Ar-H), 7.29 (2H, m, Ar-H), 4.96 (2H, d, J 11.2, CH₂) 1.76 (3H, s, CH₃), 1.72 (6H, s, 2 × CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 183.76 (q), 166.09 (q), 147.04 (q), 138.73 (q), 131.83 (Ar-H), 131.64 (Ar-H), 124.79 (Ar-H), 119.25 (Ar-H), 118.69 (q), 111.77 (CH₂), 41.96 (q), 25.71 (CH₃), 19.71 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 270.1349, measured = 270.1353.

Reaction of 2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene with trimethylphosphite



A solution of 2-(2'-azidoaryl)-5-(ethylthio)-6,6,7,7-tetramethyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.16 g, 0.50 mmol) and trimethylphosphite (0.12 mL, 1.01 mmol), were stirred together in tetrahydrofuran for 24 hours at room temperature under an atmosphere of nitrogen. Water (0.091 mL, 5.05

mmol) was added via syringe in one portion and the reaction was left to stir under a nitrogen atmosphere for a further 24 hours. The sample was concentrated under vacuum and purified using flash silica column chromatography (eluent: petroleum ether:ethyl acetate/1:2) to yield **the phosphoramidate (206d)**; 0.13 g, 65% yield) as a yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 3046.9 (m), 2956.2 (m), 1582.1 (w), 1492.1 (w), 1265.6 (s).

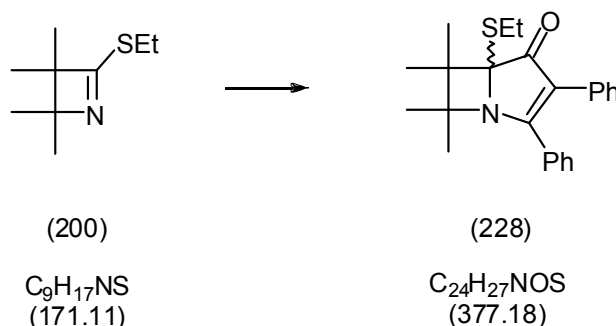
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.34 (1H, d, J 9.0 N-H), 7.48 (1H, d, J 7.7, Ar-H), 7.40 (1H, d, J 8.2, Ar-H), 7.31 (1H, m, Ar-H), 6.95 (1H, t, J 7.4, Ar-H), 3.78 (6H, t, J 7.4, 2 × OMe), 2.59 (2H, m, CH₂), 1.54 (3H, s, CH₃), 1.29 (3H, s, CH₃), 1.22 (3H, t, 7.2, CH₃), 0.93 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 159.20 (C=N), 139.33 (q), 131.52 (CH), 129.57 (CH), 120.69 (CH), 117.31 (q), 116.62 (CH), 113.82 (q), 113.71 (q), 72.40 (q), 53.41 (2 × CH₃), 52.13 (q), 29.40 (CH₂), 21.64 (CH₃), 21.09 (CH₃), 19.50 (CH₃), 14.51 (CH₃), 11.25 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 414.1578, measured = 414.1564.

Synthesis of 5-(ethylthio)-6,6,7,7-tetramethyl-2,3-diphenyl-1-azabicyclo[3.2.0]-hept-2-en-4-one



To a stirred solution of 2-(ethylthio)-3,3,4,4-tetramethyl-1-azetidine (0.10 g, 0.54 mmol) in dry acetonitrile (10 mL) was added, with stirring, diphenylcyclopropenone (0.11 g, 0.53 mmol) in one portion. The reaction was

left to stir under an inert atmosphere of dry nitrogen for 96 hours (monitored by tlc until completion). The crude sample was concentrated under vacuum and purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1) to yield **the title compound (228)**; 0.20 g, 91% yield) as a yellow solid, melting point: 162-164°C (literature melting point: 162-163°C).^{27a}

Compound data

IR: ν_{\max} (cm⁻¹): 3356.2 (m), 1637.8 (s), 1496.8 (m), 1375.7 (w), 1171.8 (m)

NMR

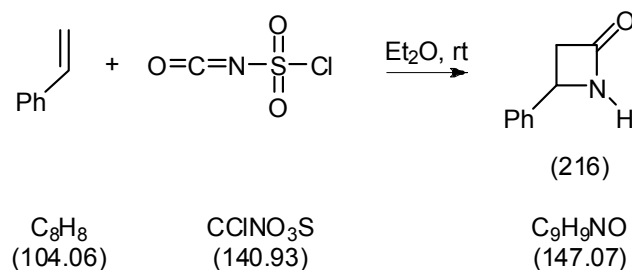
¹H: δ_{H} (400 MHz, CDCl₃): 7.53, 7.43 & 7.30 (10H, m, Ar-H), 2.47 (2H, 2 × dq, J 7.5, 4.4, and 7.4, 4.4 CH₂ (SEt)), 1.74 (3H, s, CH₃), 1.32 (3H, s, CH₃), 1.25 (3H, s, CH₃) 1.18 (3H, t, J 7.5, CH₃), 0.74 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 202.25 (C=O), 175.06 (q), 133.62 (q), 131.36 (q), 131.13 (CH), 129.41 (CH), 128.77 (CH), 128.46 (CH), 128.14 (CH), 126.56 (CH), 123.32 (q), 84.13 (q), 70.14 (q), 42.31 (q), 27.91 (CH₃), 23.01 (CH₃), 22.50 (CH₃), 22.34 (CH₂), 19.66 (CH₃), 14.36 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 378.1886, measured = 378.1888.

5.3 Synthesis and Reactions of 2-(ethylthio)-4-phenyl-1-azetine

Synthesis of 4-Phenylazetid-2-one



To a stirring solution of styrene (3.95 mL, 37.9 mmol) in anhydrous ether (10 mL), under an inert atmosphere of nitrogen, was added chlorosulfonyl isocyanate (3 mL, 34.5 mmol) in anhydrous ether (5 mL), dropwise over 15 minutes at ambient temperature. The reaction mixture was left to stir

overnight, at which point it was concentrated *in vacuo* to produce a white solid which was subsequently redissolved in fresh ether (20 mL). The solution was added to a vigorously stirred solution of water (30 mL), ice (20 g), sodium hydrogen carbonate (9 g) and sodium sulfite (6 g) which was stirred at 0°C for four hours. The resulting solution was extracted with ether (5x20 mL), the organic layers combined, dried over magnesium sulfate and concentrated under vacuum, to yield **4-phenylazetididin-2-one (216)**; 3.39 g, 80% yield) as a white solid.

Compound data

IR: ν_{\max} (cm⁻¹): 3412.0 (m), 1757.9 (vs), 1456.2 (w), 1361.8 (w).

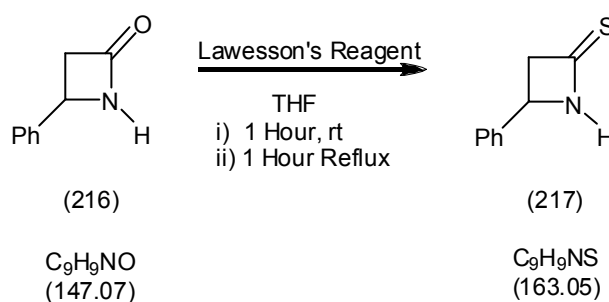
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.40 (5H, m, 5 × Ar-H), 6.65 (1H, s, N-H), 4.73 (1H, dd, J 16.2, 5.7 CH), 3.46 (1H, dd, J 16.1, 5.6 CH), 2.88 (1H, m, CH).

¹³C: δ_{C} (100 MHz, CDCl₃): 168.35 (C=O), 140.25 (q), 128.85 (Ar-H), 128.21 (Ar-H), 125.67 (Ar-H), 50.38 (CH), 47.96 (CH₂).

Low Resolution Mass Spectroscopy (CV ES+): 59.5, 79.4, 106.3, 107.3, 148.3, 165.3.

Synthesis of 4-Phenylazetididin-2-thione



To 4-phenylazetididin-2-one (2.89 g, 19.7 mmol) dissolved in dry tetrahydrofuran (30 mL) at room temperature, under a nitrogen atmosphere, was added Lawesson's reagent (3.98 g, 9.85 mmol) in one portion, with stirring. The mixture was left to stir for one hour at room temperature after which time all the solid had dissolved to give a clear yellow liquid. The reaction was heated at reflux for a further hour (monitored for completion by

tlc). Upon cooling to room temperature the solution was concentrated by rotary evaporation and purified using flash silica column chromatography (eluent: petroleum ether:ethyl acetate/3:1), to yield **4-phenylazetid-2-thione (217)**; 1.52 g, 47% yield) as a white solid.

Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3392.4 (w), 3019.3 (s), 1494.8 (m), 1474.5 (s), 1453.2 (s), 1215.7 (vs).

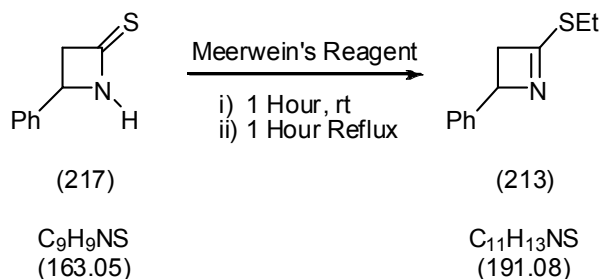
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.70 (1H, s, N-H), 7.30 (5H, m, 5 × Ar-H), 5.10 (1H, dd, J 16.1, 5.6 CH), 3.42 (1H, 16.0, J 5.7 CH), 2.92 (1H, m, CH).

¹³C: δ_{C} (100 MHz, CDCl₃): 203.76 (C=S), 137.43 (q), 128.36 (Ar-H), 128.09 (Ar-H), 125.10 (Ar-H), 58.31 (CH), 50.49 (CH₂).

Low Resolution Mass Spectroscopy: 103.3, 105.3, 106.3, 123.2, 130.3, 131.3, 164.2, 166.2.

Synthesis of 2-(ethylthio)-4-phenyl-1-azetine



Thiolactam (**217**) (1.52 g, 9.33 mmol) was dissolved in Meerwein's reagent (1M in methylene chloride, 13.9 mL, 14.0 mmol) at room temperature with stirring under an inert nitrogen atmosphere. The solution was stirred for one hour at ambient temperature, before being heated at reflux for a further hour and was clear, orange in colour. The sample was cooled to room temperature and added dropwise over 30 minutes to an ice cold solution of potassium carbonate (50%) at -10°C and stirred for one hour. The sample was filtered through celite and the filtrate extracted into methylene chloride. The organic layers were combined, dried over sodium sulfate, filtered and concentrated in

vacuo to yield a clear, orange oil. The sample was purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1), to yield **2-(ethylthio)-4-phenyl-1-azetine (213)**; 0.48 g, 86% yield) as a clear, yellow oil.

Compound data

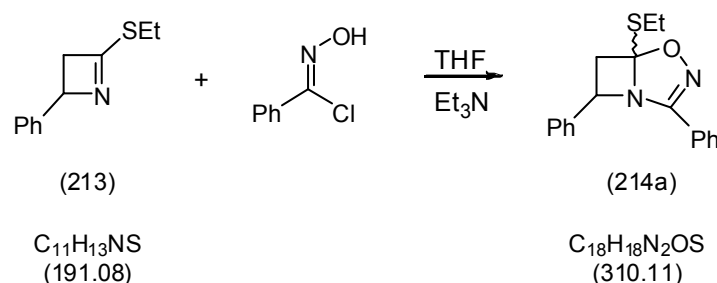
IR: ν_{\max} (cm⁻¹) (liquid film): 3004.3 (m), 1712.1 (vs), 1420.6 (m), 1363.6 (s), 1222.4 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.25 (5H, m, 5 × Ar-H), 4.95 (1H, m, CH), 3.49 (1H, dd, J 16.0, 4.0 CH), 2.99 (1H, dq, J 7.5, 2.6 SCH₂), 2.89 (1H dd, J 16.0, 4.0 CH), 1.34 (3H t, J 7.5, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 170.46 (q), 140.24 (q), 127.77 (Ar-H), 126.74 (Ar-H), 125.36 (Ar-H), 64.50 (CH), 59.71 (CH₂), 22.77 (CH₂), 20.37 (CH₃).

Synthesis of 5-(ethylthio)-2,7-diphenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene



To a stirred solution of the phenylazetine (0.40 g, 2.11 mmol) and chloroxime (0.32 g, 2.11 mmol) in dry tetrahydrofuran (10 mL) was added, with stirring, under an inert atmosphere of nitrogen, triethylamine (0.32 mL, 2.32 mmol) in dry tetrahydrofuran (5 mL) dropwise, over 5 hours. The reaction was allowed to stir overnight, at ambient temperature. The sample was reduced in volume and purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/10:1), to yield **the title compound (214a)**; 0.13 g, 20% yield) as a clear, yellow oil.

Compound data

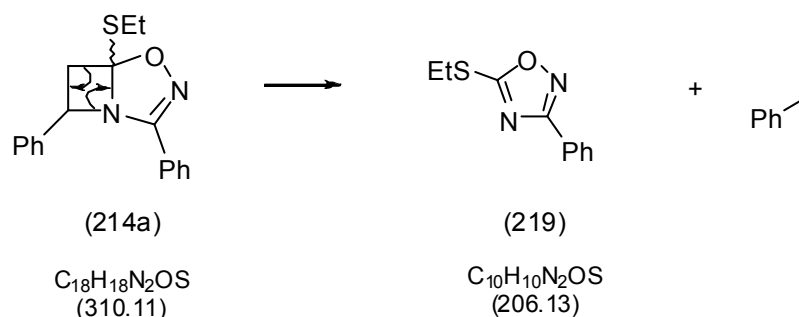
IR: ν_{\max} (cm⁻¹) (liquid film): 3423.1 (m, broad), 3054.2 (w), 1592.7 (w), 1421.9 (w), 1265.3 (vs).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.4-7.5 (10H, m, 10 × Ar-H), 4.85 (1H, q, J 8.4 CH(Ph)), 3.71 (1H, q, J 8.4, CH₂), 2.89 (1H, m, CH₂), 2.77 (2H m, SEt), 1.37 (3H t, J 8.0, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 192.21 (q), 160.73 (q), 156.07 (q), 140.49 (q), 130.85 (Ar-CH), 128.87 (Ar-CH), 128.78 (Ar-CH), 128.67 (Ar-CH), 128.12 (Ar-H), 127.16 (Ar-CH), 66.67 (CH), 45.40 (CH₂), 22.53 (CH₂), 14.66 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 311.1213, measured = 311.1214.

Thermolysis reaction of 5-(ethylthio)-2,7-diphenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene

A solution of 5-(ethylthio)-2,7-diphenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.13 g), in toluene (10 mL) was heated at reflux, under an inert atmosphere of nitrogen. The reaction was then heated at reflux temperature and the progress of the reaction was monitored throughout by tlc, showing completion within a 48 hour period, after which the sample was concentrated by rotary evaporation and purified using column chromatography (eluent: petroleum ether:ethyl acetate/16:1), to yield **5-(ethylthio)-3-phenyl-1,2,4-oxadiazole (219)**; 0.072 g, 83% yield) as a clear, yellow oil.

Compound data

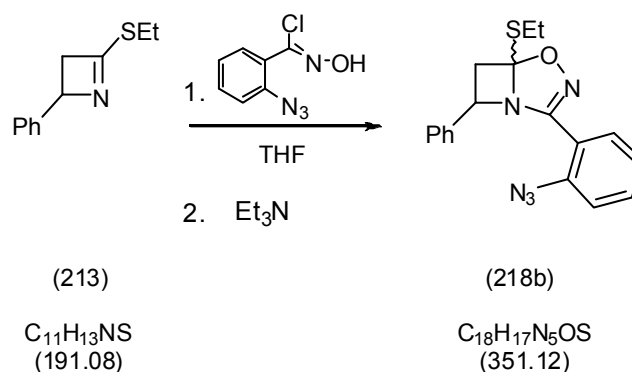
IR: ν_{\max} (cm⁻¹) (liquid film): 2934.6 (m), 1543.7 (m), 1522.1 (s), 1473.9 (m), 1359.3 (m), 1265.8 (s), 1194.6 (w).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.18-7.33 (5H, m, Ar-H), 3.38 (2H, q, J 7.5, CH₂ (SEt)), 1.56 (3H t, J 7.4, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 137.84 (q), 130.85 (Ar-CH), 128.87 (Ar-CH), 126.08 (q), 125.34 (Ar-CH), 28.89 (CH₂), 21.43(CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 207.1404, measured = 207.1407.

Synthesis of 2-(2'-azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene

The chloroxime (0.21 g, 1.05 mmol) and the azetine (0.2 g, 1.05 mmol) were dissolved in dry tetrahydrofuran (10 mL) at room temperature, under an atmosphere of dry nitrogen. To this solution was added triethylamine (0.16 mL, 1.16 mmol) in dry tetrahydrofuran (5 mL) dropwise over 6 hours. The sample was left to stir overnight before being concentrated on the rotary evaporator and purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/6:1), to yield **the title compound (218b)**; 0.22 g, 60% yield) as a clear, orange oil.

Compound data

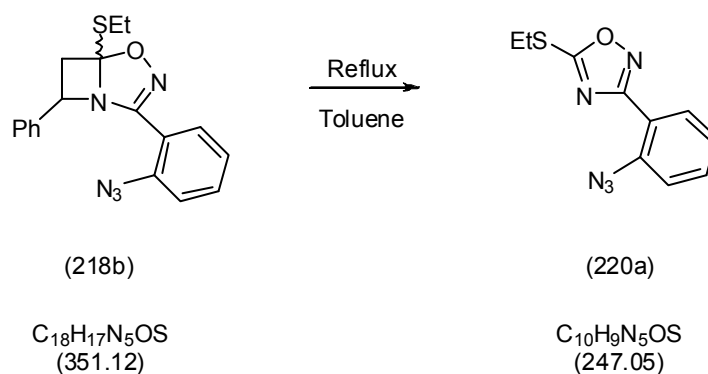
IR: ν_{\max} (cm⁻¹) (liquid film): 2929.9 (w), 2128.7 (vs), 1597.7 (m), 1582.5 (s), 1493.1 (s), 1300.3 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.3 - 7.5 (9H, m, 9 × Ar-H), 4.82 (1H, dd, J 7.2, 4.2, CH(Ph)), 3.69 (1H, dd, J 7.5, 4.2, CH₂) 2.86 (2H, m, CH₂ (SEt)), 2.76 (1H, m, CH₂), 1.37 (3H, t, J 7.6, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 158.81 (q), 140.67 (q), 139.09 (q), 131.85 (Ar-CH), 131.22 (Ar-CH), 128.79 (Ar-CH), 128.25 (Ar-CH), 126.36 (Ar-CH), 124.79 (Ar-H), 119.59 (Ar-H), 117.47 (q), 111.14 (q), 67.04 (CH), 45.45 (CH₂), 22.74 (CH₂), 14.86 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 352.1227, measured = 352.1230.

Thermolysis reaction on 2-(2'-azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene

A solution of 2-(2'-azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.19 g, 0.54 mmol), in toluene (10 mL) was heated at reflux, under an inert atmosphere of nitrogen and monitored for completion by tlc (7 hours). The sample was concentrated and purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/7:1), to yield **3-(2'-azidophenyl)-5-(ethylthio)-1,2,4-oxadiazole (220a)**; 0.044 g, 33% yield) as a clear, yellow oil.

Compound data

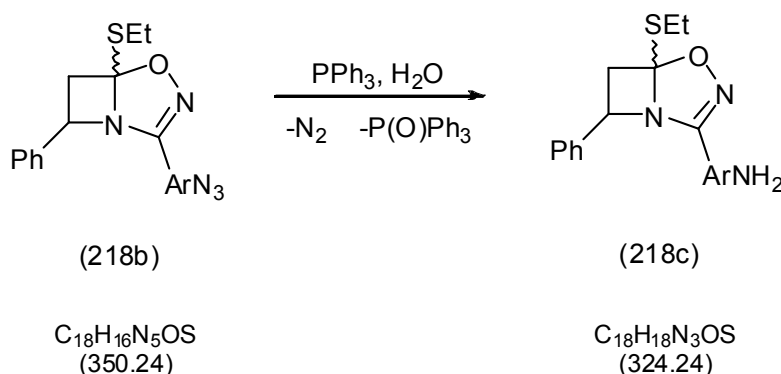
IR: ν_{\max} (cm⁻¹) (liquid film): 2931.3 (w), 2129.5 (vs), 2098.3 (vs), 1582.5 (m), 1520.1 (s), 1470.7 (s), 1339.3 (s), 1303.8 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.90 (1H, dd, J 7.4, 5.3, Ar-H), 7.45 (1H, m, Ar-H), 7.20 (2H, m, Ar-H), 3.26 (2H, q, J 7.5 CH₂ (SEt)), 1.45 (3H t, J 7.5, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 176.94 (q), 165.97 (q), 138.17 (q), 131.44 (Ar-CH), 130.90 (Ar-CH), 124.20 (Ar-CH), 118.65 (Ar-CH), 117.49 (q), 26.60 (CH₂), 14.10 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 248.0601, measured = 248.0601.

Reaction of 2-(2'-azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene with trimethylphosphite

A solution of 2-(2'-azidophenyl)-5-(ethylthio)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]-hept-2-ene (0.0468 g, 0.13 mmol) and triphenylphosphine (0.039 g, 0.15 mmol), were stirred together in tetrahydrofuran (5 mL) for 24 hours at room temperature under an atmosphere of nitrogen. Water (0.05 mL, 5.05 mmol) was then added in one portion and the reaction was heated at reflux for a further 24 hours. The sample was concentrated under vacuum and purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/6:1) to yield **the corresponding amine (218c)**; 0.015 g, 35% yield) as a yellow oil.

Compound data

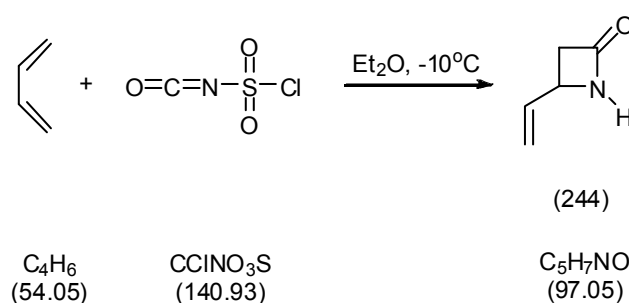
IR: ν_{\max} (cm⁻¹): 3448.2 (w), 2976.5 (m), 2847.6 (m), 1593.0 (s), 1412.2 (m), 1389.9 (m), 1301.6 (w), 1178.2 (m).

NMR

¹H: δ_{H} (500 MHz, CDCl₃): 7.55 (2H, m, Ar-H), 7.35 (2H, m, Ar-H), 7.30 (1H, m, Ar-H), 7.05 (1H, m, Ar-H), 6.89 (1H, dd, J 5.0, 1.0, Ar-H), 6.63 (1H, dd, J 10.0, 1.0, Ar-H), 6.35 (1H, m, Ar-H), 5.39 (2H, s, NH₂), 4.75 (1H, dd, J 10.0, 5.0, CH), 3.57 (1H, dd, 10.0, 10.0, PhCHCH₂), 2.76 (1H, m, PhCHCH₂), 2.67 (2H, m, CH₃CH₂), 1.27 (3H, t, J 7.5, CH₃).

¹³C: δ_{C} (125 MHz, CDCl₃): 161.87 (q), 147.13 (q), 140.71 (q), 131.59 (CH), 129.72 (CH), 128.81 (CH), 128.35 (CH), 126.68 (CH), 116.64 (CH), 115.72 (CH), 110.03 (q), 106.86 (q), 67.44 (CH), 45.16 (CH₂), 29.69 (CH₂), 14.79 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 325.2435, measured = 325.2445.

5.4 Synthesis and Reactions of 4-vinyl-1-azetines with DPP**Synthesis of 4-ethenyl-2-azetidinone**

To 1,3-butadiene (10 mL) condensed into dry ether (40 mL) at -10°C, was added a solution of chlorosulfonyl isocyanate (3.0 ml, 34.5 mmol) in dry ether (10 mL) over one hour, under atmospheric nitrogen. The temperature was maintained at -10°C for a further period of 3 hours and warmed slowly to room temperature overnight, to produce a clear, yellow solution. The solution was added to an ice cold mixture of water (70 mL), ice (30 g), NaHCO₃ (9.0 g) and Na₂SO₃ (6.0 g) and stirred for one hour at -10°C. The reaction was allowed to

warm to room temperature before being extracted with ether (6×20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield 4-ethenyl-2-azetidinone (**244**; 2.01 g, 60% yield) as a clear, yellow oil.

Compound data

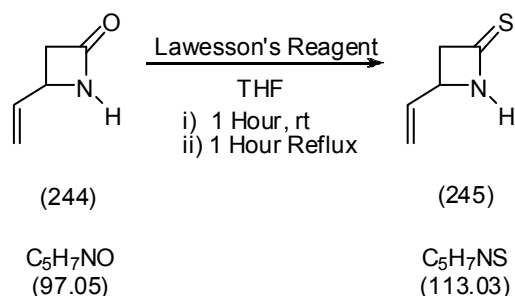
IR: ν_{\max} (cm⁻¹) (liquid film): 3274.6 (m, broad), 1755.4 (s), 1448.2 (m), 1413.8 (m), 1380.1 (m), 1254.7 (w).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.49 (1H, s, N-H), 5.92 (1H, ddd, J 17.2, 10.2, 3.2, CH), 5.32 (1H, d, J 17.2, CH₂), 5.20 (1H, d, J 10.2, CH₂), 4.13 (1H, m, CH), 3.25 (1H, m, CH₂), 2.70 (1H, d, J 17.2 CH₂).

¹³C: δ_{C} (100 MHz, CDCl₃): 167.82 (C=O), 137.43 (CH), 116.93 (CH₂), 49.40 (CH₂), 48.93 (CH).

Synthesis of 4-ethenyl-azetidin-2-thione



To the lactam (1.00 g, 10.3 mmol) dissolved in dry THF (15 mL), was added Lawesson's reagent (2.08 g, 5.15 mmol) in one portion, with stirring. The reaction was stirred at ambient temperature, under an inert atmosphere of dry nitrogen for one hour, before being heated at reflux for an additional hour. The reaction was monitored for completion by tlc and was subsequently cooled to room temperature, to give a crude product as a clear orange liquid. The sample was concentrated by rotary evaporation and purified using silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1), to yield **4-ethenyl-azetidin-2-thione (245)**; 0.67 g, 58% yield) as a clear, yellow oil.

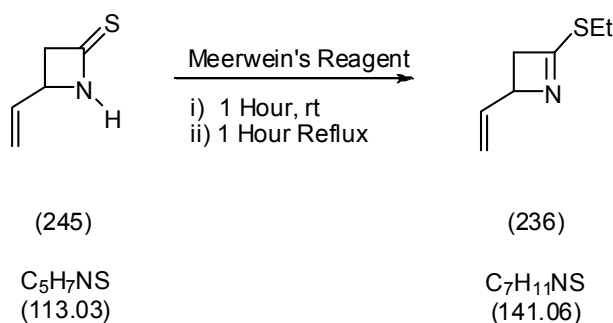
Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3174.1 (m, broad), 1482.6 (s), 1426.0 (m), 1407.2 (w), 1237.1 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.68 (1H, s, N-H), 5.96 (1H, ddd, J 17.1, 10.3, 3.0, CH), 5.35 (1H, d, J 17.1, CH₂), 5.26 (1H, d, J 10.3, CH₂), 4.62 (1H, m, CH₂), 3.30 (1H, m, CH₂), 2.84 (1H, m, CH).

¹³C: δ_{C} (100 MHz, CDCl₃): 203.65 (C=S), 135.14 (CH), 118.34 (CH₂), 58.01 (CH), 48.34 (CH₂).

Synthesis of 2-ethylthio-4-ethenyl-1-azetine

To **4-ethenyl-azetidion-2-thione** (0.67 g, 5.93 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (1M in methylene chloride, 8.9 mL, 8.89 mmol) dropwise over 2 minutes at ambient temperature, under an inert atmosphere of nitrogen. The solution was stirred for one hour at room temperature and heated to reflux for an additional hour. The reaction was cooled to room temperature, before being added to an ice cold aqueous solution of potassium carbonate (50%) dropwise over 20 minutes. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (3×30 mL). The organic layers were combined, dried over sodium sulfate, filtered and the solvent evaporated under vacuum to yield an orange oil. The crude sample (0.6 g) was purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1), to yield **2-ethylthio-4-vinyl-1-azetine (236)**; 0.35 g, 42% yield) as a clear, yellow oil.

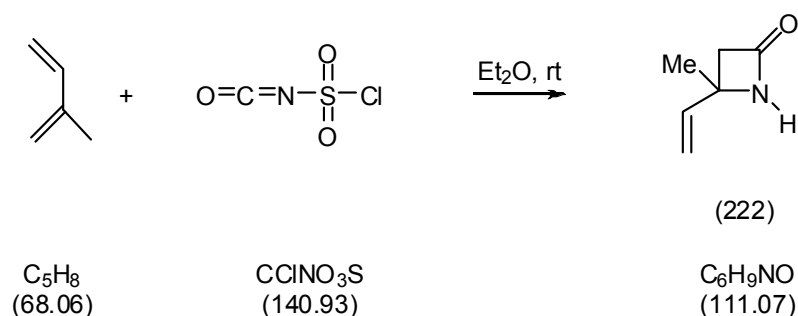
Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 2978.8 (w), 2930.5 (w), 1530.1 (m), 1374.0 (w), 1357.0 (w), 1171.3 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.00 (1H, ddd, J 17.1, 10.3, 3.8 CH), 5.30 (1H, m, CH), 5.18 (1H, d, J 10.3, CH), 4.42 (1H, m, CH), 3.32 (1H, dd, J 14.6, 4.2, CH₂), 3.02 (2H, d, J 7.4 CH₂ of SEt), 2.82 (1H, dd, J 14.6, 1.9, CH₂), 1.36 (3H, t, J 7.4, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 182.96 (q), 137.67 (CH), 116.20 (CH₂), 64.44 (CH), 41.22 (CH₂), 23.21 (CH₂), 14.55 (CH₃).

Synthesis of 4-methyl-4-ethenyl-2-azetidinone

A solution of isoprene (10.3 mL, 103.2 mmol) dissolved dry ether (30 mL) under an inert atmosphere of nitrogen gas was cooled to -65°C. To this solution was added chlorosulfonyl isocyanate (9 mL, 103.2 mmol) in dry ether (10 mL), dropwise over one hour throughout which the temperature was maintained at -65°C to produce a clear and colourless solution. After the addition was complete the reaction was allowed to warm to -10°C and the flask subsequently transferred to an ice-salt bath. The sample was added dropwise over five minutes to an ice cold solution of water (150 mL), ice (80 g), NaHCO₃ (27 g) and Na₂SO₃ (18 g) and stirred for one hour at -10°C. The reaction was allowed to warm to room temperature before being extracted with ether (6×50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced

pressure to yield **4-methyl-4-ethenyl-2-azetidinone (222)**; 8.66 g, 75% yield) as a clear, yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3265.6 (m, broad), 1743.6 (m), 1413.4 (w), 1376.3 (w).

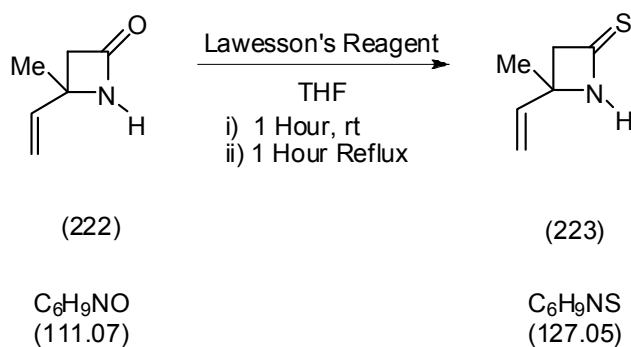
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.75 (1H, s, N-H), 6.03 (1H, dd, J 17.2, 10.6, CH), 5.24 (1H, d, J 17.2, CH₂), 5.11 (1H, d, J 10.6, CH₂), 2.82 (2H, s, CH₂), 1.53 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 167.32 (C=O), 141.08 (CH), 113.66 (CH₂), 54.36 (q), 50.71 (CH₂), 24.68 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 112.1022, measured = 112.1023.

Synthesis of 4-methyl-4-vinylazetidin-2-thione



To 4-methyl-4-ethenyl-2-azetidinone (1.00 g, 9.01 mmol) dissolved in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.82 g, 4.50 mmol) in one portion. The reaction was stirred at ambient temperature, under an inert atmosphere of dry nitrogen for one hour. The sample was heated at reflux for a further hour, before being cooled to room temperature. The sample was concentrated under vacuum and purified by flash silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1), to yield **4-methyl-4-ethenylazetidin-2-thione (223)**; 0.99 g, 87% yield) as a clear, yellow oil.

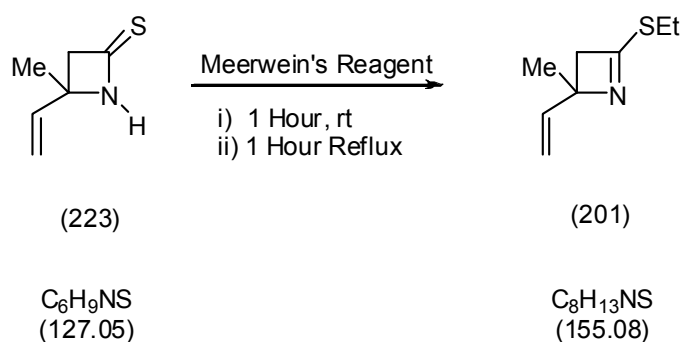
Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3159.2 (m, broad), 2971.6 (m), 1477.1 (s), 1406.5 (m), 1219.4 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.89 (1H, s, N-H), 6.05 (1H, dd, J 17.2, 10.6, CH), 5.28 (1H, d, J 17.2, CH₂), 5.21 (1H, d, J 10.6, CH₂), 2.95 (2H, s, CH₂), 1.61 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 202.12 (C=S), 138.96 (CH), 114.95 (CH₂), 63.59 (q), 54.49 (CH₂), 23.68 (CH₃).

Synthesis of 2-ethylthio-4-methyl-4-ethenyl-1-azetine

To thiolactam (0.98 g, 7.72 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (1M in methylene chloride, 11.6 mL, 11.6 mmol) in one portion at ambient temperature under an inert atmosphere of nitrogen. The solution was stirred for one hour at room temperature and heated at reflux for an additional hour. The reaction was cooled to room temperature, before being added to an ice cold solution of potassium carbonate (50%) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (3×30 mL). The lower layers were combined, dried over sodium sulfate, filtered and the solvent evaporated *in vacuo*. The crude product (0.47 g) was purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/5:1), to yield **2-ethylthio-4-methyl-4-ethenyl-1-azetine (201)**; 0.34 g, 28% yield) as a clear, orange oil.

Compound data

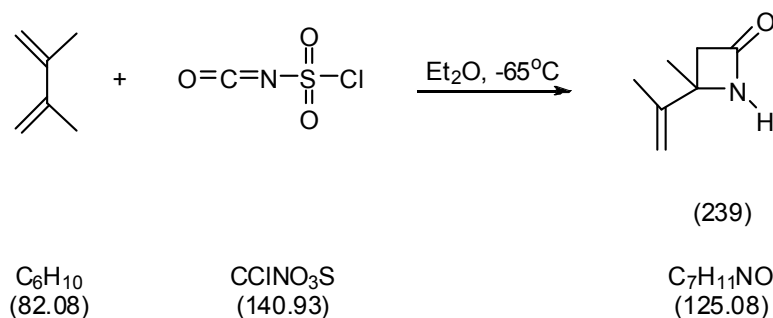
IR: ν_{\max} (cm⁻¹) (liquid film): 2970.8 (m), 2930.5 (m), 1526.9 (m), 1449.6 (w), 1412.9 (w), 1225.2 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.06 (1H, dd, J 17.2, 10.6, CH), 5.21 (1H, d, J 17.2, CH₂), 5.15 (1H, d, J 10.6, CH₂), 3.02 (2H, q, J 7.6, CH₂), 2.94 (1H, s, CH), 2.91 (1H, s, CH), 1.47 (3H, s, CH₃), 1.38 (3H, t, J 7.6, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 180.78 (C=N), 141.55 (CH), 113.41 (CH₂), 67.18 (q), 46.55 (CH₂), 24.76 (CH₃), 23.83 (CH₂), 14.53 (CH₃).

High Resolution Mass Spectroscopy: EI [M-H]⁻, calc. = 154.0685, measured = 154.0684.

Synthesis of 4-methyl-4-(propen-2-yl)-1-azetidin-2-one

A solution of 2,3-dimethyl-1,3-butadiene (1.9 mL, 17.2 mmol) in dry ether (10 mL) was cooled to -65°C and left to stir for 10 minutes under a nitrogen atmosphere mixture. To this reaction was added chlorosulfonyl isocyanate (1.5 mL, 17.2 mmol) in dry ether (5 mL), dropwise over 20 minutes throughout which the temperature was maintained at -65°C, producing a clear and colourless solution. After the addition was complete, the reaction was allowed to warm to -10°C and the flask subsequently transferred to an ice-salt bath. The solution was added dropwise over five minutes to an ice cold solution of water (50 mL), ice (20 g), NaHCO₃ (9 g) and Na₂SO₃ (6 g) and stirred for one hour at -10°C before being warmed to room temperature. The mixture was extracted with ether (4×30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness under

reduced pressure to yield **the title compound (239)**; 1.64 g, 76% yield) as a clear and colourless oil.

Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3242.6 (s, broad), 2972.8 (m), 1762.2 (vs), 1446.2 (m), 1412.3 (m), 1373.3 (m).

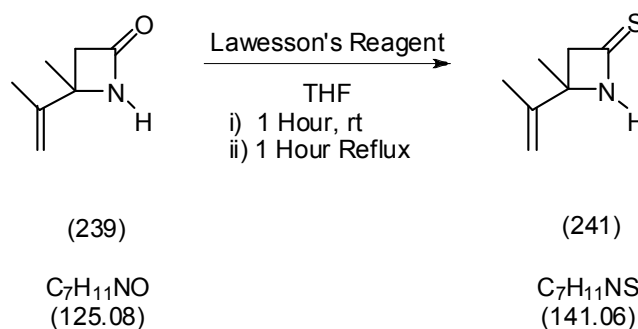
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 6.80 (1H, s, N-H), 4.93 (1H, s, CH₂), 4.86 (1H, s, CH₂), 2.85 (1H, d, J 14.5, CH₂), 2.75 (1H, d, J 14.5 CH₂), 1.82 (3H, s, CH₃), 1.53 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 167.63 (C=O), 146.74 (q), 110.50 (CH₂), 57.31 (CH₂), 49.55 (q), 24.99 (CH₃), 18.72 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 126.0913, measured = 126.0914.

Synthesis of 4-methyl-4-(propen-2-yl)-1-azetidin-2-thione



To 4-methyl-4-(propen-2-yl)-1-azetidin-2-one (1.64 g, 13.1 mmol) dissolved in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (2.65 g, 6.56 mmol) in one portion. The reaction was stirred at ambient temperature, under an inert atmosphere of dry nitrogen for one hour. The sample was then heated at reflux for a further hour, before being cooled to room temperature. The sample was concentrated under vacuum and purified by silica flash column chromatography (eluent: petroleum ether:ethyl acetate/3:1), to yield **the title compound (241)**; 1.40 g, 76% yield) as a clear, orange oil.

Compound data

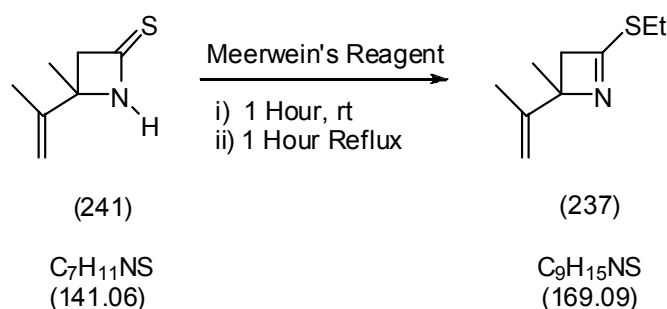
IR: ν_{\max} (cm⁻¹) (liquid film): 3019.1 (m, broad), 2978.5 (m), 1599.9 (m), 1503.8 (m), 1474.3 (m), 1215.8 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 9.45 (1H, s, N-H), 4.96 (2H, s, CH₂), 2.96 (1H, d, J 14.7, CH₂), 2.92 (1H, d, J 14.7 CH₂), 1.78 (3H, s, CH₃), 1.64 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 202.10 (C=S), 145.02 (q), 111.46 (CH₂), 66.60 (q), 53.45 (CH₂), 24.02 (CH₃), 18.36 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 142.0685, measured = 142.0684.

Synthesis of 2-ethylthio-4-methyl-4-(propen-2-yl)-1-azetine

To 4-methyl-4-(propen-2-yl)-1-azetid-2-thione (1.40 g, 9.93 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (1M in methylene chloride, 14.9 mL, 14.89 mmol) in one portion at ambient temperature under an inert atmosphere of nitrogen. The solution was stirred for one hour at room temperature and heated to reflux for an additional hour, forming a clear red liquid. The reaction was cooled to room temperature, before being added to an ice cold aqueous solution of potassium carbonate (50%) dropwise over 30 minutes, producing a yellow liquid. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (3×30 mL). The lower layers were combined, dried over sodium sulfate, filtered and the solvent evaporated under vacuum. The crude product was purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/5:1), to yield **the title compound (237)**; 1.15 g (CRUDE), 1.03 g, (PURE), 61% yield) as a clear, yellow oil.

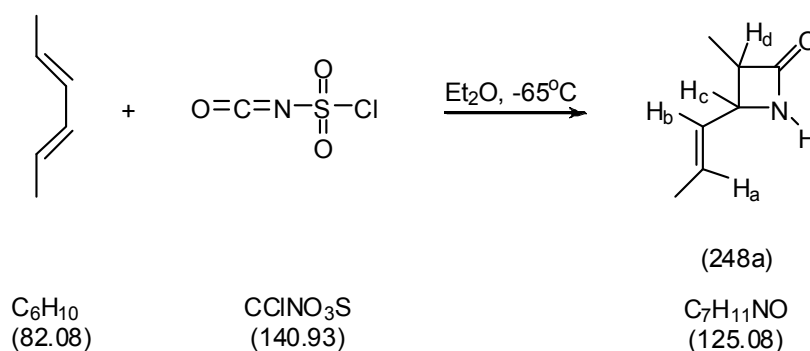
Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 2929.0 (w), 1530.0 (m), 1375.1 (w), 1249.1 (m), 1216.4 (w).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 4.93 (1H, s, CH₂), 4.84 (1H, s, CH₂), 2.98 (1H, d, 14.3, ring CH₂), 2.83 (1H, d, J 14.3, ring CH₂), 1.78 (3H, s, CH₃), 1.46 (3H, s, CH₃), 1.25 (3H, t, J 7.1, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 171.07 (q), 147.76 (q), 110.44 (CH₂), 69.39 (q), 46.30 (CH₂), 24.82 (CH₃), 23.31 (CH₂), 14.58 (CH₃), 14.13 (CH₃).

Synthesis of 3-methyl-4-(1-propen-1-yl)-1-azetidin-2-one

To a solution of 2,4-hexadiene (0.98 mL, 17.2 mmol) dissolved in dry ether (10 mL), was added a mixture of chlorosulfonyl isocyanate (1.5 mL, 17.2 mmol) and dry ether (10 mL) dropwise over 30 minutes. The reaction was carried out at -10°C, under an atmosphere of dry nitrogen. The mixture was warmed slowly to room temperature over 3 hours before the clear and colourless solution was added dropwise to an ice cold solution of water (40 mL), ice (20 g), NaHCO₃ (9 g) and Na₂SO₃ (6 g). The aqueous solution was left to stir for one hour at -10°C and warmed slowly to room temperature. The sample was extracted with ether (4×30 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield **3-methyl-4-(1-propen-1-yl)-1-azetidin-2-one (248a)**; 0.96 g, 45% yield) as a mixture of diastereoisomers, a clear and colourless oil.

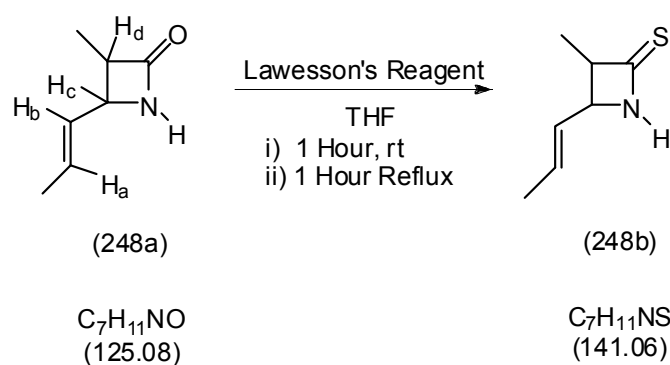
Compound data

IR: ν_{\max} (cm^{-1}) (liquid film): 3252.3 (m, broad), 2934.3 (m), 1752.4 (vs), 1453.4 (m), 1381.3 (m), 1175.3 (m).

NMR

^1H : δ_{H} (500 MHz, CDCl_3): 6.31 (1H, s, N-H), 5.72 (1H, dq, J 15.3, 6.6, CH - Ha), 5.50 (1H, ddq, J 15.3, 7.6, 1.6, CH - Hb), 4.18 (1H, dd, J 6.6, 1.3, CH - Hc²) and 3.69 (1H, dd, J 7.6, 1.9, CH - Hc¹), 3.35 (1H, m, CH - Hd²) and 3.12 (1H, m, CH - Hd¹), 1.75 (3H, dd, J 6.6, 1.2, CH₃ - 2) and 1.71 (3H, dd, J 6.4, 1.6, CH₃ - 1), 1.31 (3H, d, J 7.5, CH₃ - 2) and 1.13 (3H, d, J 7.6, CH₃ - 1).

^{13}C : δ_{C} (125 MHz, CDCl_3): 172.19 (C=O), 171.61 (C=O), 130.23 (CH), 130.18 (CH), 128.65 (CH), 127.40 (CH), 57.89 (CH), 53.36 (CH), 53.11 (CH), 49.51 (CH), 17.75 (CH₃), 17.54 (CH₃), 12.54 (CH₃), 9.68 (CH₃).

Synthesis of 3-methyl-4-(propen-1-yl)-1-azetidin-2-thione

To 3-methyl-4-(1-propen-1-yl)-1-azetidin-2-one (0.96 g, 7.71 mmol) dissolved in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.60 g, 3.85 mmol) in one portion. The reaction was stirred at ambient temperature, under an inert atmosphere of dry nitrogen for one hour. The sample was heated at reflux for a further hour, before being cooled to room temperature. The sample was concentrated under vacuum and purified by silica flash column chromatography (eluent: petroleum ether:ethyl acetate/4:1, silica gel, Aldrich, 70-230 mesh, 60 Ångstrom for column chromatography) to yield **the title compound (248b)**; 0.62 g, 57% yield) as a mixture of diastereoisomers, a clear, orange oil.

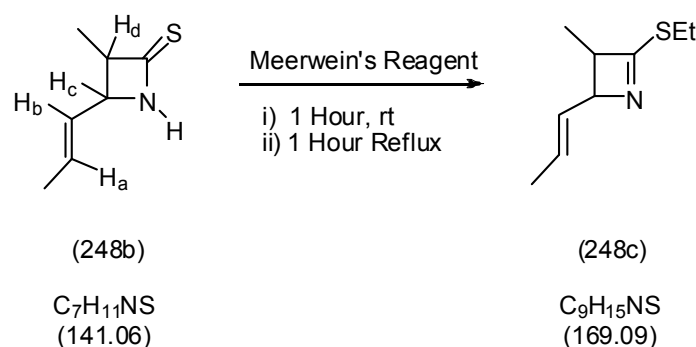
Compound data

IR: ν_{\max} (cm⁻¹) (liquid film): 3190.6 (m, broad), 2857.4 (m), 1498.1 (s), 1418.7 (m), 1278.5 (m), 1114.3 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.59 (1H, s, N-H), 5.75 (1H, m, CH - Ha), 5.55 (1H, m, CH - Hb), 4.67 (1H, dd, J 7.6, 2.7, CH - Hc²) and 3.69 (1H, d, J 8.0, CH - Hc¹), 3.29 (1H, m, CH - Hd²) and 2.84 (1H, dq, J 14.9, 7.7, CH - Hd¹), 1.74 (3H, m, CH₃), 1.33 (3H, d, J 7.3, CH₃ - 2) and 1.18 (3H, d, J 7.7, CH₃ - 1).

¹³C: δ_{C} (100 MHz, CDCl₃): 209.63 (C=S), 208.91 (C=S), 131.71 (CH), 130.29 (CH), 127.96 (CH), 125.26 (CH), 66.79 (CH), 62.62 (CH), 55.49 (CH), 52.19 (CH), 17.86 (CH₃), 17.64 (CH₃), 14.31 (CH₃), 11.78 (CH₃).

Synthesis of 2-ethylthio-3-methyl-4-(propen-1-yl)-1-azetine

To 3-methyl-4-(1-propen-1-yl)-1-azetid-2-thione (0.62 g, 4.40 mmol) was added triethylxonium tetrafluoroborate (Meerwein's reagent) (1M methylene chloride, 6.6 mL, 6.60 mmol) in one portion, with stirring, at ambient temperature and under an atmosphere of dry nitrogen. The solution was stirred for one hour at room temperature and heated at reflux for an additional hour, forming a clear orange solution. The reaction was cooled to room temperature, before being added to an ice cold solution of potassium carbonate (50%) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (3×30 mL). The lower layers were combined, dried over sodium sulfate, filtered and the solvent evaporated under vacuum. The crude product (0.77 g) was purified by silica column chromatography (eluent:

petroleum ether:ethyl acetate/5:1), to yield **the title compound (248c)**; 0.12 g, 16% yield) as a mixture of diastereoisomers, as a volatile, clear, orange oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2969.5 (m), 2929.5 (m), 1522.3 (m), 1451.7 (w), 1378.0 (w), 1216.7 (m).

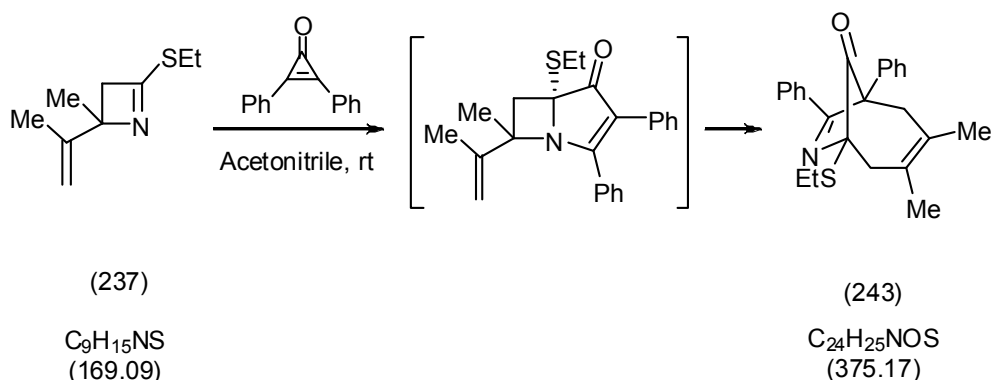
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 5.74 (1H, m, CH - Ha), 5.54 (1H, m, CH - Hb), 4.44 (1H, dd, J 7.5, 4.3, CH - Hc²) and 3.94 (1H, d, J 7.5, CH - Hc¹), 3.43 & 2.91 (1H, m, CH - Hd), 3.12 (2H, m, SEt-CH₂), 1.73 (3H, m, CH₃), 1.36 (3H, t, J 7.5, SEt-CH₃), 1.26 (3H, d, J 7.4, CH₃ - 2) and 1.07 (3H, d, J 7.5, CH₃ - 1).

¹³C: δ_{C} (100 MHz, CDCl₃): 186.96 (q), 130.24 (CH), 129.88 (CH), 128.03 (CH), 127.80 (CH), 72.14 (CH), 68.01 (CH), 49.27 (CH), 46.19 (CH), 22.52 (CH₂), 22.45 (CH₂), 18.02 (CH₃), 17.82 (CH₃), 14.62 (CH₃), 11.91 (CH₃).

7-azabicyclo[4.2.1]nonane section

Synthesis of 6-ethylthio-3,4-dimethyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one



To a stirred solution of 2-ethylthio-4-methyl-4-(propen-2-yl)-1-azetene (0.15 g, 1.06 mmol) in dry acetonitrile (10 mL) was added, with stirring diphenylcyclopropenone (0.22 g, 1.06 mmol) in one portion and the reaction placed under an inert atmosphere of dry nitrogen. The mixture was stirred at room temperature for two weeks (monitored by tlc). After two weeks the solvent was changed to CDCl₃. The reaction was continually stirred and

monitored for completion (NMR), which occurred after a week of heating at reflux. The solvent was removed by rotary evaporation and the crude product purified using column chromatography (eluent: petroleum ether:ethyl acetate/5:1, Silica gel) to yield **the title compound (243)**; 0.19 g, 51% yield) as a clear, yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2926.93 (s), 2851.87 (w), 1662.03 (vs), 1577.61 (vs), 1451.02 (w), 1416.45 (w).

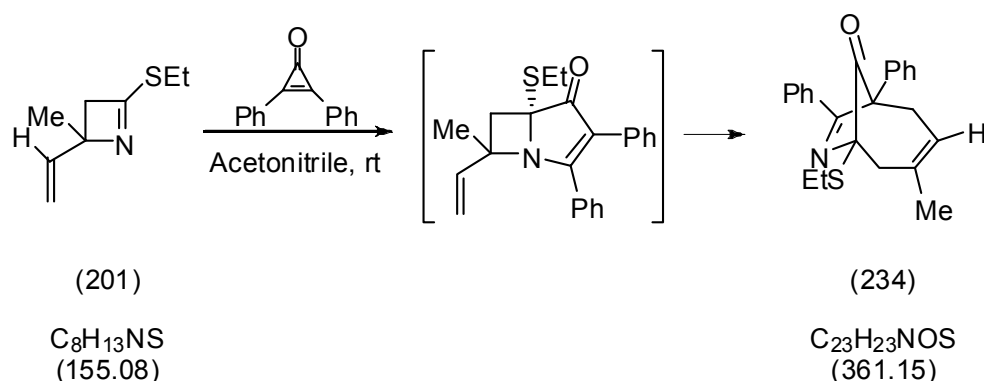
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.66 (2H, dd, J 7.5, 1.0, 2 × Ar-H), 7.32-7.39 (3H, m, 3 × Ar-H), 7.23-7.30 (3H, m, 3 × Ar-H), 7.14 (2H, dd, J 6.5, 1.6, 2 × Ar-H), 2.87 (1H, d, J 16.8, CH₂), 2.83 (1H, d, J 16.8, CH₂), 2.78 (1H, d, J 16.8, CH₂), 2.74 (1H, d, J 16.8, CH₂), 2.66 (1H, dq, J 11.5, 7.4, CH₂CH₃), 2.55 (1H, dq, J 11.3, 7.4, CH₂CH₃), 1.700 (3H, s, CH₃), 1.695 (3H, s, CH₃), 1.28 (3H, t, J 7.4, CH₃ CH₂).

¹³C: δ_{C} (100 MHz, CDCl₃): 215.10 (q), 173.72 (q), 136.75 (q), 132.20 (q), 130.84 (CH), 129.00 (CH), 128.31 (CH), 128.27 (CH), 127.90 (CH), 127.17 (CH), 125.26 (q), 124.00 (q), 83.01 (q), 63.56 (q), 46.09 (CH₂), 42.55 (CH₂), 23.87 (CH₂), 23.60 (CH₃), 23.34 (CH₃), 14.36 (CH₃).

High Resolution Mass Spectroscopy: CI (positive (NH₃), calc. = 376.1732, measured = 376.1730.

Synthesis of 6-ethylthio-4-methyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one



To a stirred solution of 2-ethylthio-4-methyl-4-ethenyl-1-azetidine (0.10 g, 0.65 mmol) in dry acetonitrile (5 mL) was added, with stirring diphenylcyclopropenone (0.13 g, 0.65 mmol) in one portion and the reaction placed under an inert atmosphere of dry nitrogen. The mixture was stirred at room temperature for two days and heated at reflux for a further five days until the reaction was complete (one week in total). The solvent was removed by rotary evaporation and the crude product was purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/7:1, silica gel, Aldrich) to yield **6-ethylthio-4-methyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one (234)**; 0.090 g, 48% yield) as a clear, yellow oil.

Compound data

IR: ν_{max} (thin film, cm^{-1}): 2963.39 (m), 2916.87 (m), 1768.70 (s), 1714.04 (s), 1671.67 (m), 1590.16 (m), 1560.98 (m), 1446.84 (m), 1283.15 (m).

NMR

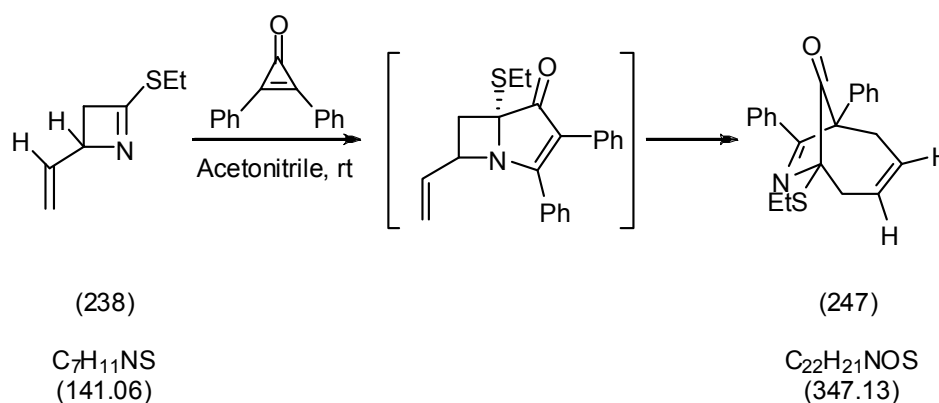
1H : δ_H (400 MHz, $CDCl_3$): 7.68 (2H, d, J 7.7, Ar-H), 7.34 (4H, m, Ar-H), 7.25 (2H, t, J 7.7, Ar-H), 7.16 (2H, d, J 7.2, Ar-H), 5.41 (1H, s, CH), 3.14 (1H, d, J 16.4, CH_2), 3.00 (1H, dd, J 9.9, 6.6, CH_2), 2.79 (2H, m, SCH_2), 2.68 (2H, m, CH_2), 1.73 (3H, s, CH_3), 1.21 (3H, t, J 7.5, CH_3).

^{13}C : δ_C (100 MHz, $CDCl_3$): 214.52 (q), 173.65 (q), 136.46 (q), 132.04 (q), 131.81 (q), 130.85 (CH), 128.94 (CH), 128.28 (CH), 128.21 (CH), 127.84

(CH), 126.97 (CH), 118.42 (CH), 82.62 (q), 63.95 (q), 42.91 (CH₂), 34.88 (CH₂), 27.53 (CH₃), 23.57 (CH₂), 14.21 (CH₃).

High Resolution Mass Spectroscopy: Cl (positive (NH₃), calc. = 362.1286, measured = 362.1291).

Synthesis of 6-ethylthio-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one



To a stirred solution of 2-ethylthio-4-ethenyl-1-azetidine (0.16 g, 0.95 mmol) in dry acetonitrile (5 mL) was added, with stirring diphenylcyclopropanone (0.20 g, 0.95 mmol) in one portion and the reaction placed under an inert atmosphere of dry nitrogen. The mixture was stirred at room temperature until the reaction was complete (one week, monitored by tlc for completion). The solvent was removed by rotary evaporation and the crude product was purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/6:1) to yield **6-ethylthio-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one (247)**; 0.27g, 62% yield) as a dark orange solid.

Compound data

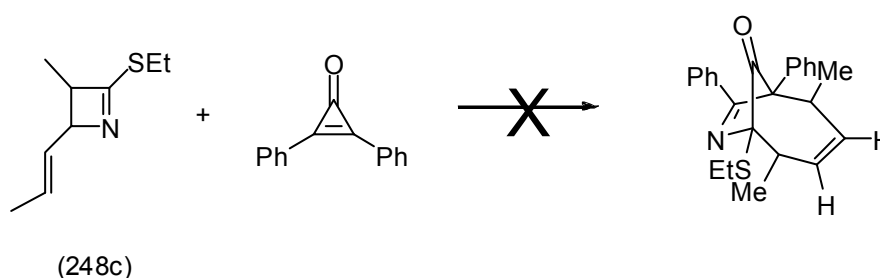
IR: ν_{\max} (cm⁻¹): 3056.9 (w), 2982.5 (m), 2929.9 (m), 1768.6 (s), 1732.2 (vs), 1592.1 (w), 1565.9 (m), 1497.9 (w), 1446.1 (m), 1266.3 (s), 1244.9 (s), 1046.8 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.69 (2H, d, J 7.8, Ar-H), 7.36 (4H, m, Ar-H), 7.26 (2H, t, J 7.8, Ar-H), 7.18 (2H, d, J 7.2, Ar-H), 5.62 (1H, m, CH), 5.53 (1H, m, CH), 3.16 (1H, m, CH₂), 3.16 (1H, m, SCH₂CH₃), 2.96 (2H, 2 × dd, J 10.0, 6.5 & J 10.0, 8.3 CH₂), 2.67 (2H, m, CH₂), 2.57 (1H, m, SCH₂CH₃), 1.28 (3H, t, J 7.5, SCH₂CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 214.62 (C=O), 173.68 (q, C=N), 136.39 (q), 131.65 (CH), 130.95 (q), 129.02 (CH), 128.32 (CH), 128.28 (CH), 127.93 (CH), 126.98 (CH), 124.70 (C=CH), 123.74 (C=CH), 82.88 (q), 63.30 (q), 38.51 (CH₂), 34.36 (CH₂), 23.63 (CH₂), 14.19 (CH₃).

High Resolution Mass Spectroscopy: Cl (positive (NH₃), calc. = 348.1417, measured = 348.1419.

Attempted synthesis of 6-ethylthio-2,5-dimethyl-1,8-diphenyl-7-azabicyclo[4.2.1]nona-3,7-dien-9-one

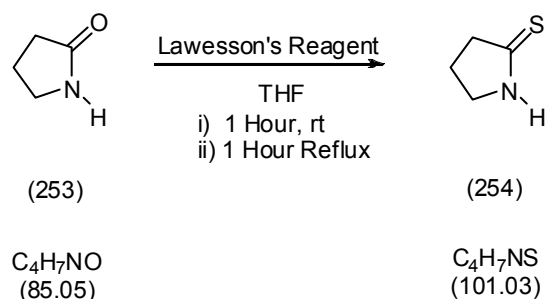
To a stirred solution of 3-methyl-4-(propen-1-yl)-1-azetidine (0.094 g, 0.56 mmol) in dry acetonitrile (5 mL) was added, with stirring diphenylcyclopropanone (0.12 g, 0.56 mmol) in one portion and the reaction placed under an inert atmosphere of dry nitrogen. The mixture was stirred at room temperature for one week and then heated at reflux for a further week, until tlc showed that no starting materials were present. The solvent was removed by rotary evaporation and the crude product was columned by silica

column chromatography (eluent: petroleum ether:ethyl acetate/3:1) in an attempt to isolate the purified product. In the event after several unsuccessful attempts, the desired compound could not be isolated.

5.5 Synthesis and Reactions of 5-, 6- and 7-membered cyclic imidates with DPP

2-pyrrolidinone system

2-pyrrolidinethione



To 2-pyrrolidinone (1.00 g, 11.76 mmol) dissolved in dry tetrahydrofuran (20 mL) was added with stirring, Lawesson's reagent (2.38 g, 5.88 mmol) in one portion. The reaction was stirred at room temperature, under an atmosphere of dry nitrogen for one hour, before being heated to reflux for a further hour. Completion of the reaction was confirmed by tlc, the solvent was removed by rotary evaporation and the crude sample purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/1:1) to yield **2-pyrrolidinethione (254)**; 1.08 g, 91% yield) as a white solid, melting point: 108-111°C.

Compound data

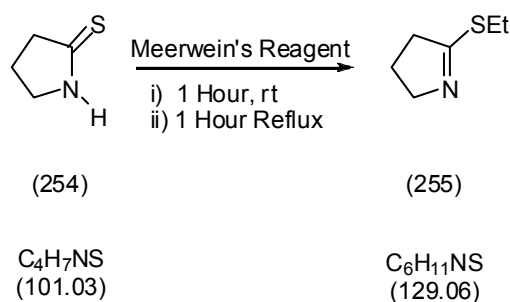
IR: ν_{\max} (thin film, cm^{-1}): 3114 (m), 3029 (w), 2832 (m), 2863 (m), 1573 (s), 1398 (m), 1326 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 8.70 (1H, s, NH), 3.68 (2H, t, J 7.5, CH_2), 2.92 (2H, t, J 7.5, CH_2), 2.23 (2H, quin., J 7.5, CH_2).

^{13}C : δ_{C} (100 MHz, CDCl_3): 22.91 (CH_2), 43.21 (CH_2), 49.65 (CH_2), 205.84 (C=S).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 102.0372, measured = 102.0372.

Synthesis of 5-Ethylthio-3,4-dihydro-2H-pyrrole

To 2-pyrrolidinethione (1.08 g, 10.7 mmol) under an atmosphere of dry nitrogen was added, in one portion, with stirring, Meerwein's reagent (1M solution in dichloromethane, 16.0 mL, 16.0 mmol). The mixture was stirred at room temperature for one hour, before being heated to reflux for an additional hour. The reaction was cooled to room temperature and subsequently added to an ice cold solution of 50% aqueous potassium carbonate (7.5 g) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (2×20 mL). The organic layers were combined, dried over magnesium sulfate, filtered and the solvent evaporated under vacuum. The crude product was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/2:1) to yield **5-ethylthio-3,4-dihydro-2H-pyrrole (255)**; 0.39 g, 28% yield) as a clear and colourless oil.

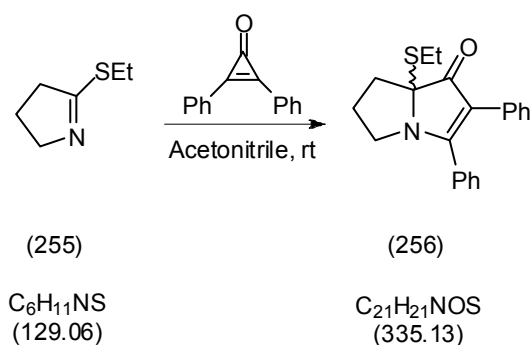
Compound data

IR: ν_{\max} (thin film, cm^{-1}): 3222 (w), 2930 (m), 2867 (m), 1690 (s), 1590 (s), 1530 (w), 1452, (w), 1429 (w), 1295 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 3.84 (2H, t, J 7.2, CH_2), 3.04 (2H, q, J 7.4, CH_2 on Et), 2.59 (2H, t, J 8.2, CH_2), 1.97 (2H, quin., J 7.7, CH_2), 1.33 (3H, t, J 7.4, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 14.37 (CH_3), 23.35 (CH_2), 24.90 (CH_2), 38.59, (CH_2) 60.76 (CH_2), 172.28 ($\text{C}=\text{N}$).

Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

To 5-ethylthio-3,4-dihydro-2H-pyrrole (0.39 g, 3.02 mmol), dissolved in dry acetonitrile (10 mL) was added, in one portion, with stirring, diphenylcyclopropenone (0.62 g, 3.02 mmol). The solution was placed under an atmosphere of dry nitrogen and stirred at ambient temperature for 24 hours, after which tlc confirmed the reaction had gone to completion. The solvent was concentrated under vacuum and the crude sample purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/4:1) to yield **5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (256;** 0.26 g, 26% yield) as a clear, yellow oil.

Compound data

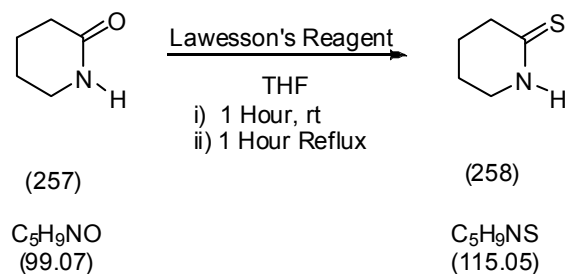
IR: ν_{\max} (thin film, cm^{-1}): 2971 (w), 1678 (s), 1602 (w), 1554 (w), 1398 (w).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 7.44-7.35 (5H, m, Ar-H), 7.21-7.12 (5H, m, Ar-H), 3.54 (1H, m, CH), 3.08 (1H, m, CH), 2.65 (1H, dq, J 7.5, 2.6, CH_2 (SEt)), 2.56 (1H, dq, J 7.5, 2.6, CH_2 (SEt)), 2.23 (2H, m, CH), 2.06 (1H, m, CH), 1.94 (1H, m, CH), 1.19 (3H, t, J 7.5, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 200.06 (C=O), 174.94 (q), 131.29 (q), 131.03 (q), 130.96 (CH), 129.51 (CH), 128.70 (CH), 128.61 (CH), 127.95 (CH), 126.05 (CH), 116.17 (q), 80.37 (q), 48.40 (CH_2), 32.85 (CH_2), 26.44 (CH_2), 23.09 (CH_2), 14.24 (CH_3).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 336.1420, measured = 336.1417.

Synthesis of thiovalerolactam

To valerolactam (3.00 g, 30.26 mmol) dissolved in dry tetrahydrofuran (25 mL) was added with stirring, Lawesson's reagent (6.12 g, 15.13 mmol) in one portion. The reaction was stirred at room temperature, under an atmosphere of dry nitrogen for one hour, before being heated to reflux for a further hour. Completion of the reaction was confirmed by tlc, the solvent was removed by rotary evaporation and the crude sample purified by silica gel column chromatography (eluent: hexane:ethyl acetate/4:1) to yield **thiovalerolactam (258)**; 2.70 g, 88% yield) as a white solid, melting point: 112-116°C.

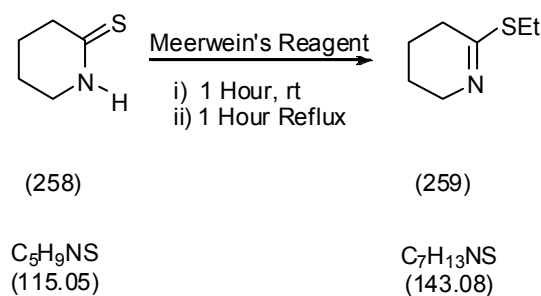
Compound data

IR: ν_{\max} (cm^{-1}): 3163 (m), 3085 (m), 2953 (m), 2863 (m), 1568 (s), 1352 (m), 1320 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 9.38 (1H, s, NH), 3.33 (2H, d, J 5.0, CH_2), 2.86 (2H, t, J 7.5, CH_2), 2.35 (2H, m, CH_2), 1.76 (2H, m, CH_2).

^{13}C : δ_{C} (100 MHz, CDCl_3): 202.30 (C=S), 44.53 (CH_2), 38.96 (CH_2), 20.61 (CH_2), 19.98 (CH_2).

Synthesis of 6-ethylthio-2,3,4,5-tetrahydropyridine

To **thiovalerolactam** (2.70 g, 26.73 mmol) under an atmosphere of dry nitrogen was added, in one portion, with stirring, Meerwein's reagent (1M solution in dichloromethane, 40.1 mL, 40.10 mmol) in 5mL portions. The mixture was stirred at room temperature for one hour, before being heated to reflux for an additional hour. The reaction was cooled to room temperature and subsequently added to an ice cold solution of 50% aqueous potassium carbonate (5 g) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water and the filtrate extracted using dichloromethane (4×30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and the solvent evaporated under vacuum. The crude product was purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/4:1) to yield **6-ethylthio-2,3,4,5-tetrahydropyridine (259)**; 0.17 g, 28% yield) as a clear and colourless oil.

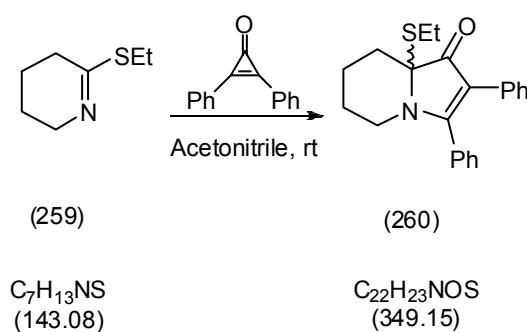
Compound data

IR: ν_{\max} (thin film, cm^{-1}): 2932 (s), 2868 (m), 1736 (w), 1633, (s), 1447 (w).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 3.65 (2H, m, $\text{CH}_2\text{-N}$), 2.89 (2H, q, J 7.3, CH_2), 2.29 (4H, m, 2 x CH_2), 1.69 (2H, m, CH_2), 1.28 (3H, t, J 7.3, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 164.30 (C=N), 49.77 (CH_2), 30.86 (CH_2), 22.15 (CH_2), 21.92 (CH_2), 19.40 (CH_2), 13.64 (CH_3).

Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one

To 6-ethylthio-2,3,4,5-tetrahydropyridine (0.19 g, 1.33 mmol), dissolved in dry acetonitrile (10 mL) was added, in one portion, with stirring, diphenylcyclopropenone (0.27 g, 1.33 mmol). The solution was placed under an atmosphere of dry nitrogen and stirred at ambient temperature for 24 hours, after which tlc confirmed the reaction had gone to completion. The solvent was concentrated under vacuum and the crude sample purified by silica gel column chromatography (eluent: hexane:ethyl acetate/3:1) to yield **5-ethylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one (260;** 0.25 g, 54% yield) as a clear, yellow oil.

Compound data

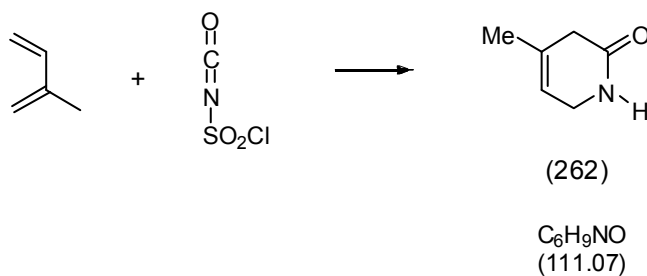
IR: ν_{\max} (thin film, cm^{-1}): 3059 (w), 3024 (w), 2971 (w), 2927 (w), 1760 (s), 1592 (m), 1564 (m), 1497 (w), 1446 (w), 1360 (s).

NMR

^1H : δ_{H} (500 MHz, CDCl_3): 7.42-7.33 (3H, m, Ar-H), 7.24-7.17 (2H, m, Ar-H), 7.07-7.00 (4H, m, Ph), 6.96-6.90 (1H, m, Ar-H), 3.54 (1H, dt, J 11.9, 6.4, N- CH_2), 3.46 (1H, dt, J 11.1, 5.9, N- CH_2), 2.45 (2H, 2 \times dq, J 9.2, 5.9, CH_2 (SEt)), 2.15 (2H, m, CH_2), 1.85 (1H, m, CH_2), 1.78 (1H, m, CH_2), 1.65 (1H, m, CH_2), 1.50 (1H, m, CH_2), 1.18 (3H, t, J 7.5, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 198.00 (C=O), 169.50 (C-S), 131.12 (q), 129.98 (CH), 128.51 (CH), 127.60 (CH), 126.71 (CH), 124.96 (CH), 109.45 (q), 72.17 (q), 41.05 (CH_2), 32.40 (CH_2), 27.85 (CH_2), 22.44 (CH_2), 19.95 (CH_2), 13.10 (CH_3).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 350.1573, measured = 350.1574.

Synthesis of 4-methyl-1,2,5,6-tetrahydropyridine-6-one

A solution of isoprene (4.4 mL, 44.1 mmol) was dissolved in dry ether (10 mL) at room temperature under an inert atmosphere of nitrogen gas. The solution was left to stir for 10 minutes before chlorosulfonyl isocyanate (4 mL, 46.0 mmol) in anhydrous ether (5 mL), was added dropwise over 10 minutes. The clear and colourless solution was left to stir at room temperature overnight under an atmosphere of dry nitrogen. The resulting solution was evaporated to dryness, dissolved in fresh ether (20 mL) and then added dropwise over 20 minutes to an ice cold solution of water (30 mL), ice (20 g), NaHCO_3 (9 g) and Na_2SO_3 (6 g). The resulting solution was then stirred for one hour at -10°C .

The mixture was allowed to warm to room temperature before being extracted with ether (6×50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure to yield **4-methyl-1,2,5,6-tetrahydropyridine-6-one** (**262**; 0.51 g, 26% yield) as a yellow oil.

Compound data

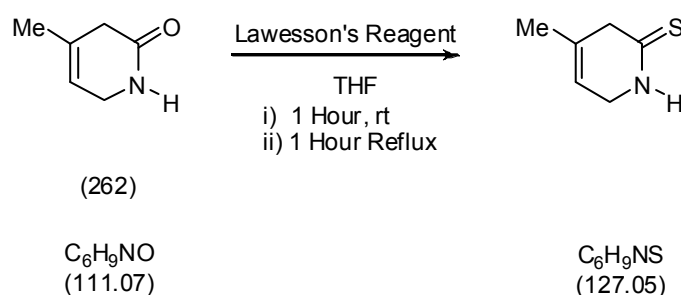
IR: ν_{\max} (cm⁻¹): 3303 (w), 3221 (w), 2976 (w), 2915 (w), 1737 (m), 1666 (s), 1499 (w).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.26 (1H, s, NH), 5.44 (1H, m, CH), 3.92 (2H, m, CH₂), 2.80 (2H, t, J 7.4, CH₂), 1.75 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 170.42 (C=O), 129.76 (q), 114.67 (CH), 43.29 (CH₂), 35.63 (CH₂), 22.01 (CH₃).

Synthesis of 4-methyl-1,2,5,6-tetrahydropyridine-6-thione



To 4-methyl-1,2,5,6-tetrahydropyridine-6-one (0.20 g, 1.80 mmol) dissolved in dry tetrahydrofuran (10 mL) was added with stirring, Lawesson's reagent (0.36 g, 0.90 mmol) in one portion. The reaction was stirred at room temperature, under an atmosphere of dry nitrogen for one hour, before being heated to reflux for a further hour. Completion of the reaction was confirmed by tlc, the solvent was removed by rotary evaporation and the crude sample purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/1:1) to yield **4-methyl-1,2,5,6-tetrahydropyridine-6-thione** (0.19 g, 66% yield) as a white solid, melting point: 127-130°C.

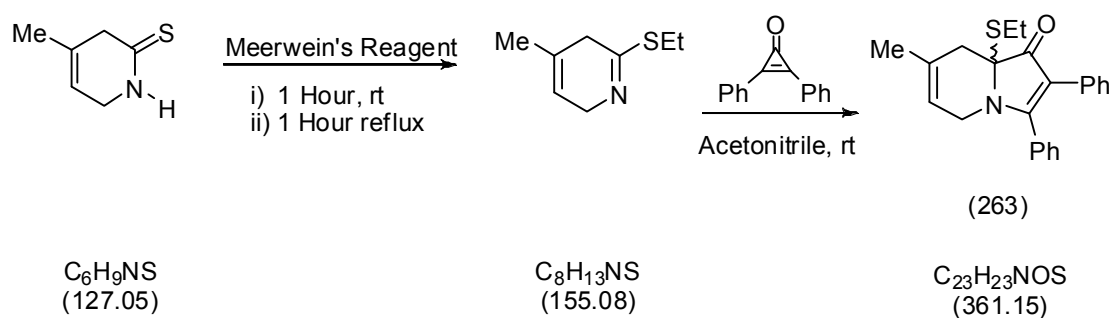
Compound data

IR: ν_{\max} (cm⁻¹): 3200 (m), 2972 (m), 2931 (m), 1731 (m), 1633 (s), 1520 (s), 1433 (w), 1338 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 9.09 (1H, s, NH), 5.49 (1H, s, CH), 3.91 (2H, m, CH₂), 3.36 (2H, t, J 7.5, CH₂), 1.73 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 198.83 (C=S), 129.61 (q), 112.97 (CH), 45.47 (CH₂), 43.45 (CH₂), 21.64 (CH₃).

Synthesis of 7-Methyl-5-ethylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-en-4-one

To 4-methyl-1,2,5,6-tetrahydropyridine-6-thione (0.10 g, 0.79 mmol) under an atmosphere of dry nitrogen was added, in one portion, with stirring, Meerwein's reagent (1M solution in CH₂Cl₂, 1.18 mL, 1.18 mmol) in 5 mL portions. The mixture was stirred at room temperature for one hour, before being heated to reflux for an additional hour. The reaction was cooled to room temperature and subsequently added to an ice cold solution of 50% potassium carbonate (2.5 g) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water (20 mL) and the filtrate extracted using dichloromethane (4×30 mL). The organic layers were combined, dried over sodium sulfate, filtered and the solvent evaporated in vacuo. The crude product was isolated and then reacted immediately with diphenylcyclopropanone (0.16g, 0.79 mmol) in dry acetonitrile (5 mL) added in one portion, with stirring. The reaction was placed under an atmosphere of dry nitrogen and stirred at ambient temperature until tlc showed the reaction had gone to completion (one week). The solvent was concentrated under

vacuum and the crude sample purified by silica gel column chromatography (eluent: hexane:ethyl acetate/5:1) to yield **the title compound (263)**; 0.15 g, 34% yield, 2 steps) as a dark brown solid, melting point 176-178°C.

Compound data

IR: ν_{\max} (thin film, cm^{-1}): 2970.36 (m), 2926.97 (m), 1766.10 (s), 1713.34 (s), 1673.07 (m), 1595.06 (m), 1563.45 (m), 1446.84 (m), 1358.12 (s), 1015.34 (s).

NMR

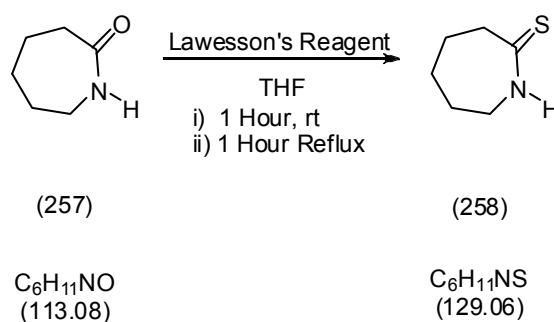
^1H : δ_{H} (500 MHz, CDCl_3): 7.46 (3H, m, Ar-H), 7.26 (2H, m, Ar-H), 7.03 (3H, m, Ar-H), 5.59 (1H, s, C=CH), 3.69 (2H, m, NCH_2), 2.60 (2H, m, CH_2CSEt), 2.59-2.51 (2H, 2 \times dq, J 12.1, 7.5, and 12.1, 7.5, SCH_2Me), 1.73 (3H, s, CH_3), 1.21 (3H, t, J 7.5, S CH_2CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 195.44 (q), 171.87 (q), 135.97 (q), 131.04 (q), 130.36 (CH), 130.10 (CH), 129.00 (CH), 128.32 (CH), 127.65 (CH), 125.47 (CH), 119.48 (q), 113.24 (q), 74.22 (q), 39.23 (CH_2), 31.25 (CH_2), 23.36 (CH_2), 22.94 (CH_3), 14.15 (CH_3).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 362.1573, measured = 362.1577.

ϵ -Caprolactam system

Conversion of ϵ -Caprolactam into ϵ -Thiocaprolactam



To ϵ -caprolactam (1.00 g, 8.85 mmol) dissolved in dry tetrahydrofuran (20 mL) was added with stirring, Lawesson's reagent (1.79 g, 4.42 mmol) in one portion. The reaction was stirred at room temperature, under an atmosphere of dry nitrogen for one hour, before being heated to reflux for a further hour. Completion of the reaction was confirmed by tlc, the solvent was removed by rotary evaporation and the crude sample purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/3:1) to yield ϵ -thiocaprolactam (**258**; 1.12 g, 98% yield) as a white solid, melting point: 117-121°C.

Compound data

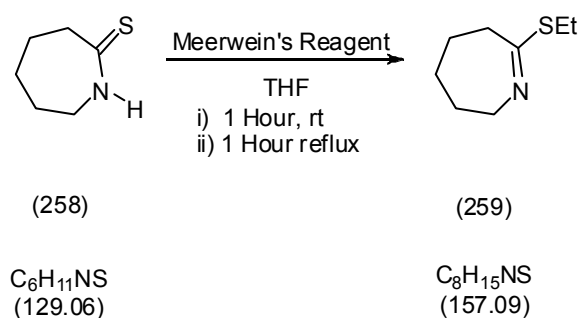
IR: ν_{\max} (cm^{-1}): 3180 (m), 2928 (s), 1552 (s), 1439 (s), 1368 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 9.21 (1H, s, NH), 3.39 (2H, d, J 6.0, CH_2), 3.36 (2H, d, J 6.0, CH_2), 1.89 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.67 (2H, m, CH_2).

^{13}C : δ_{C} (100 MHz, CDCl_3): 209.94 (C=S), 46.89 (CH_2), 44.77 (CH_2), 30.16 (CH_2), 27.84 (CH_2), 24.28 (CH_2).

Synthesis of 7-ethylthio-3,4,5,6-tetrahydro-2H-azepine



To ϵ -thiocaprolactam (1.14 g, 8.84 mmol) under an atmosphere of dry nitrogen was added, in one portion, with stirring, Meerwein's reagent (1M solution in dichloromethane, 13.3 mL, 13.3 mmol). The mixture was stirred at room temperature for one hour, before being heated to reflux for an additional hour. The reaction was cooled to room temperature and subsequently added to an ice cold solution of 50% potassium carbonate (7.5 g) dropwise over 30 minutes. The mixture was filtered through celite, the cake washed with water

(20 mL) and the filtrate extracted using dichloromethane (3×20 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under vacuum. The crude product was purified by flash silica column chromatography (eluent: petroleum ether:ethyl acetate/2:1) to yield **7-ethylthio-3,4,5,6-tetrahydro-2H-azepine (259)**; 0.90 g, 65% yield) as a clear and colourless oil.

Compound data

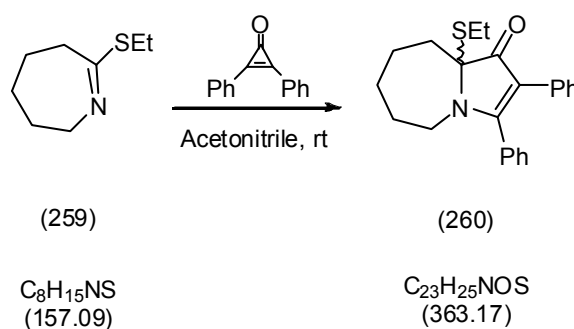
IR: ν_{\max} (thin film, cm^{-1}): 2929 (s), 2855, (m), 1688 (vs), 1632 (s), 1440 (m).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 3.64 (2H, m, $\text{CH}_2\text{-N}$), 2.84 (2H, q J 7.5, SCH_2), 2.43 (2H, m, CH_2), 1.77 (2H, m, CH_2), 1.52 (2H, m, CH_2), 1.25 (3H, t, J 7.5, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 171.39 (C=N), 52.67 (CH_2), 36.90 (CH_2), 31.17 (CH_2), 26.91 (CH_2), 24.17 (CH_2), 24.00 (CH_2), 13.77 (CH_3).

Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[5.3.0]dec-2-en-4-one



To 7-ethylthio-3,4,5,6-tetrahydro-2H-azepine (0.60 g, 3.82 mmol), dissolved in dry acetonitrile (10 mL) was added, in one portion, with stirring, diphenylcyclopropenone (0.79 g, 3.02 mmol). The solution was placed under an atmosphere of dry nitrogen and stirred at ambient temperature for 24 hours, after which tlc confirmed the reaction had gone to completion. The solvent was concentrated under vacuum and the crude sample purified by silica gel column chromatography (eluent: petroleum ether:ethyl acetate/4:1) to yield the title compound (**260**; 0.25 g, 18% yield) as a clear, yellow oil.

Compound data

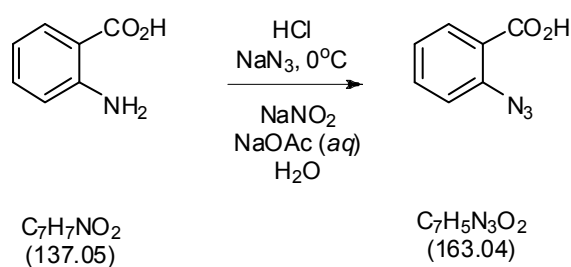
IR: ν_{\max} (thin film, cm^{-1}): 2977 (s), 2929 (s), 1688 (vs), 1602 (s), 1508 (s), 1447 (s).

NMR

^1H : δ_{H} (400 MHz, CDCl_3): 7.47-7.33 (5H, m, Ar-H), 7.12-7.04 (5H, m, Ar-H), 3.81 (1H, m, CH), 3.43 (1H, m, CH), 2.77 (1H, dd, J 8.0, 14.8, CH), 2.50 (2H, q, J 7.5, CH_2), 1.79-1.68 (3H, m, CH and $\text{SEt}(\text{CH}_2)$), 1.48 (2H, m, CH_2), 1.26 (2H, m, CH_2), 1.17 (3H, t, J 7.5, CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 197.55 (C=O), 173.57 (C=C), 131.51 (q), 130.68 (q), 130.15 (CH), 129.03 (CH), 128.51 (CH), 128.22 (CH), 127.74 (CH), 125.30 (CH), 112.64 (q), 60.37 (q), 42.99 (CH_2), 37.44 (CH_2), 29.31 (CH_2), 29.16 (CH_2), 23.45 (CH_2), 22.51 (CH_2), 14.01 (CH_3).

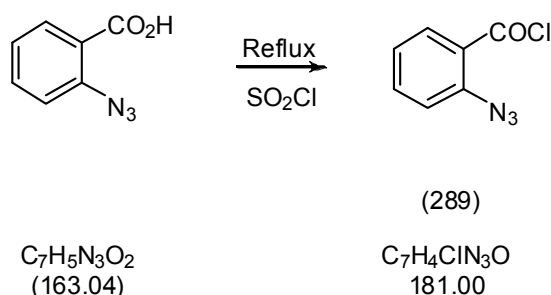
High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 364.1729, measured = 364.1729.

5.6 Experimental for The Use of 4-Vinyl- β -lactams in the Synthesis of Pyrrolobenzodiazepine Analogues**Synthesis of o-azidobenzoic acid**

To a stirring solution of anthranilamide (1.00 g, 7.34 mmol) in concentrated hydrochloric acid (15 mL) and water (15 mL), was added a solution of sodium nitrite (0.51 g, 7.34 mmol) in water (10 mL), dropwise at 0°C. The resulting mixture was stirred for 30 minutes at 0°C and it was observed that all the solid material had gone into solution. The mixture was subsequently added to an ice cold solution of sodium azide (0.48 g, 7.34 mmol) and sodium acetate (30 g) in water (100 mL), resulting in the formation of a cream precipitate

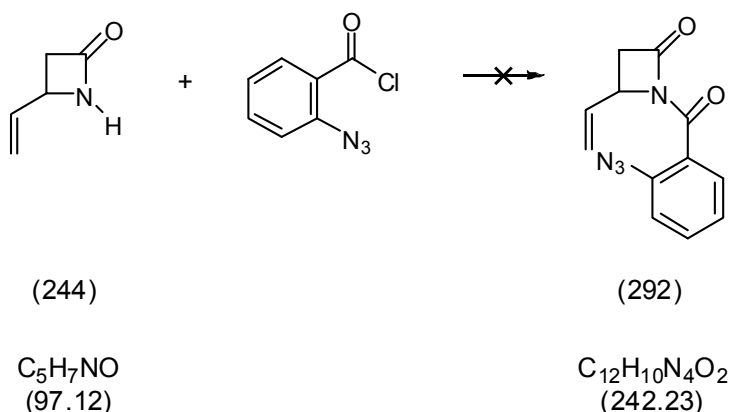
(observed as a floating foam), which was filtered and washed with water (3×50 mL). The sample was dried overnight at $\leq 100^\circ\text{C}$, to yield ***o*-azidobenzoic acid** (0.78 g, 65% yield) as a pale yellow solid.

Synthesis of *o*-azidobenzoyl chloride



A stirring solution of *o*-azidobenzoic acid (0.3 g) in thionyl chloride (10 mL) was heated at reflux, under an atmosphere of dry nitrogen for 2 hours. The reaction mixture was cooled to room temperature and excess thionyl chloride was removed by rotary evaporation, redissolved in methylene chloride which was removed by rotary evaporation (4×5 mL), to yield ***o*-azidobenzoylchloride** as a brown oil. This product was used without further purification.

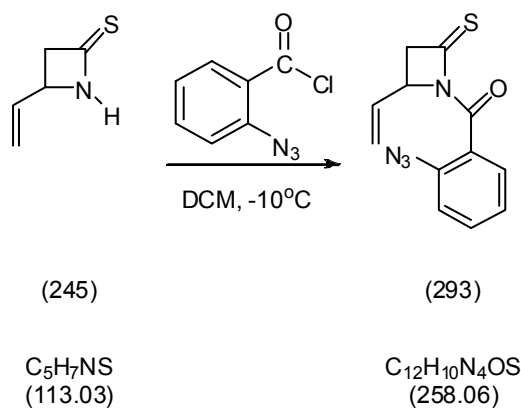
Attempted syntheses of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidin-2-one



To a solution of lactam (**244**) (0.25 g, 2.58 mmol) and dimethylaminopyridine (0.1 g, 0.82 mmol) in dry dichloromethane (20 mL), was added with stirring and under an atmosphere of dry nitrogen, *o*-azidobenzoylchloride (0.50 g) in

dry dichloromethane (10 mL), dropwise over 20 minutes at -78°C and -10°C . The reaction was stirred for 30 minutes before triethylamine (0.72 mL, 5.15 mmol) was added dropwise over 10 minutes and allowed to warm from -78°C and -10°C . The reaction mixture was then warmed and left to stir at ambient temperature for 24-72 hours, before being concentrated by rotary evaporation and subjected to flash silica column chromatography (eluent: petroleum ether:ethyl acetate/3:1). The reaction did not yield the desired product after repeated attempts. Identical attempts using *o*-azidobenzoylchloride (0.2 g) were similarly unsuccessful.

Synthesis of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidin-2-thione



To a solution of 4-ethenyl-1-azetidin-2-one (0.16 g, 1.42 mmol) and dimethylaminopyridine (0.1 g, 0.82 mmol) in dry dichloromethane (20 mL), was added with stirring and under an atmosphere of dry nitrogen, *o*-azidobenzoylchloride (0.28 g, 1.56 mmol) in dry dichloromethane (10 mL), dropwise over 20 minutes at -10°C . The reaction was stirred for 30 minutes before triethylamine (0.29 mL, 2.83 mmol) was added dropwise over 10 minutes at -10°C . The reaction mixture was warmed to room temperature and left to stir at ambient temperature for 24 hours, before being concentrated by rotary evaporation and purified by flash silica column chromatography (eluent: petroleum ether:ethyl acetate/4:1) to yield **1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidin-2-thione (293)**; 0.26 g, 71% yield) as a yellow solid, melting point: $79-82^{\circ}\text{C}$.

Compound data

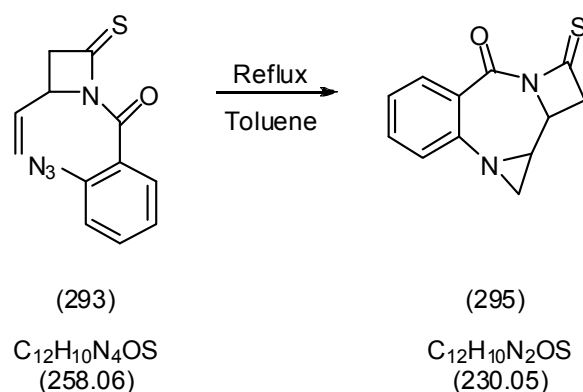
IR: ν_{\max} (cm⁻¹): 2927.9 (s), 2853.4 (s), 2128.3 (s), 1687.0 (s), 1462.9 (m), 1375.5 (m), 1303.6 (m).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.53 (1H, td, J 7.8, 1.5, ArH), 7.39 (1H, dd, J 7.6, 1.2, ArH), 7.21 (2H, m, 2×ArH), 6.09 (1H, ddd, J 17.2, 10.4, 7.0, CH), 5.49 (1H, d, J 17.2, CH), 5.38 (1H, d, J 10.4, CH), 5.15 (1H, m, CH), 3.24 (1H, dd, J 17.1, 5.9, CH), 2.84 (1H, dd, J 17.1, 3.1, CH).

¹³C: δ_{C} (100 MHz, CDCl₃): 47.10 (CH₂), 59.42 (CH), 118.52 (CH), 119.46 (CH₂), 124.97 (CH), 126.06 (q), 129.32 (CH), 132.40 (CH), 133.59 (CH), 163.97 (C=O), 201.89 (C=S).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 259.0648, measured = 259.0648.

Synthesis of (Aziridino[1,2-a]azetidino[2,1-c])[1,4]benzodiazepine-7-one-9-thione

A solution of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidino-2-thione (0.074 g) dissolved in dry toluene (6 mL) was heated at reflux under an atmosphere of dry nitrogen for 24 hours when TLC confirmed that the reaction had gone to completion. The sample was cooled to room temperature and purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/1:2) to yield **the title compound (295)**; 0.032 g, 48% yield) as a yellow oil.

Compound data

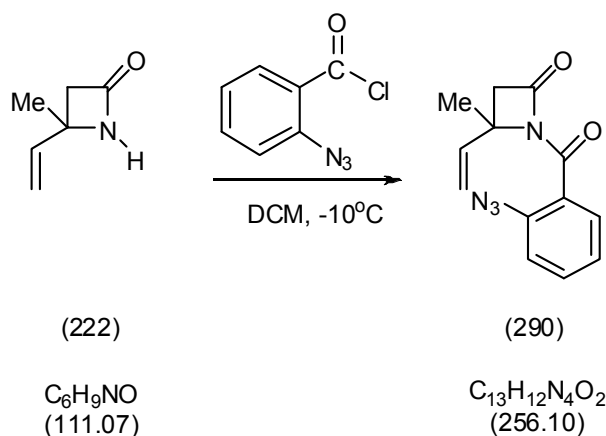
IR: ν_{\max} (cm⁻¹): 2873.3 (w), 1698.2 (s), 1653.5 (s), 1601.9 (m), 1483.4 (m), 1355.8 (m), 1345.6 (s), 1195.4 (m).

NMR

¹H: δ_{H} (500 MHz, CDCl₃): 7.80 (1H, dd, J 8.1, 1.6, ArH), 7.45 (1H, dt, J 7.7, 1.6, ArH), 7.17 (1H, d, J 8.1, ArH), 7.10 (1H, dt, J 0.8, 7.6, ArH), 4.20 (1H, ddd, J 8.9, 5.7, 2.9, CH), 3.31 (1H, dd, J 16.8, 5.7, CH), 3.17 (1H, ddd, J 8.9, 4.3, 3.5, CH), 3.10 (1H, dd, J 16.8, 2.7, CH), 2.81 (1H, d, J 4.5, CH), 2.26 (1H, d, J 3.5, CH).

¹³C: δ_{C} (125 MHz, CDCl₃): 35.13 (CH₂), 42.00 (CH), 45.14 (CH₂), 58.86 (CH), 122.90 (CH), 123.47 (CH), 132.20 (CH), 133.76 (CH), 150.04 (q), 163.89 (C=O), 199.55 (C=S).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 231.0587, measured = 231.0588.

Synthesis of 1-(o-azidobenzoyl)-4-methyl-4-ethenyl-1-azetid-2-one

To a solution of 4-methyl-4-vinyl-2-azetidinone (0.25 g, 2.25 mmol) and dimethylaminopyridine (0.1 g, 0.82 mmol) in dry dichloromethane (20 mL), was added with stirring and under an atmosphere of dry nitrogen, *o*-azidobenzoylchloride (0.45 g, 2.48 mmol) in dry dichloromethane (10 mL), dropwise over 20 minutes at -10°C. The reaction was stirred for 30 minutes before triethylamine (0.63 mL, 4.50 mmol) was added dropwise over 10 minutes at -10°C. The reaction mixture was warmed to room temperature and

left to stir at ambient temperature for 24 hours, before being concentrated by rotary evaporation and purified by flash silica column chromatography (eluent: petroleum ether:ethyl acetate/6:1) to yield **1-(o-azidobenzoyl)-4-methyl-4-ethenyl-1-azetidin-2-one (290)**; 0.20 g, 35% yield) as a yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2927.3 (w), 2855.4 (w), 2133.0 (vs), 1793.0 (vs), 1681.3 (s), 1599.7 (m), 1580.4 (w), 1488.8 (m), 1448.9 (m), 1330.4 (vs), 1280.2 (s).

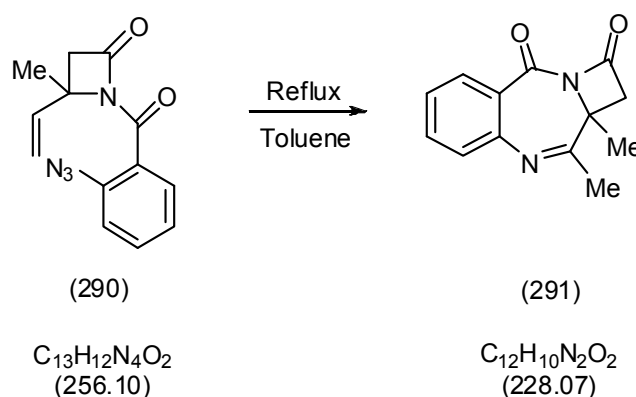
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.47 (1H, m, ArH), 7.41 (1H, m, ArH), 7.21 (2H, m, ArH), 6.22 (1H, dd, J 17.3, 10.8, CH₂), 5.47 (1H, d, J 17.3, CH), 5.38 (1H, d, J 10.8, CH), 3.09 (1H, d, J 16.1, CH), 2.98 (1H, d, J 16.2, CH), 1.87 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 22.46 (CH₃), 50.21 (CH₂), 54.94 (q), 115.92 (CH₂), 118.52 (CH), 124.67 (CH), 126.80 (CH), 129.09 (q), 132.16 (CH), 138.07 (CH), 138.14 (q), 163.45 (q), 163.49 (q).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 257.1045, measured = 257.1046.

Formation of 9,9a-Dimethyl-azetidino[2,1-c][1,4]benzodiazepine-1,3-dione



A solution of 1-(o-azidobenzoyl)-4-methyl-4-ethenyl-1-azetidin-2-one (0.15 g) dissolved in dry toluene (7 mL) was heated at reflux under an atmosphere of dry nitrogen. After 24 hours TLC confirmed that the reaction had gone to

completion. The reaction was cooled to room temperature and the crude sample purified by column chromatography (eluent: methylene chloride :ether/1:1) to yield **the title compound (291)**; 0.060 g, 40% yield) as a pale yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2923.3 (w), 1800.1 (m), 1721.3 (s), 1685.5 (vs), 1655.9 (vs), 1609.2 (s), 1463.5 (s), 1350.1 (s), 1325.8 (s), 1116.9 (m).

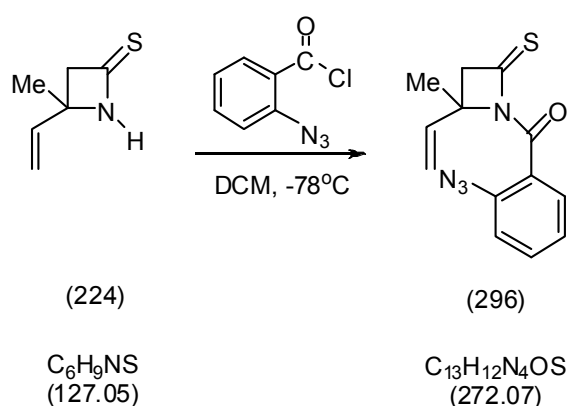
NMR

¹H: δ_{H} (500 MHz, CDCl₃): 8.20 (1H, dd, J 8.0, 1.2, ArH), 7.67 (1H, td, J 7.7, 1.4, ArH), 7.59 (1H, d, J 8.1, ArH), 7.40 (1H, t, J 7.6, ArH), 3.67 (1H, d J 16.0, CH), 3.32 (1H, d, J 16.0, CH), 2.37 (3H, s, CH₃), 1.89 (3H, s, CH₃).

¹³C: δ_{C} (125 MHz, CDCl₃): 19.93 (CH₃), 26.23 (CH₃), 43.43 (CH₂), 73.20 (q), 123.65 (q), 126.52 (CH), 126.91 (CH), 127.15 (CH), 134.15 (CH), 149.45 (q), 155.06 (q), 157.88 (C=O), 204.15 (C=O).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 229.0973, measured = 229.0974.

Synthesis of 1-(o-azidobenzoyl)-4-methyl-4-ethenyl-1-azetid-2-thione



To a solution of 4-methyl-4-vinylazetid-2-thione (0.25 g, 1.97 mmol) and dimethylaminopyridine (0.2 g, 1.64 mmol) dissolved in dry dichloromethane (30 mL), was added with stirring and under an atmosphere of dry nitrogen, o-azidobenzoylchloride (0.45 g, 2.48 mmol) in dry dichloromethane (10 mL), dropwise over 15 minutes at -78°C. The reaction was stirred for 30 minutes at

-78°C before triethylamine (0.27 mL, 1.97 mmol) was added dropwise over 10 minutes at -78°C. The reaction mixture was warmed and left to stir at ambient temperature for 48 hours, before being concentrated by rotary evaporation and purified by flash column chromatography (eluent: petroleum ether:ethyl acetate/5:1) to yield **1-(o-azidobenzoyl)-4-methyl-4-ethenyl-1-azetidino-2-thione (296)**; 0.26 g, 49% yield) as a yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2924.3 (vs), 2853.0 (vs), 2128.7 (m), 1687.3 (s), 1485.7 (w), 1463.3 (s), 1404.1 (w), 1376.0 (s), 1304.1 (s).

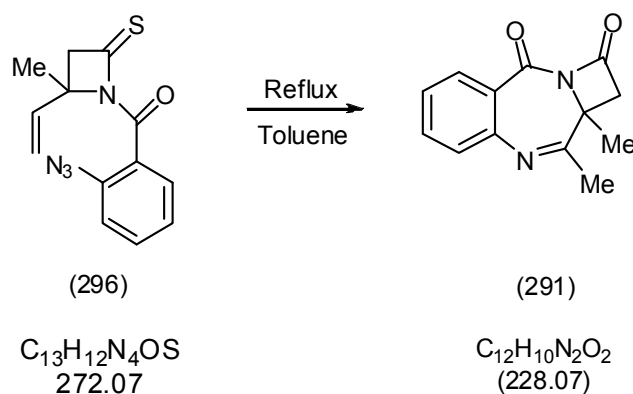
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 7.41 (1H, td, J 7.8, 1.5, ArH), 7.24 (1H, dd, J 7.6, 1.4, ArH), 7.10 (2H, m, 2×ArH), 6.20 (1H, dd, J 17.3, 10.8, CH), 5.34 (1H, d, J 17.3, CH), 5.25 (1H, d, J 10.8, CH), 2.93 (1H, d, J 16.9 CH), 2.81 (1H, d, J 16.9, CH), 1.78 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 22.08 (CH₃), 54.25 (CH₂), 67.30 (q), 116.07 (CH₂), 118.32 (CH), 125.88 (CH), 126.44 (q), 128.63 (CH), 131.88 (CH), 137.50 (CH), 138.08 (q), 163.92 (C=O), 201.40 (C=S).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 273.0723, measured = 273.0725.

Formation of 9,9a-Dimethyl-azetidino[2,1-c][1,4]benzodiazepine-1,3-dione



A solution of thiolactam (296) (0.26 g, 0.96 mmol) was dissolved in toluene (15 mL) and heated at reflux. The reaction was monitored by TLC and showed the formation of a new product after 48 hours. The mixture was subsequently concentrated under vacuum and purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/5:1) to yield **the title compound (291)**; 0.20 g, 91% yield) as a clear, yellow oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2923.7 (w), 1799.9 (m), 1721.0 (s), 1684.9 (vs), 1655.1 (vs), 1609.1 (s), 1463.1 (s), 1349.8 (s), 1325.4 (s), 1116.3 (m).

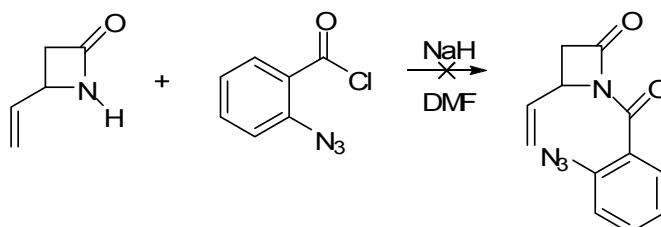
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.20 (1H, dd, J 8.0, 1.2, ArH), 7.67 (1H, td, J 7.7, 1.4, ArH), 7.59 (1H, d, J 8.1, ArH), 7.40 (1H, t, J 7.6, ArH), 3.67 (1H, d, J 16.0, CH), 3.32 (1H, d, J 16.0, CH), 2.37 (3H, s, CH₃), 1.89 (3H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 19.93 (CH₃), 26.23 (CH₃), 43.43 (CH₂), 73.20 (q), 123.65 (q), 126.52 (CH), 126.91 (CH), 127.15 (CH), 134.15 (CH), 149.45 (q), 155.06 (q), 157.88 (C=O), 204.15 (C=O).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 229.0972, measured = 229.0975.

Attempted synthesis of 1-(o-azidobenzoyl)-4-ethenyl-1-azetid-2-one using NaH



To a suspension of sodium hydride (0.1 g) (pre-washed with petroleum ether 3 × 5 mL) in dimethylformamide (12 mL) at 0°C under an atmosphere of dry nitrogen, was added 4-ethenyl-azetid-2-one (0.25 g, 2.58 mmol) in dry tetrahydrofuran (10 mL). The yellow opaque mixture was stirred for 15

minutes after which *o*-azidobenzoylchloride (0.47 g, 2.58 mmol) in dry tetrahydrofuran (10 mL) was injected through a septum dropwise over 10 minutes, which darkened to a brown colour. The solution was warmed slowly to ambient temperature and left to stir overnight, under dry nitrogen. The reaction was unsuccessful as confirmed by TLC, showing that only starting materials were present in the mixture.

Attempted synthesis of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidin-2-one using DMF and pyridine

To a stirring solution of 4-ethenyl-azetidin-2-one (0.31 g, 3.18 mmol) in dimethylformamide (30 mL)/dichloromethane (30 mL) at -10°C or 0°C and under an atmosphere of dry nitrogen, was added pyridine (0.45 mL, 5.51 mmol) dropwise over 5 minutes. To this mixture was added *o*-azidobenzoylchloride (0.25 g, 1.38 mmol) dropwise over 20 minutes and the solution was then warmed slowly to room temperature over 1 hour. The reaction was heated to 60°C and monitored by TLC for completion, but was subsequently shown to be unsuccessful.

Attempted synthesis of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetidin-2-one using 1,1-carbonyldiimidazole

A sample of 4-ethenyl-azetidin-2-one (0.25 g, 2.56 mmol) was dissolved in freshly distilled ethyl acetate (30 mL), under an atmosphere of dry nitrogen at room temperature. To this solution was added *o*-azidobenzoic acid (0.42 g, 2.58 mmol) dissolved in freshly distilled ethyl acetate (5 mL) in one portion, followed by 1,1-carbonyldiimidazole (0.50 g, 3.09 mmol), at an equivalent rate of addition. The mixture was heated at reflux and monitored by TLC for completion. The resulting light orange sample was concentrated under vacuum and subjected to silica column chromatography (eluent: petroleum ether:ethyl acetate/1:1). No identifiable product could be isolated.

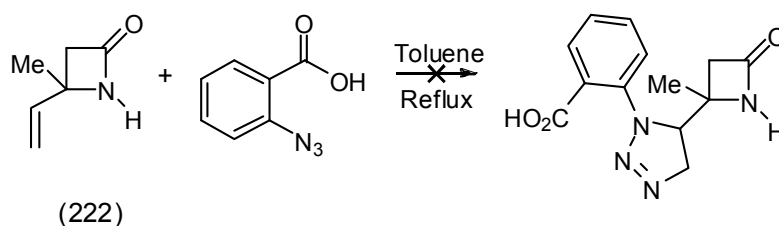
Attempted synthesis of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetid-2-one using LDA

To a solution of diisopropylamine (0.25 mL, 1.76 mmol) dissolved in dry tetrahydrofuran (10 mL) was added butyllithium, dropwise (1.6M solution in hexane, 1.1 mL, 1.76 mmol) at -78°C, under an inert atmosphere of nitrogen. The mixture was warmed to between -10°C and 0°C and the clear yellow solution was stirred for 30 minutes. To the above solution was added 4-ethenyl-azetid-2-one (0.2 g, 1.60 mmol) in dry tetrahydrofuran (3 mL) dropwise over 10 minutes, followed by *o*-azidobenzoyl chloride (0.32 g, 1.76 mmol) in dry tetrahydrofuran (5 mL) dropwise over 10 minutes. The resulting dark orange opaque solution was stirred at 0°C for 3 hours, before being warmed to room temperature and left to stir for 24 hours. Saturated aqueous ammonium chloride solution (10 mL) was syringed into the reaction (2 × 5 mL portions) and the sample opened to the atmosphere and stirred for 30 minutes at ambient temperature. The aqueous layer was subsequently separated, extracted with ethyl acetate (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under vacuum. The desired product was not present in the mixture.

Attempted synthesis of 1-(*o*-azidobenzoyl)-4-ethenyl-1-azetid-2-one using potassium carbonate

To a solution of potassium carbonate (0.53 g, 3.86 mmol) in deionised water (5.3 mL) was added in one portion, with stirring, 4-ethenyl-azetid-2-one (0.24 g, 1.93 mmol) in dichloromethane (2.4 mL). The solution was stirred at ambient temperature for 5 minutes before *o*-azidobenzoylchloride (0.35 g, 1.93 mmol) in dichloromethane (3.5 mL) was added dropwise over 5 minutes. The reaction was left to stir at room temperature for 72 hours, before water (11.2 mL) was added in one portion. The sample was extracted with dichloromethane (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. No product corresponding to the title compound was present in the mixture.

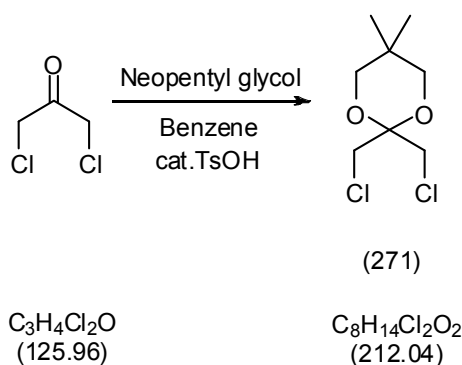
Attempted synthesis of *o*-([5-(4-methyl-1-azetidin-2-on-4-yl)-1,2,3-triazolin-1-yl])benzoic acid



To a solution of lactam (222) (0.1 g, 0.90 mmol) in dry toluene (5 mL) was added *o*-azidobenzoic acid (0.15 g, 0.90 mmol) under a dry atmosphere of nitrogen, at ambient temperature. The reaction was heated at reflux for 72 hours and the mixture purified by silica column chromatography (eluent: petroleum ether:ethyl acetate/1:1). The desired product was not present.

5.7 Cyclopropenone work

Synthesis of 1,3-dichloroacetone acetal



A mixture of 1,3-dichloroacetone (15 g, 118.1 mmol), neopentyl glycol (13.53 g, 130.0 mmol) and *p*-toluenesulfonic acid (0.45 g, 2.36 mmol) was dissolved in benzene (10 mL) and refluxed for 24 hours, with azeotropic [Dean-Stark] removal of water. The resulting solution was partitioned between hexane (50 mL) and saturated sodium hydrogen carbonate (20 mL). The organic layer was decanted and subsequently washed with water (10 mL) and saturated sodium chloride (10 mL), before being dried over magnesium sulfate, filtered and concentrated under vacuum to produce a clear, yellow oil. The crude sample was distilled (bp 130-131°C, 50 mmHg, literature value bp 99-100°C,

3.5 mmHg) to yield pure **1,3-dichloroacetone acetal (271)**; 18.20 g, 72% yield) as a clear and colourless oil.

Compound data

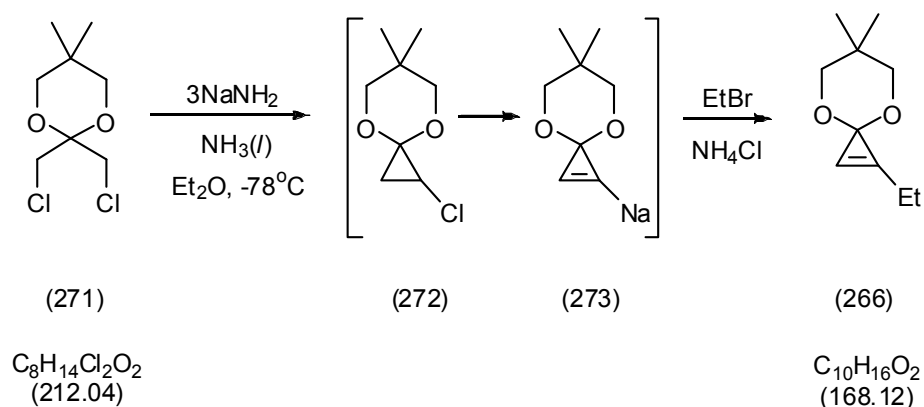
IR: ν_{\max} (cm⁻¹): 2961 (m), 2871 (m), 1473 (w), 1430 (w), 1397 (w), 1326 (w), 1256 (w), 1217 (m), 1107 (vs), 1032 (s).

NMR

¹H: δ_{H} (400 MHz, CDCl₃): 3.80 (4H, s, CH₂-Cl), 3.57 (4H, s, CH₂-O-), 1.00 (6H, s, CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 97.16 (q), 70.95 (CH₂), 41.83 (CH₂), 29.75 (q), 22.30 (CH₃).

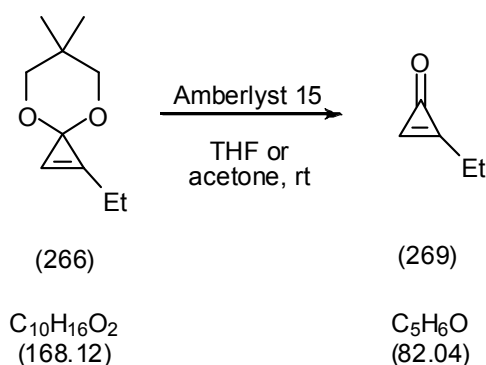
Synthesis of 2-Ethylcyclopropenone Acetal



To suspension of sodium amide (5.12 g, 131.0 mmol) in dry ammonia (70 mL) cooled at -70°C, was added a solution of dichloroacetone acetal (9 g, 42.3 mmol) in freshly distilled ether (25 mL) over 30 minutes. After this period the reaction was stirred for 1 hour and the temperature was maintained at or below -50°C. An additional portion of sodium amide (1 g) was added to the reaction and stirring was continued for a further 30 minutes at -50°C. Bromoethane (3.2 mL, 42.3 mmol) in dry ether (15 mL) was added slowly over a period of 45 minutes at -70°C and the reaction stirred for a further 10 minutes. The cooling bath was allowed to warm slowly to -50°C over 30 minutes before ammonium chloride (6 g) was added in 0.5 g portions. The cooling bath was removed and the ammonia left to evaporate, during which

time ether (70 mL) was added slowly. The reaction was warmed to room temperature and left to stir overnight. The ethereal solution was subsequently filtered and concentrated by rotary evaporation to yield a brown opaque oil, as crude 2-ethylcyclopropenone acetal (266), which was used without purification.

Synthesis of ethylcyclopropenone – (THF METHOD)



To crude 2-ethylcyclopropenone acetal (7.15 g), dissolved in tetrahydrofuran (40 mL) was added Amberlyst 15 catalyst, (0.2 g) with stirring. The solution was stirred at ambient temperature and monitored by tlc and IR. Upon completion of the reaction (2 hours 30 minutes), the Amberlyst was removed by filtration, the sample concentrated on the rotary evaporator and subsequently purified using column chromatography (eluent: hexane:ethyl acetate/1:2) to yield **ethylcyclopropenone (269)**; 0.46 g) as a clear, orange oil (data as below).

Synthesis of ethylcyclopropenone – (ACETONE METHOD)

To crude 2-ethylcyclopropenone acetal (4.00 g), dissolved in freshly distilled acetone (200 mL) was added Amberlyst 15 catalyst, (0.6 g) with stirring. The solution was stirred for 1 hour at ambient temperature under an atmosphere of dry nitrogen and monitored by tlc and IR. Upon completion (3½ hours), the reaction was quenched with triethylamine (0.3 mL, 21.5 mmol) added in one portion and the sample stirred for a further 5 minutes. The resin was removed by filtration, the solvent evaporated and the residue purified by column

chromatography (eluent: hexane:ethyl acetate/1:2) to yield **ethylcyclopropenone (269)**; 0.38 g) as a clear, orange oil.

Compound data

IR: ν_{\max} (cm⁻¹): 2983 (w), 1831 (vs), 1739 (vs), 1592 (m), 1374 (m), 1243 (vs).

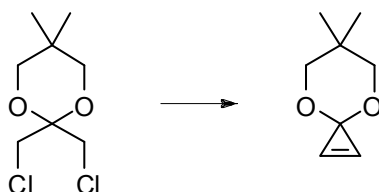
NMR

¹H: δ_{H} (400 MHz, CDCl₃): 8.41 (1H, s, CH), 2.65 (2H, q, J 7.5, CH₂), 1.25 (3H, t, J 7.5, CH₃)

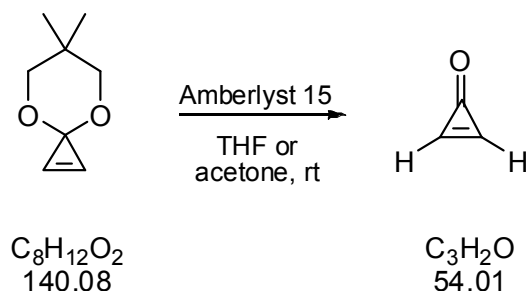
¹³C: δ_{C} (100 MHz, CDCl₃): 170.62 (C=O), 158.10 (CH), 147.67 (q), (CH₂), (CH₃),

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 83.0490, measured = 83.0492.

Synthesis of cyclopropenone acetal



To a suspension of sodium amide (6.05 g, 167.4 mmol) in dry liquid ammonia (80 mL) cooled at -70°C, was added a solution of dichloroacetone acetal (11.5 g, 54.0 mmol) in freshly distilled ether (30 mL) over 30 minutes. After this period the opaque, yellow solution was stirred for 1 hour and the temperature was maintained at or below -50°C. An additional portion of sodium amide (1 g) was then added to the reaction and stirring was continued for a further 30 minutes at -50°C. The cooling bath was allowed to warm slowly to -50°C over 30 minutes before ammonium chloride (4 g) was added in 0.5 g portions, resulting in an opaque, orange solution. The cooling bath was removed and the ammonia left to evaporate, during which time ether (80 mL) was added slowly. The reaction was warmed to room temperature and left to stir overnight. The ethereal solution was subsequently filtered and concentrated by rotary evaporation to yield the crude product as a clear, orange oil.

Attempted synthesis of unsubstituted cyclopropenone – (THF METHOD)

To the crude cyclopropenone acetal (2 g), dissolved in tetrahydrofuran (12 mL) was added Amberlyst 15 catalyst, (0.2 g) with stirring. The solution was stirred at ambient temperature overnight and monitored by tlc and IR. The Amberlyst was removed by filtration, the sample concentrated on the rotary evaporator and subsequently purified using column chromatography (eluent: petroleum ether:ethyl acetate/1:1). Column purification was unsuccessful and did not yield the desired **cyclopropenone**. All attempts to isolate the pure material were unsuccessful. In subsequent reactions, the crude material was used as a solution in THF.

Crude cyclopropenone was prepared from cyclopropenone acetal (2 g) as above. The mixture was added to Amberlyst 15 catalyst (0.2 g) in THF (12 mL) and the solution was stirred for five hours at ambient temperature, under an atmosphere of dry nitrogen. Careful monitoring by IR and tlc indicated formation of the desired cyclopropenone after 4½ hours. The resulting crude solution was partitioned between water and dichloromethane in an attempt to facilitate the separation of the impeding glycol from the desired cyclopropenone. This resulted in a significant reduction of glycol present in the sample. The crude product obtained still contained a small proportion of glycol, but this material was further reacted with imines **(252)**, **(256)** and **(259)** shown below.

The general procedure for the reaction of imines (252), (256) and (259) with crude cyclopropenone

To a solution of imine **(252)**, **(256)** and **(259)** (0.25 g) in dry acetonitrile (10 mL) was added crude cyclopropenone in one portion. The reaction was stirred at room temperature under an atmosphere of dry nitrogen and monitored by tlc. After 72 hours it was shown that each reaction had gone to completion. Therefore the sample was concentrated under vacuum and purified by column chromatography (eluent: hexane:ethyl acetate). The various bicyclic compounds were obtained in yields below 20% and the data for each compound is shown below.

Compound data for reaction with 5-ethylthio-3,4-dihydro-2H-pyrrole

IR: ν_{\max} (cm⁻¹): 2997 (m), 2956 (m), 1666 (s), 1614 (s), 1598 (w), 1522 (w), 1435 (m), 1350 (m), 1217 (m), 1017 (m).

NMR

¹H: δ_{H} (500 MHz, CDCl₃): 7.66 (1H, d, J 3.6, C=CH), 5.24 (1H, d, J 3.6, C=CH), 3.45 (1H, ddd, J 11.1, 7.6, 6.0, CH₂CHHN), 3.24 (1H, m, CH₂CHHN), 2.41 (2H, 2 × dq, J 11.8, 7.6 and 11.8, 7.6, SCH₂CH₃), 2.10 (1H, m, CH₂CH₂N), 2.00 (1H, ddd, J 13.2, 7.8, 6.0, CH₂CH₂N), 1.90 (1H, ddd, 17.2, 13.2, 7.7, CH₂CSEt), 1.81 (1H, ddd, J 13.2, 8.1, 6.0, CH₂CSEt), 1.11 (3H, t, J 7.5, S-CH₂CH₃).

¹³C: δ_{C} (100 MHz, CDCl₃): 164.73 (C=O), 140.00 (CH), 105.12 (CH), 78.90 (CH₂), 70.42 (q), 70.31 (CH₂), 37.14 (CH₂), 29.82 (CH₂), 21.89 (CH₃)

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 184.0793, measured = 184.0795.

Compound data for reaction with 6-ethylthio-2,3,4,5-tetrahydropyridine

IR: ν_{\max} (cm^{-1}): 2989 (m), 2941 (m), 1689 (s), 1601 (s), 1522 (w), 1417 (m), 1375 (m), 1249 (m).

NMR

^1H : δ_{H} (500 MHz, CDCl_3): 7.39 (1H, d, J 13.1, C=CH), 5.66 (1H, d, J 13.1, C=CH), 3.85 (2H, dt, J 12.1, 6.6, $\text{CH}_2\text{CH}_2\text{N}$), 2.45 (1H, dq, J 12.0, 7.5, S- CH_2CH_3), 2.35 (1H, dq, J 12.0, 7.6, S- CH_2CH_3), 1.85 (2H, m, $\text{CH}_2\text{CH}_2\text{N}$), 1.75 (1H, dddd, J 13.0, 11.1, 3.9, 3.9, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CSEt}$), 1.66 (1H, bd, 9.8, CH_2CSEt), 1.60 (1H, m, CH_2CSEt), 1.45 (1H, dddd, 13.2, 12.3, 4.2, 3.9, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CSEt}$), 1.18 (3H, t, J 7.5, SCH_2CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 170.89 (C=O), 151.47 (CH), 83.93 (CH), 67.94 (CH_2), 67.87 (CH_2), 36.82 (q), 26.57 (CH_2), 24.81 (CH_2), 21.62 (CH_3), 19.62 (CH_2).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 198.0949, measured = 198.0949.

Compound data for reaction with 7-ethyl-3,4,5,6-tetrahydro-2H-azepine

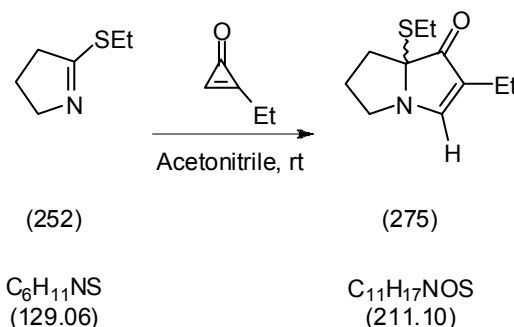
IR: ν_{\max} (cm^{-1}): 2907 (m), 2876 (w), 1676 (s), 1588 (s), 1487 (w), 1427 (w).

NMR

^1H : δ_{H} (500 MHz, CDCl_3): 7.55 (1H, s, C=CH), 7.47 (1H, s, C=CH), 4.02 (1H, d, J 11.1, $\text{CH}_2\text{CH}_2\text{N}$), 3.88 (1H, d, J 11.1, $\text{CH}_2\text{CH}_2\text{N}$), 3.46 (2H, m, CH_2CSEt), 3.20 (2H, dd, J 12.0, 1.8, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.97 (1H, dq, J 12.0, 7.5, SCH_2CH_3), 1.83 (1H, dq, 12.0, 7.5 S- CH_2CH_3), 1.66 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.47 (1H, m, $\text{CH}_2\text{CH}_2\text{CSEt}$), 1.35 (1H, m, $\text{CH}_2\text{CH}_2\text{CSEt}$), 0.86 (3H, t, J 7.5, S- CH_2CH_3).

^{13}C : δ_{C} (100 MHz, CDCl_3): 166.45 (C=O), 149.90 (CH), 133.02 (CH), 97.16 (q), 68.83 (CH_2), 55.96 (CH_2), 33.87 (CH_2), 28.57 (CH_2), 27.12 (CH_2), 24.58 (CH_2), 21.64 (CH_3).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 212.1108, measured = 212.1108.

Synthesis of 5-ethylthio-3-ethyl-1-azabicyclo[3.3.0]oct-2-en-4-one

To a solution of 5-ethylthio-3,4-dihydro-2H-pyrrole (0.05 g, 0.39 mmol) in dry acetonitrile (5 mL) was added 2-ethylcyclopropanone (0.06 g, 0.78 mmol) in one portion. The reaction was stirred at room temperature under an atmosphere of dry nitrogen for 72 hours at which point TLC showed the reaction was complete. The sample was concentrated under vacuum and purified by column chromatography (eluent: hexane:ethyl acetate/2:1) to yield **the title compound (275)**; 0.043 g, 50% yield) as a clear, yellow oil.

Compound data

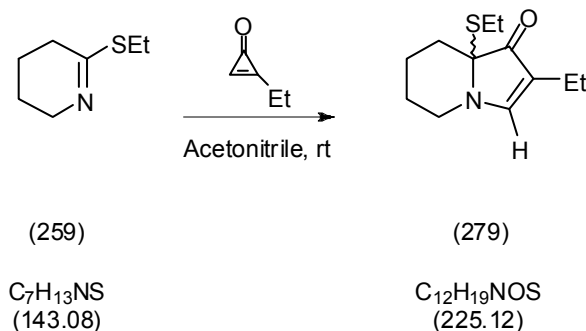
IR: ν_{max} (cm^{-1}): 2966 (m), 2930 (m), 2874 (w), 1681 (vs), 1591 (s), 1456 (w), 1375 (m).

NMR

1H : δ_H (500 MHz, $CDCl_3$): 7.41 (1H, s, CH), 3.38 (1H, m, CH_2 next to nitrogen), 3.15 (1H, m, CH_2 next to nitrogen), 2.38 (2H, q, J 7.6, CH_2 on ring Et), 2.09 (2H, q J 7.6, CH_2 of SEt), 2.00 (2H, m, CH_2), 1.79 (2H, m, CH_2), 1.09 (3H, t, J 7.5, CH_3 of SEt), 1.00 (3H, t, J 7.4, CH_3 , ring Et).

^{13}C : δ_C (100 MHz, $CDCl_3$): 203.64 (C=O), 164.95 (CH), 121.36 (q), 80.01 (q), 48.83 (CH_2), 33.78 (CH_2), 26.57 (CH_2), 23.12 (CH_2), 15.73 (CH_2), 14.05 (CH_3), 12.99 (CH_3).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 212.1105, measured = 212.1108.

Synthesis of 5-ethylthio-3-ethyl-1-azabicyclo[4.3.0]non-2-en-4-one

To a solution of 6-ethylthio-2,3,4,5-tetrahydropyridine (0.10 g, 0.79 mmol) in dry acetonitrile (3 mL) was added 2-ethylcyclopropenone (0.065 g, 0.79 mmol) in one portion. The reaction was stirred at room temperature under an atmosphere of dry nitrogen for 24 hours until TLC showed the reaction was complete. The sample was concentrated under vacuum and purified by column chromatography (eluent: hexane:ethyl acetate/2:1) to yield **the title compound (279)**; 0.081 g, 45% yield) as a clear, yellow oil.

Compound data

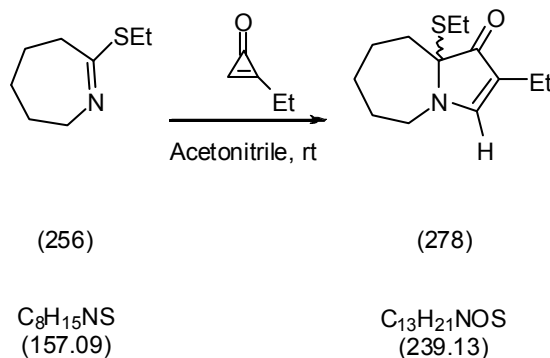
IR: ν_{max} (cm^{-1}): 2960.57 (s), 2929.21 (s), 2870.74 (w), 1647.33 (s), 1570.11 (s), 1440.04 (w), 1326.87 (w).

NMR

^1H : δ_{H} (500 MHz, CDCl_3): 7.57 (1H, s, CH), 3.64 (1H, ddd, J 13.2, 13.2, 3.4 NCH₂), 3.47 (1H, dd, J 13.3, 4.9, NCH₂), 2.35 (1H, dq, J 12.0, 7.4, SCH₂), 2.23 (1H, dq, J 12.0, 7.4, SCH₂), 2.19 (2H, q, J 7.5 CCH₂CH₃), 2.01 (1H, bd, J 14.1, CH₂CSEt), 1.83 (1H, ddd, J 13.1, 3.3, 3.3, CH₂CH₂N), 1.75 (1H, m, CH₂CH₂CSEt), 1.69 (1H, ddd, J 13.4, 3.3, 3.3, CH₂CH₂CSEt), 1.49 (1H, ddd, J 14.0, 13.8, 3.8, CH₂CSEt), 1.38 (1H, dddd, 13.1, 13.0, 4.2, 4.2, CH₂CH₂CH₂N), 1.14 (3H, t, J 7.5, SCH₂CH₃), 1.09 (3H, t, J 7.5, CH₂CH₃).

^{13}C : δ_{C} (100 MHz, CDCl_3): 202.62 (C=O), 159.28 (CH), 111.46 (C=C), 72.48 (q), 45.33 (CH₂), 32.76 (CH₂), 27.48 (CH₂), 21.86 (CH₂), 20.33 (CH₂), 15.40 (CH₂), 14.18 (CH₃), 13.70 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 226.1260, measured = 226.1260.

Synthesis of 5-ethylthio-3-ethyl-1-azabicyclo[5.3.0]dec-2-en-4-one

To a solution of 7-ethyl-3,4,5,6-tetrahydro-2H-azepine (0.05 g, 0.32 mmol) in dry acetonitrile (5 mL) was added 2-ethylcyclopropanone (0.08 g, 0.96 mmol) in one portion. The reaction was stirred at room temperature under an atmosphere of dry nitrogen for 72 hours until TLC showed the reaction was complete. The sample was concentrated under vacuum and purified by column chromatography (eluent: petroleum:ethyl acetate/2:1) to yield **the title compound (278)**; 0.05 g, 63% yield) as a yellow oil.

Compound data

IR: ν_{max} (cm^{-1}): 2926.93 (s), 2851.87 (w), 1662.03 (vs), 1577.61 (vs), 1451.02 (w), 1416.45 (w).

NMR

1H : δ_H (500 MHz, $CDCl_3$): 7.66 (1H, s, C=CH), 3.52 (1H, bd, J 14.8, NCH₂), 3.39 (1H, ddd, J 13.4, 13.4, 1.2, NCH₂), 2.40 (1H, dd, J 14.4, 7.7, CH₂CSEt), 2.21 (1H, dq, J 12.0, 7.5, S-CH₂CH₃), 2.18 (2H, dq, J 12.0, 7.5, S-CH₂CH₃), 2.13 (2H, q, J 7.3, CCH₂CH₃), 1.78 (2H, m, CH₂CH₂CH₂CH₂N), 1.51 (2H, m, CH₂CH₂CSEt), 1.35 (1H, ddd, J 13.2, 3.8, 3.8, CH₂CH₂CH₂N), 1.17 (1H, m, CH₂CH₂CH₂N), 1.04 (3H, t, J 7.5, S-CH₂CH₃), 1.01 (3H, t, J 7.3, CH₂CH₃), 0.73 (1H, m, CH₂CH₂CSEt).

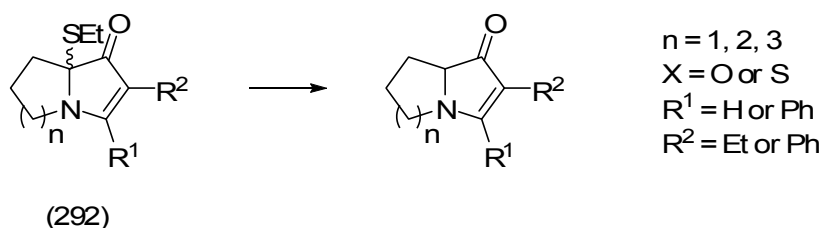
^{13}C : δ_C (100 MHz, $CDCl_3$): 200.60 (C=O), 162.14 (CH), 113.98 (q), 60.17 (q), 45.84 (CH₂), 32.18 (CH₂), 31.02 (CH₂), 29.48 (CH₂), 23.07 (CH₂), 22.06 (CH₂), 15.48 (CH₂), 13.72 (CH₃), 13.70 (CH₃).

High Resolution Mass Spectroscopy: Electrospray (positive), calc. = 240.1418, measured = 240.1420.

Future Work

There is the potential as part of a programme of future work to investigate alternative routes to the synthesis of 1,2-thiazetidin-1,1-dioxides, which were not explored in this thesis due to alternative areas of work being developed concurrently. This work may investigate the possibility of employing anhydrous conditions in the Lawesson's step of the synthesis, to preclude and eliminate the theory that hydrolysis is taking place back to the 1,2-thiazetidin-3-one (196). There would therefore be the potential for the synthesis of the desired novel bicyclic β -sultams and β -lactams as analogues of biologically relevant systems, such as penicillins.

In sections 4.6 and 4.7 of this thesis one of the strengths of the route to adducts (292) is the versatility of the reaction. This is due to the high level of diversity available in both the thioimide and cyclopropenone reaction partners. The second potential strength of this reaction, which could also be explored as part of a programme of future work, is the ease with which the functionality of the reaction partners can be manipulated. This will enable future applications to be developed in the synthesis of natural products as well as interesting non-natural analogues of the pyrrolizidines, indolizidines and pyrroloazepines. One such process would be the desulfurisation of compound (292) shown in Scheme 102.



Scheme 102

Other possible transformations of adducts of compound (292) may include conjugate addition, reduction, aziridation and bridgehead thioether/ether manipulation together with possible asymmetric versions of the cyclopropenone addition reaction. The latter part of this work would also involve the synthesis of further cyclopropenones and the subsequent exploration of this interesting area of heterocyclic chemistry.

Section 4.8 of this thesis details the synthesis of azetidinobenzodiazepines, which are analogues of the well documented pyrrolobenzodiazepines. The PBDs have been shown to have antitumour/antibiotic properties. Part of a programme of future work would involve the synthesis of further examples of the azetidino adducts via the intramolecular azide to alkene 1,3-dipolar cycloadditions shown in section 4.8. These compounds could then be further investigated for any potential biological activity as they have a very similar structure to the PBDs and may well have the same affinity for fitting into the minor groove of the DNA strand.

References

1. (a) Shvekhgeimer, M.-G. A. *Chemistry of Heterocyclic Compounds* **2003**, 39, 405-445; (b) Peddibhotla, S.; Tepe, J. J. *J. Am. Chem. Soc.* **2004**, 126, 12776-12777.
2. Murai, T.; Sano, H.; Kawai, H.; Aso, H.; Shibahara, F. *J. Org. Chem.* **2005**, 70, 8148-8153.
3. Katritzky, A. R.; Zhu, L.; Lang, H.; Denisko, O.; Wang, Z. *Tetrahedron* **1995**, 51, 13272-13276.
4. (a) Saluste, C. G.; Whitby, R. J.; Furber, M. *Tetrahedron Lett.* **2001**, 42, 6191-6194; (b) Kosugi, M.; Ogata, T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, 1197-1200.
5. Kuduk, S. D.; Ng, C.; Chang, R. K.; Bock M. G. *Tetrahedron Lett.* **2003**, 44, 1437-1440.
6. Oganisyan, A. S.; Grigoryan, G.O.; Noravyan, A.S. *Khimiya Geterotsiklicheskikh Soedinenii* **2001**, 8, 1116-1119.
7. Coustard, J-M. *Tetrahedron* **1996**, 52, 9509-9520.
8. Cousson, A.; Coustard, J-M. *Tetrahedron* **1998**, 54, 6523-6528.
9. Hamid, A.; Elomri, A.; Daïch, A. *Tetrahedron Lett.* **2006**, 47, 1777-1781.
10. Agami, C.; Amiot, F.; Couty, F.; Dechoux, L. *Tetrahedron Lett.* **1998**, 39, 5373-5374.
11. Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197-1218.
12. Soellner, M. B.; Nilsson, B. L.; Raines, R. T. *J. Am. Chem. Soc.* **2006**, 128, 8820-8828.
13. (a) Restituyo, J. A.; Comstock, L. R.; Petersen, S. G.; Stringfellow, T.; Rajski, S. R. *Org. Lett.* **2003**, 5, 4357- 4360; (b) Rose, M. W.; Xu, J.; Kale, T. A.; O'Doherty, G.; Barany, G.; Distefano, M. D. *Peptide Sci.* **2005**, 80, 164-171.
14. Pleynet, D. P. M.; Dutton, J. K.; Thornton-Pett, M.; Johnson A. P. *Tetrahedron Lett.* **1995**, 36, 6321-6324.
15. Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M.; Wynants, C. *Tetrahedron* **1995**, 51, 11021-11042.
16. Schaeffer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, 26, 2778.

17. Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hoffman, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.
18. Ghosez, L.; Jnoff, E.; Bayard, Ph.; Sainte, F.; Beaudegnies, R. *Tetrahedron* **1999**, 55, 3387-3400.
19. Alvarez-Ibarra, C.; Csáky, A. G.; Martínez, M.; Luz Quiroga, M. *Tetrahedron Lett.* **1996**, 36, 6573-6574.
20. Ito, H.; Imai, N.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1996**, 37, 1799-1800.
21. Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, 59, 1243-1245.
22. Graf, R. *Justus Liebigs Ann. Chem.* **1963**, 661, 111.
23. Meerwein, H. *Org. Syn.* **1966**, 46, 120.
24. Paquette, L. A.; Kakihana, T.; Hansen, J. F.; Phillips, J. C. *J. Am. Chem. Soc.* **1970**, 93, 152-161.
25. Durst, T.; O'Sullivan, M. J. *J. Org. Chem.* **1970**, 35, 2043-2044.
26. Hemming, K.; Morgan, D. T.; Smalley, R. K. *J. Fluorine Chem.* **2000**, 106, 83-86.
27. Hemming, K.; Redhouse, A. D.; Smalley, R. K.; Thompson, J. R.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1992**, 33, 2231-2234.
28. Hemming, K.; Luheshi, A.-B. N.; Redhouse, A. D.; Smalley, R. K.; Thompson, J. R.; Kennewell, P. D.; Westwood, R. *Tetrahedron* **1993**, 49, 4383-4408.
29. Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, 87, 229-238.
30. Scrowston, R. M.; Miller, D. J.; Kennewell, P. D.; Westwood, R. *Tetrahedron* **1994**, 50, 5159-5168.
31. North, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2209-2229.
32. Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, 7, 3363-3366.
33. Dufour, E.; Tam, W.; Nägler, D. K.; Storer, A. C.; Ménard, R. *FEBS Letters*, **1998**, 433, 78-82.
34. Dufour, E.; Storer, A.; Ménard, R. *Biochemistry* **1995**, 34, 16382-16388.

35. Khouri, L.; Kaloustian, M. K. *J. Org. Chem.* **1981**, 46, 5052-5054.
36. Scrowston, R. M.; Miller, D. J.; Kennewell, P. D.; Westwood, R. *Tetrahedron* **1992**, 48, 7703-7712.
37. Luheshi, A.-B. N.; Smalley, R. K.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1990**, 31, 123-126.
38. Luheshi, A.-B. N.; Smalley, R. K.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1990**, 31, 127-130.
39. Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, 9, 1349-1351.
40. Paquette, L. A.; Wyvratt, M. J.; Allen, Jr., G. R. *J. Am. Chem. Soc.* **1970**, 92, 1763.
41. Schulenberg, J.; Archer, S. *Org. React.* **1965**, 14, 1.
42. Chapman, A. W. *J. Chem. Soc.* **1925**, 127, 1992.
43. Yamada, H.; Shizuka, H.; Matsui, K. *J. Org. Chem.* **1975**, 40, 1351-1352.
44. Meyer, R. *J. Org. Chem.* **1963**, 28, 2902-2903.
45. Anbazhagan, M.; Dixit, A. N.; Rajappa, S. *J. Chem Soc, Perkin Trans. I* **1997**, 2421.
46. Chang, R. K.; DiPardo, R. M.; Kuduk, S. D. *Tetrahedron Lett.* **2005**, 46, 8513-8516.
47. Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, 59, 3099-3108.
48. Rubinov, D. B.; Rubinova, I. L. *Russian Journal of Organic Chemistry* **2004**, 40, 1187-1189.
49. Mmutlane, E. M.; Harris, J. M.; Padwa, A. *J. Org. Chem.* **2005**, 70, 8055-8063.
50. Michael, J. P. *Nat. Prod. Rep.* **2000**, 17, 603-620.
51. Coppola, G. M. *Synthesis* **1980**, 505-536.
52. O'Mahony, G.; Nieuwenhuyzen, M.; Armstrong, P.; Stevenson, P. J. *J. Org. Chem.* **2004**, 69, 3968-3971.
53. Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, 96, 505-522.
54. Daly, J. W. *J. Med. Chem.* **2003**, 46, 445.
55. Shanghai, Y.; Wei, Z.; Dawei, M. *J. Org. Chem.* **2005**, 70, 7364-7370.
56. Colombo, L.; Di Giacomo, M. *Tetrahedron Lett.* **1995**, 36, 625-628.

57. Giovenzana, G. B.; Sisti, M.; Palmisano, G. *Tetrahedron Asymm.* **1997**, 8, 515-518.
58. Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Decker, M. W.; Sullivan, J. P.; Williams, M.; *Nat. Prod. Rep.* **2000**, 17, 131-135.
59. Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, 38, 4347-4350.
60. Tong, S. T.; Barker, D. *Tetrahedron Lett.* **2006**, 47, 5017-5020.
61. Kumareswaran, R.; Gallucci, J.; RajanBabu, T. V. *J. Org. Chem.* **2004**, 69, 9151-9158.
62. Kim, N.; Choi, J.; Cha, J. K. *J. Org. Chem.* **1993**, 58, 7096-7099.
63. Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, 46, 2101-2103.
64. Toyooka, N.; Dejun, Z.; Nemoto, H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron Lett.* **2006**, 47, 577-580.
65. Smith (III), A. B.; Kim, D. *J. Org. Chem.* **2006**, 71, 2547-2557.
66. Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.; Poon, Y.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, 55, 5719-5738.
67. Williams, I.; Kariuki, B. M.; Reeves, K.; Cox, L. R. *Org. Lett.* **2006**, 8, 4389-4392.
68. Mann, J. *Chemical Aspects of Biosynthesis*, Oxford University Press **1994**.
69. Mattock, A. R. "Chemistry and Toxicology of Pyrrolizidine Alkaloids", *Academic Press, London*, **1986**.
70. Duvall, J. R.; Fanghui, W.; Snider, B. B. *J. Org. Chem.* **2006**, 71, 8579-8590.
71. Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 15, 2670-2680.
72. Daly, J. W. *Cell. Mol. Neurobiol.* **2005**, 25, 513-552.
73. (a) Colombo, L.; Di Giacomo, M.; Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, 36, 625-628; (b) Robl, J. A. *Tetrahedron Lett.* **1994**, 35, 393-396; (c) Genin, M. J.; Ojala, W. H.; Gleason, W. B.; Johnson, R. L.; *J. Org. Chem.* **1993**, 58, 2234-2337.
74. Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, 119, 3409-3410.

75. Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, 37, 3911-3914.
76. For a review, see: Mansell, H. L. *Tetrahedron* **1996**, 52, 6025-6061.
77. (a) Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron* **2000**, 56, 309-315; (b) Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, 55, 1367-1371; (c) Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, 6, 1329-1331.
78. Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science* **1975**, 187, 542.
79. Spivak, C. E.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1980**, 18, 384.
80. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, 114, 3475.
81. Hjelmggaard, T.; Søtofte, I.; Tanner, D. *J. Org. Chem.* **2005**, 70, 5688-5697.
82. Wilmouth, R. C.; Kassamally, S.; Westwood, N. J.; Sheppard, R. J.; Claridge, T. D. W.; Aplin, R. T.; Wright, P. A.; Pritchard, G. J.; Schofield, C. J. *Biochemistry* **1999**, 38, 7989.
83. Schaumann, E.; Rohr, A.; Adiwidjaja, G.; *Tetrahedron Lett.* **1980**, 4277.
84. Mihova, T. R.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta.* **1996**, 79, 2067.
85. Pifferi, P.; Consonni, P.; Pelizza, G.; Testa, E.; *J. Het. Chem.* **1967**, 4, 619-624.
86. Zhang, H.; Chan, W, H.; Lee A, W, M.; Xia, P, F.; Wong, W, Y. *Letters in Organic Chemistry*, **2004**, 1, 63-66.
87. Macor, J. E.; Ordway, T.; Smith, R, L.; Verhoest, P. R.; Mack, R. A. *J. Org. Chem.* **1996**, 61, 3228-3229.
88. Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, 2, 635.
89. Freitag, D.; Schwab, P.; Metz, P, *Tetrahedron Lett.* **2004**, 45, 3589-3592.
90. Singh, G, S. *Tetrahedron* **2003**, 59, 7631-7649.
91. The use of fresh Meerwein's reagent improved the yields of the 1-azetines.

92. (a) Eicher, T.; Rohde, R. *Synthesis* **1985**, 619-625; (b) Eicher, T.; Abdesaken, F.; Franke, G.; Weber, J. L. *Tetrahedron Lett.* **1975**, 16, 3915-3918.
93. Heimgartner, H.; Stierli, F.; Prewo, R.; Bieri, J. H. *Helv. Chim. Acta* **1983**, 66, 1366-1375.
94. Gomma, M. A. M. *J. Chem. Soc. Perkin Trans 1* **2002**, 341-344.
95. (a) Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, 36, 4787-4790; (b) Viallon, L.; Reinaud, O.; Capdevielle, P.; Maumy, M. *Tetrahedron* **1996**, 52, 13605-13614.
96. Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2004**, 6, 1329-1331;
97. (a) Takada, N.; Iwatsuki, M.; Suenaga, K.; Uemura, D. *Tetrahedron Lett.* **2000**, 41, 6425-6428; (b) Kigoshi, H.; Hayashi, N.; Uemura, D. *Tetrahedron Lett.* **2001**, 42, 7469-7471.
98. Breslow, R.; Haynie, R.; Mirra, J. *J. Am. Chem. Soc.* **1959**, 81, 247-248.
99. (a) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron* **1992**, 48, 2045-2057; (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev* **2003**, 103, 1295-1326.
100. Poloukhine, A.; Popik, V. V. *J. Org. Chem.* **2003**, 68, 7833-7840.
101. *Organic Synthesis*, Coll. Vol. 6, p361 (1998); Vol. 57, p 41 (1977).
102. (a) Hemming, K.; Patel, N. *Tetrahedron Lett.* **2004**, 45, 7553-7556; (b) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, 94, 433-465; (c) O'Neil, I. A.; Thompson, S.; Kalindjian, S. B.; Jenkins, T. C. *Tetrahedron Lett.* **2003**, 44, 7809-7812.
103. Gregson, S. J.; Howard, P. W.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *Chem. Commun.* **1999**, 797-798.
104. Artico, M.; Silvestri, R.; Pagnozzi, E.; Stefancich, G.; Massa, S.; Loi, A. G.; Putzolu, M.; Corrias, S.; Spiga, M. G.; La Colla, P. *Bioorg. Med. Chem.* **1996**, 4, 837-850.
105. (a) Giannotti, D.; Viti, G.; Sbraci, P.; Pestellini, V.; Volterra, G.; Borsini, F.; Lecci, A.; Meli, A.; Dapporto, P.; Paoli, P. *J Med. Chem.* **1991**, 34, 1356-1362; (b) Krülle, T. M.; Wijkmans, J. C. H. M. *Tetrahedron* **2001**, 57, 7021-7026.
106. Hadjivassileva, T.; Thurston, D. E.; Taylor, P. W. *Journal of Antimicrobial Chemotherapy* **2005**, 56, 513-518.

107. Hemming, K.; Loukou, C.; Elkatip, S.; Smalley, R. K. *Synlett* **2004**, 101-105.
108. Hemming, K.; Loukou, C. *Tetrahedron* **2004**, 60, 3349-3357.
109. Anwar, B.; Grimsey, P.; Hemming, K.; Krajniewski, M.; Loukou, C. *Tetrahedron Lett.* **2000**, 41, 10107-10110.
110. Madrigal, A.; Grande, M.; Avendaño, C. *Tetrahedron Asymmetry* **1998**, 9, 3115-3123.
111. (a) Ducray, R.; Cramer, N.; Ciufolini, M, A. *Tetrahedron Letters* **2001**, 42, 9175-9178; (b) Garanti, L.; Molteni, G.; Brogini, G. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1816-1819 (c) Guo, Z.; Schultz, A. *Tetrahedron Lett.* **2004**, 45, 919-921.
112. Purwono, B.; MSc Thesis, University of Salford, **1991**.
113. Page, M. I. *Acc. Chem. Res.* **2004**, 34, 297-303.
114. Hemming, K.; O’Gorman, P. A.; Page, M. I. *Tetrahedron Lett.* **2006**, 47, 425-428.
115. Molina, P.; Díaz, I.; Tárraga, A. *Tetraherdon*, **1995**, 51, (19), 5617-5636.