The formation of cyclopropenones and their use in the synthesis of heterocyclic pyrrolo natural products

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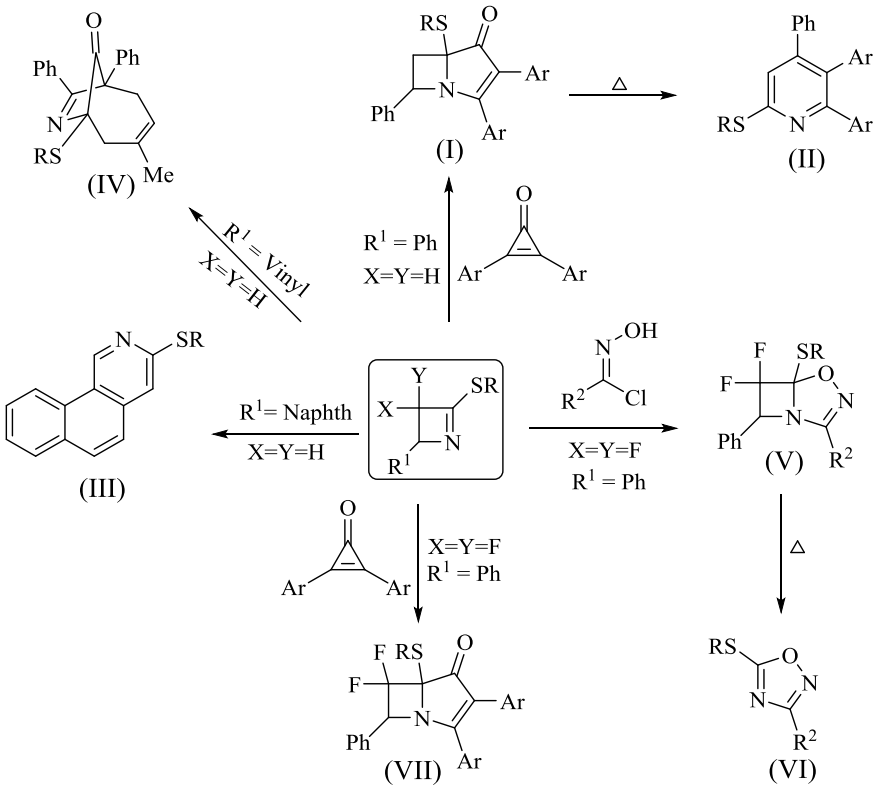
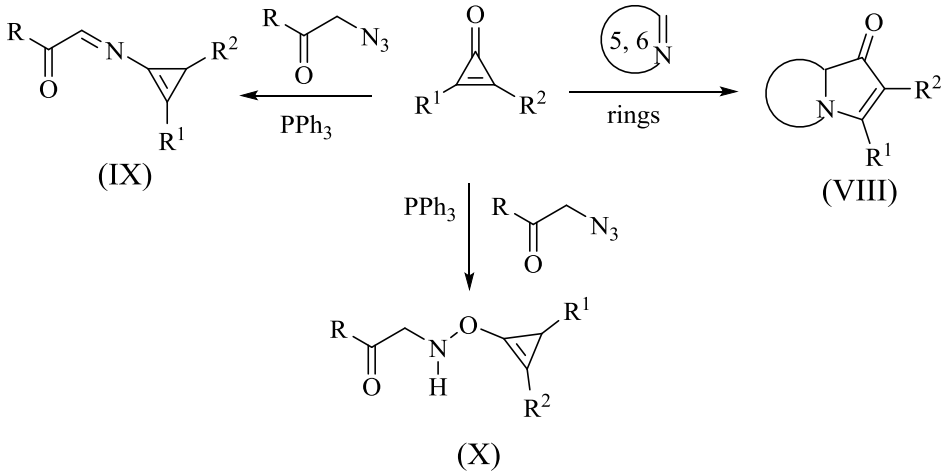
Abstract

In this project, a wide range of cyclic imines and cyclopropenones were synthesised to form highly fuctionalised heterocyclic products *via* a formal [3+2]-cycloaddition reaction. The synthesis of pyridines (II) will be described in this thesis and was achieved by heating azabicyclo[3.2.0]hept-2-en-4-ones (I) that were obtained from the reaction of 4-membered ring cyclic imines with cyclopropenones *via* a formal [3+2]-cycloaddition reaction. Some of the 1-azetines (R = naphth) underwent an unexpected ring expansion to give the alkylsulfanylbenzo[*f*] isoquinolines (III). 1,2,4-Oxadiazoles (VI) have been synthesised from a 4-aryl-3,3-difluoro-1-azetine *via* the formation of the nitrile oxide cycloadduct (V). The reactivity of 4-aryl-3,3-difluoro-1-azetine towards cyclopropenones to try to form (VII) will also be discussed. Homotropane related heterocycle (IV) was obtained when a 4-vinyl-1-azetine was treated with diphenylcyclopropenone.

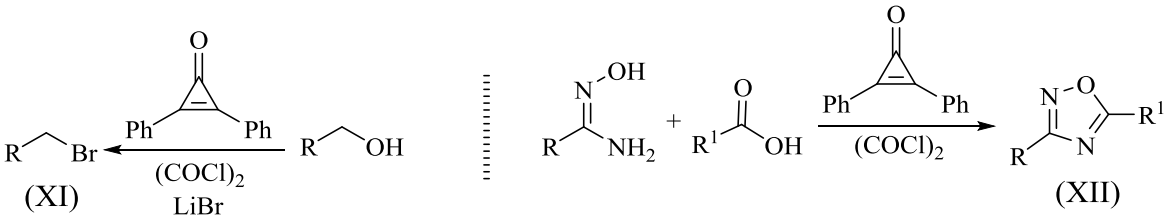


The use of 5- and 6-membered cyclic imines for the synthesis of pyrrolo-fused heterocycles (VIII) i.e. pyrrolizidines, indolizidines, pyrrolo-isoquinolines and pyrrolo-β-carbolines which

are widespread in natural products and medicinal chemistry is also discussed. The reactivity of cyclopropenones with azides is also discussed, *via* conversion into iminophosphoranes followed by aza-Wittig reaction to give products (IX) and (X).



Finally, a methodology has been developed for the catalytic coupling reactions of amidoxime and alcohol substrates using cyclopropenones. A series of alkyl bromides (XI) and novel 1,2,4-oxadiazoles (XII) has been synthesised with the involvement of diphenylcyclopropenone as a catalyst. These 1,2,4-oxadiazoles are important due to their roles in drug discovery and as ligands in supramolecular chemistry.



Acknowledgements

First and above all, I praise God who is the merciful of the whole world and thank you to providing me this opportunity and giving me the capability to complete this work.

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I wish to express my love and gratitude to my mother for her love and load of prayers for my success which make me all the time happy, thank you my sweet mother. I don't know how is it possible to wash out the memories from thoughts which are related to my late father, unfortunately, and I just want to say thank you with a few drops of tears in my eyes. I would like to dedicate this thesis to my parents and all my family members Humayun, Sazia, Samraiz, Nazia, Yasir, Hamad, Sherry, Awais, Zoby, Janat, Ftima, Amina, Ali, Hajra, Omer, Miryam, Mohammad for their affection, love and prayers throughout my whole life.

The author would also like to convey a message of thank you to all members of Hemming's group both past and present especially Gabriel, Muslih, Jack, Heidi, Vishnu and Naveed Khan due to their entertainment behaviours and valuable advice. I would like to say thank you to all the Faculty, technical and administrative staff from the University of Huddersfield for providing me the laboratory, office and research facilities and a lot of affection. I would also like to say thank you to all my office and lab fellows and all students of applied sciences.

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List of abbreviations

Ar	Aromatic
Boc	*Tert*-butyloxycarbonyl
b.p.	Boiling point
ºC	Degree Celsius
COSY	Two dimensional proton/proton correlated spectroscopy
^{13}C NMR	Carbon nuclear magnetic resonance
DACP	Dianisylcyclopropenone
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPEA	*N,N*- Diisopropylethylamine
DMA	*N,N*-Dimethylacetamide
DMAP	*N,N*-Dimethyl-4-aminopyridine
DMF	*N,N*-Dimethylformamide
DPCP	Diphenylcyclopropenone
DTCP	Ditolylcyclopropenone
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
DMSO	Dimethylsulfoxide
DABCO	1,4-Diazabicyclo[2.2.2]octane
$ES^{+/-}$	Electrospray (positive or negative mode)
Et	Ethyl
g	Grams

^{1}H NMR	Proton nuclear magnetic resonance
Hz	Hertz
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
HMBC	Heteronuclear multiple bond coherence
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
IR	Infrared
m	Multiplet
M	Molarity
MS	Mass spectrometry
Ms_2O	Methanesulfonic anhydride
m/z	Mass-to-charge ratio
ppm	Parts per million
Ph	Phenyl
q	Quartet
s	Singlet
t	Triplet
TMSOTf	Trimethylsilyl trifluromethanesulfonate
TBAT	Tetra-*n*-butylammonium difluorotriphenylsilicate
TsCl	*p*-Toluenesulfonyl chloride
δ	Chemical shift (in ppm)

Chapter 1

Introduction

1.1. Chemistry and biological roles of cyclopropenones

The first synthesis of a cyclopropenone was reported by Breslow *et al.*[1] and then Volpin and his co-workers,[2] both in 1959. After that, cyclopropenones attracted significant attention among organic chemists due to their exceptional electronic and structural properties.[3] The aromatic behaviour of cyclopropenone according to Hückel's rule,[4] means that the derivatives of cyclopropenone have derived a special attention in the world of organic synthesis. The delocalisation of π-electrons on the oxygen atom of carbonyl functional group makes the oxygen atom more electronegative than ordinary carbonyl compounds **(Figure 1.1)**.[5]

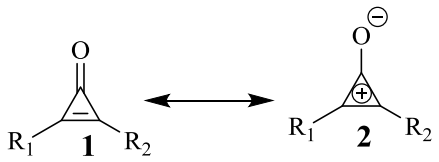


Figure 1.1: Stability of cyclopropenone.

Cyclopropenones are amphiphilic molecules so that electrophilic reagents attack the electron-rich O-atom of the C=O group, and nucleophilic reagents react readily with carbonium ion of the three-membered carbocycle to give a wide range of organic reactions.[3-5] Also, cyclopropenones have a large ring strain,[6] which allows cycloaddition reactions and transformations such as ring opening[7] and ring enlargement.[8] Cyclopropenones can also be used as building blocks for the construction of biologically active compounds,[9] and as catalysts.[10] The cyclopropenone ring has been found in naturally occuring compounds such as antibiotic penitricin **3** which was isolated from the culture filtrate of *penicillium aculeatum* and it was found to show anti-*Gram*-negative activity,[11] and its derivatives **4** & **5.**[12]

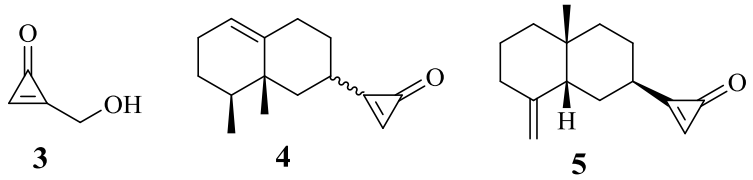


Figure 1.2: Naturally occurring derivatives of cyclopropenone.

Later on, penitricin **3** and its derivatives **6**, **7** were synthesised and showed significant antibacterial activity[13] whereas derivative **8** showed inhibitory activity against XIIIa factor.[14]

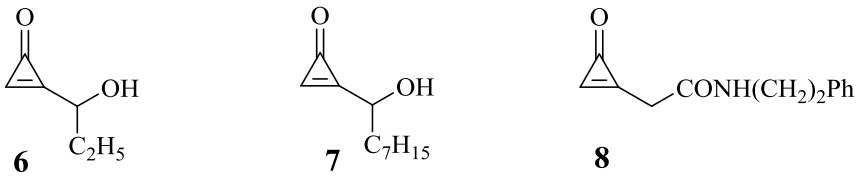


Figure 1.3: Synthesised derivatives of cyclopropenone.

Cohen *et al.* have described that the synthetic peptidyl cyclopropenone **9**[15] behaves as an irreversible covalent inhibitor of a cysteine protease, alkylating the catalytic cysteine of papain. They also reported that it could be used as an alternative substrate for the enzyme.

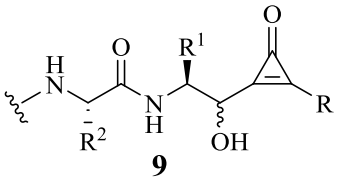


Figure 1.4: Structure of peptidyl cyclopropenone.

1.2. Cyclopropenones as catalysts

Nucleophilic substitution reactions of alcohols and their derivatives are important transformations in organic chemistry.[16] The Mitsunobu reaction[17] has become a key method for the nucleophilic substitution reactions of alcohols that convert an alcohol into a variety of functional groups with inversion of stereochemistry, using triphenylphosphine and an azodicarboxylate such as diethyl azodicarboxylate or diisopropyl azodicarboxylate. There are some drawbacks in Mitsunobu reaction, including the toxic and explosive nature of diazocarboxylate and separation of desired product from triphenylphosphine oxide and dicarboxyhydrazine byproducts.[18] Alternative methods are needed despite the efforts that there have been with recent advances in Mitsunobu reaction.[10] In this regard, Lambert and co-workers established a strategy for the promotion of dehydration reactions including

alcohols,[19] carboxylic acid chlorodehydration,[20] and the Beckmann rearrangement[21] based on cyclopropenium ions **(Figure 1.5)**.[22]

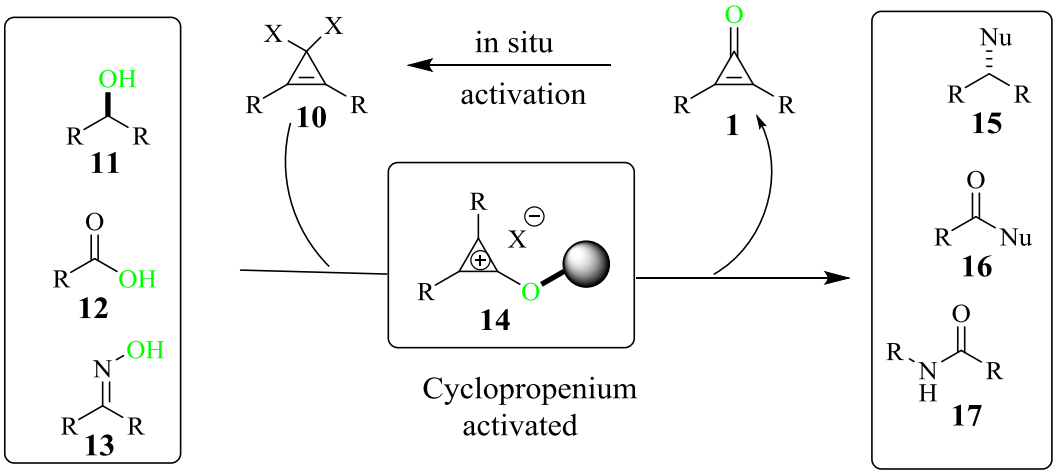


Figure 1.5: Reactivity of cyclopropenone as a catalyst.

The treatment of alcohols, carboxylic acids or oximes with cyclopropenone that reacted rapidly with an activating reagent to produce cyclopropenium salt as described in **Figure 1.5**. Then, cyclopropenium ion was treated with alcohols, carboxylic acids or oximes to generate a cyclopropenium activated intermediate that could undergo the final nucleophilic substitution and produce the cyclopropenone as the byproduct,[21] regenerating the catalyst. The mechanism proposed by Lambert and his co-workers for alcohol dehydration is shown in **Figure 1.6**.[21] The cyclopropenone was reacted with oxalyl chloride to produce the 1,1-dichlorocyclopropene **19** that converted into cyclopropenium chloride salt **20** by ionization. After that, this salt was reacted with alcohol substrate **21** to generate protonated cyclopropenyl ether **22**. The neutral cyclopropene re-ionized to provide the alkoxy cyclopropenium salt after deprotonation of cyclopropenyl ether **23**. Finally, the nucleophilic attack of chloride ion on cyclopropenium salt **24** produced the desired aryl chloride **25** and regenerated the catalyst diphenylcyclopropenone **18**.[22]

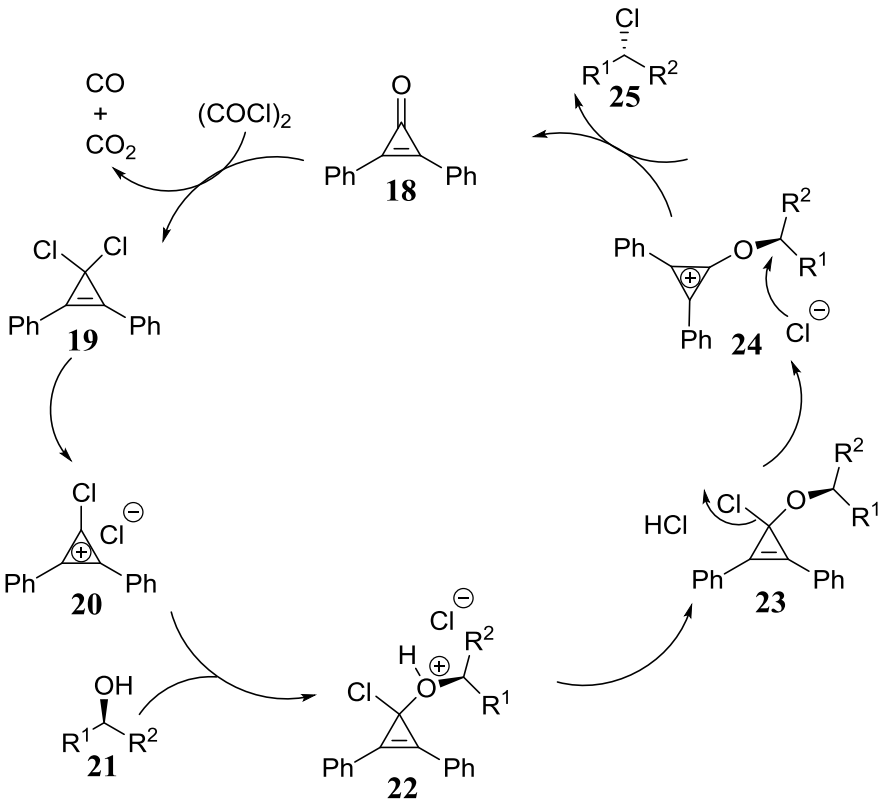
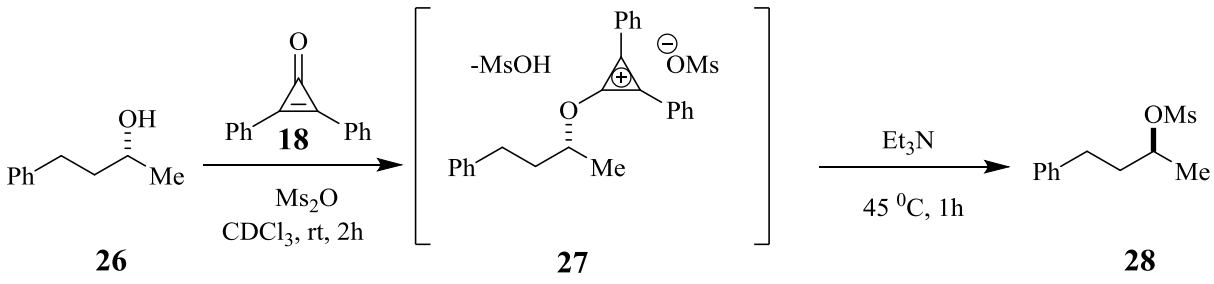


Figure 1.6: Mechanism for the formation of alkyl halide using DPCP as catalyst.

In 2013, Lambert *et al.* also developed a strategy for the nucleophilic substitution of alcohols using methanesulfonate ion with inversion of configuration in the presence of diphenylcyclopropenone as catalyst **(Scheme 1.1)**.[23]



Scheme 1.1: Catalytic reaction of DPCP.

1.3. Synthesis of cyclopropenones

There are four main routes for the synthesis cyclopropenones as follows: [3a]

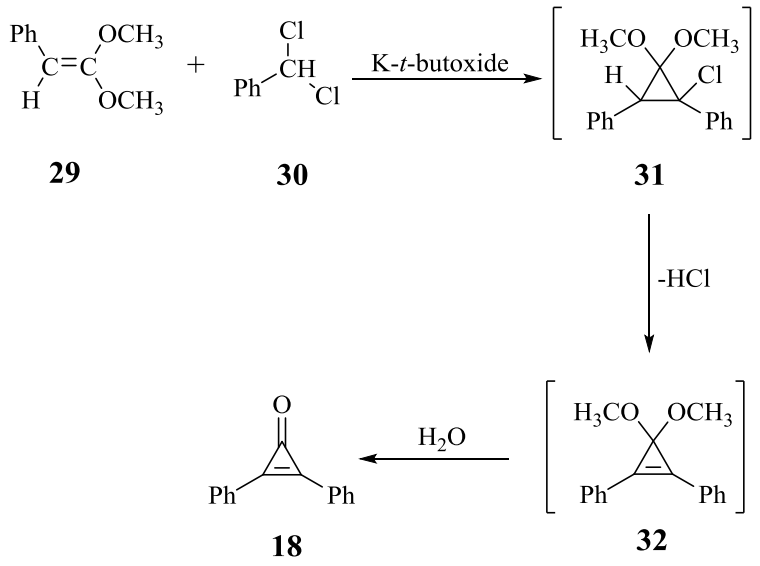
(a) Cyclopropene Ketal Route

(b) Carbene-Insertion Route

(c) Trichlorocyclopropenylium Ion Route

(d) Tetrachlorocyclopropene Route

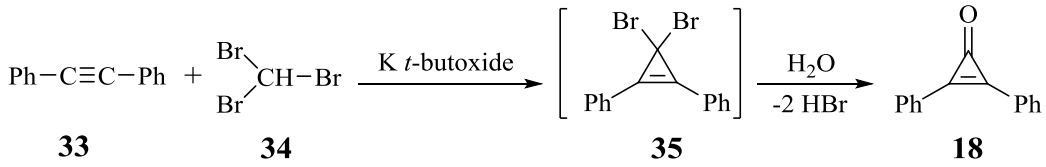
All four methods involve the hydrolysis of 3,3-disubstituted cyclopropene derivatives to give the cyclopropenones.[3a] The first method (cyclopropene ketal route) to the synthesis of diphenylcyclopropenone, reported the reaction of benzyl dichloride **30** with (2,2-dimethoxyvinyl)benzene **29** in the presence of potassium *t*-butoxide.[1] The proposed mechanism involved the addition of benzyl dichloride **30** to the double bond of ketene acetal **29** to give the cyclopropene ketal intermediate 1-chloro-2,3-diphenyl-2,3-diphenyl-3,3-dimethoxycyclolopropane **31** which converted to intermediate **32** by the β-elimination of HCl followed by hydrolysis to give the required diphenylcyclopropenone (DPCP) (**Scheme 1.2)**.



Scheme 1.2: Synthesis of DPCP.

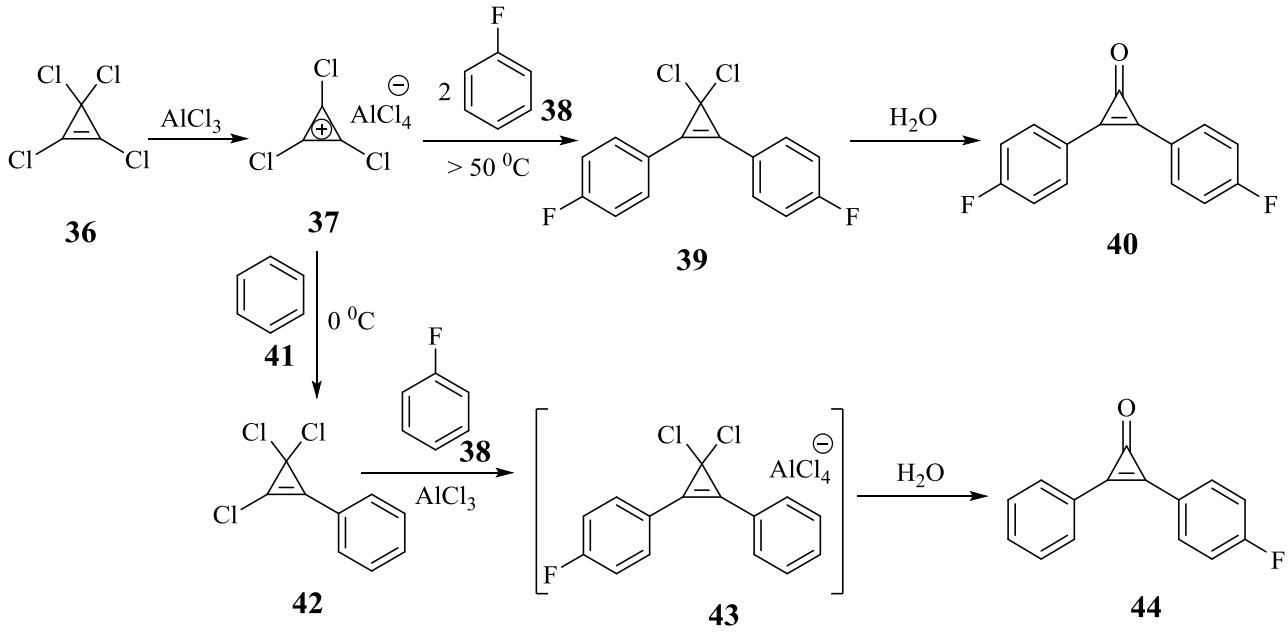
Similarly, Vol'pin *et al.*[2] synthesised diphenylcyclopropenone by the treatment of diphenylacetylene **33** with dibromocarbene which was produced in the reaction mixture by the reaction of bromoform **34** with potassium *t*-butoxide to obtain 3,3-dibromo-1,2-

diphenylcyclopropene **35** as an intermediate which was hydrolysed to give the diphenylcyclopropenone **(Scheme 1.3)**.



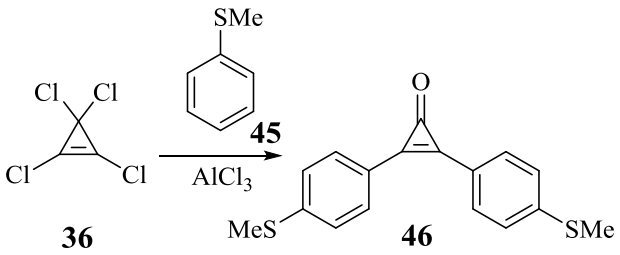
Scheme 1.3: Preparation of DPCP.

West *et al.*[24] synthesised a series of symmetrical and unsymmetrical disubstituted diarylcyclopropenones **40** and **44** using a trichlorocyclopropenium ion **37** which was generated by the reaction of tetrachlorocyclopropene **36** with aluminium chloride **(Scheme 1.4)**.



Scheme 1.4: Synthesis of symmetrical and unsymmetrical disubstituted diarylcyclopropenones.

Recently, Lambert *et al.*[21] prepared the dithioanisylcyclopropenone **46** by the reaction of tetrachlorocyclopropene with thioanisole **45** in the presence of aluminium chloride **(Scheme 1.5)**.



Scheme 1.5: Synthesis of dithioanisylcyclopropenone.

The mechanism involved in the synthesis of cyclopropenone from tetrachlorocyclopropene by the reaction of benzene derivatives with trichlorocyclopropenium occurs *via* a Friedel-Crafts route[25] and followed by hydrolysis,[26] as seen in (**Figure 1.7)**.

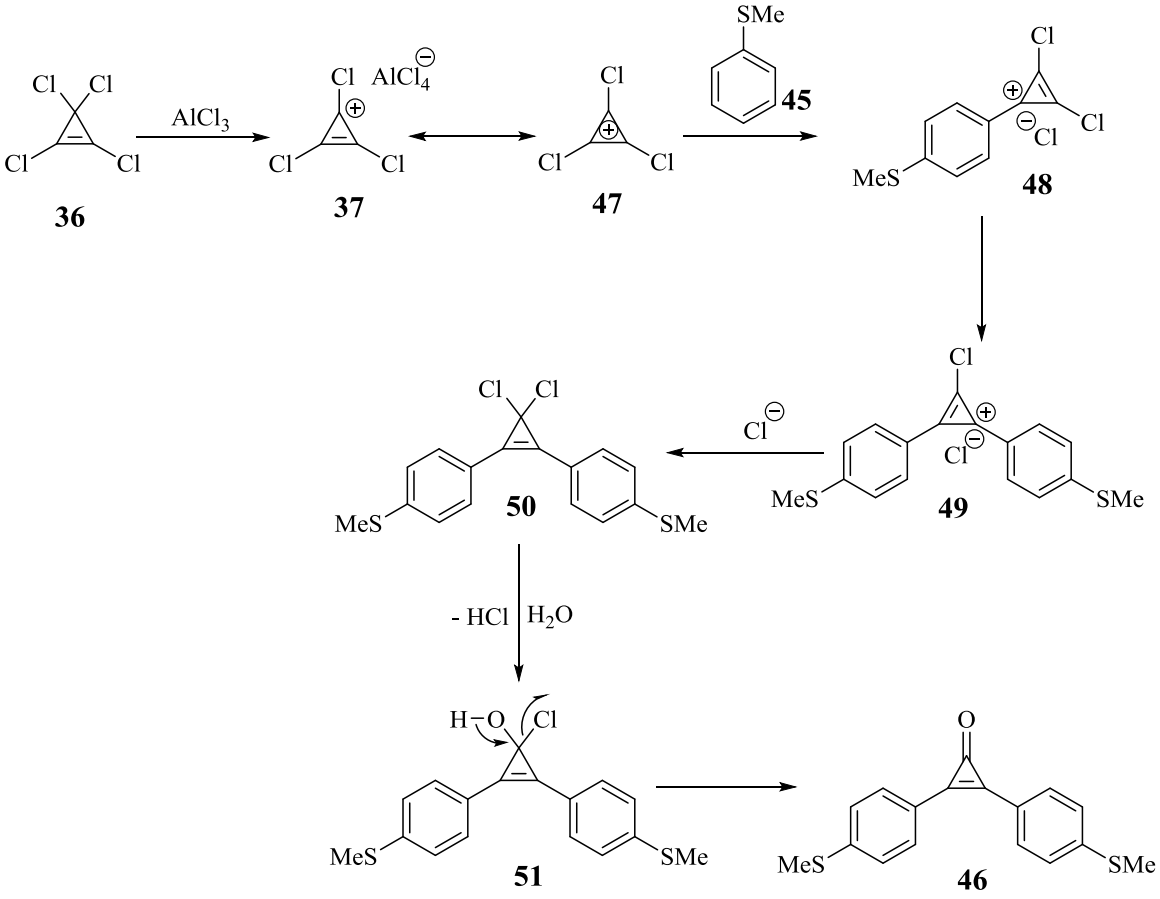
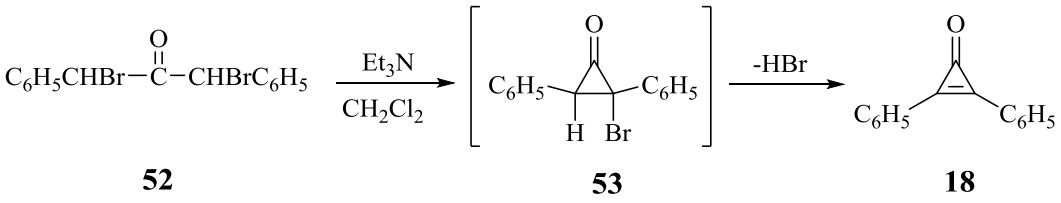


Figure 1.7: Mechanism for the synthesis of dithioanisylcyclopropenone.

A modified Favorskii reaction was introduced by Breslow *et al.*[27] which involved the ring closure of 1,3-dibromo-1,3-diphenypropan-2-one **52**, followed by elimination of HBr from intermediate **53** caused by reaction with an triethyl amine **(Scheme 1.6)**.

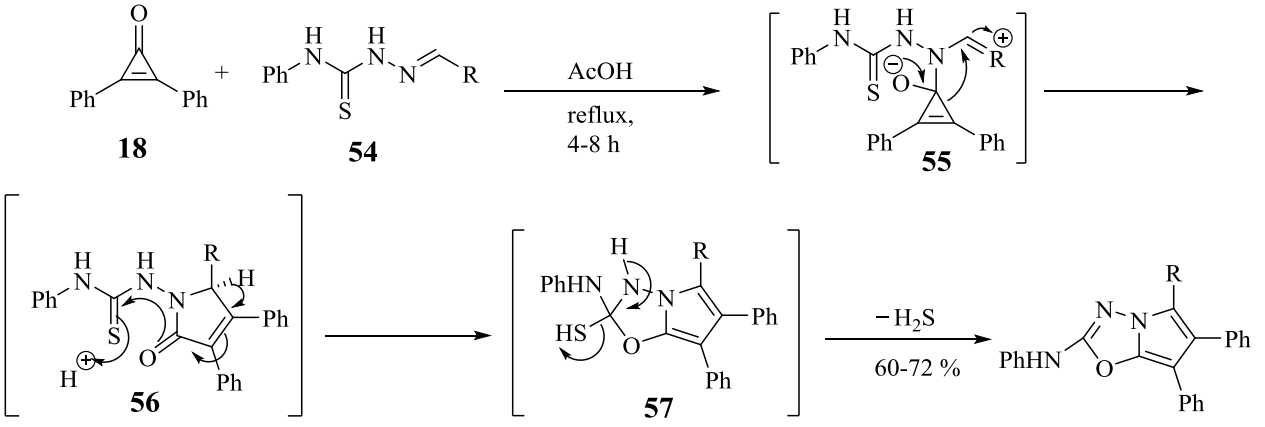


Scheme 1.6: Synthesis of DPCP *via* Favorskii reaction.

1.4. Reactivity of diphenylcyclopropenone

Diphenylcyclopropenone has been shown to react with a wide range of compounds containing the *C=N* moiety, usually to form highly functionalised heterocyclic compounds *via* a formal [3+2] cycloaddition reaction.[28] This type of reaction is used frequently in this thesis and so is briefly reviewed here.

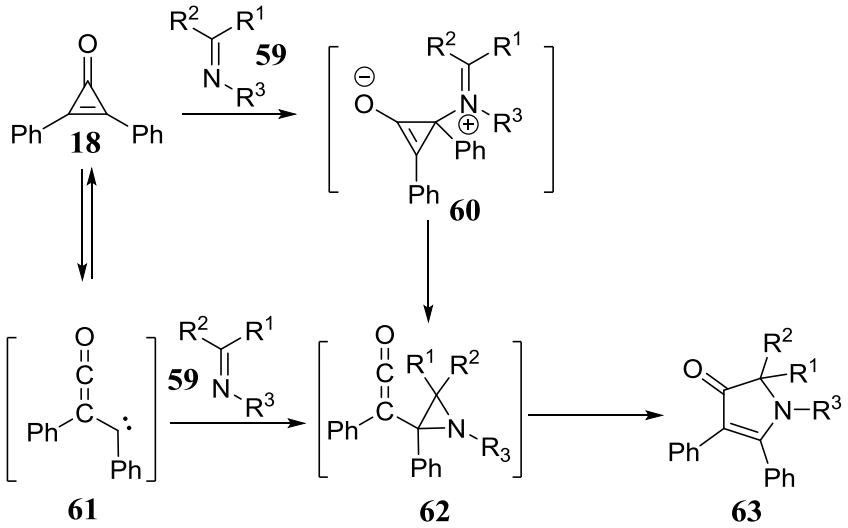
While investigating the utility of diphenylcyclopropenone for the synthesis of heterocycles, Aly and his co-workers have reported the synthesis of pyrrolo[2,1-*b*]1,3,4-oxadiazoles **(58a-e, Scheme 1.7)**.[28c] They proposed in their mechanism that the diphenylcyclopropenone attaches across the *C=N* double bond of compound **54** *via* formal [3+2] cycloaddition reaction to give the intermediate **56** which is then followed by aromatisation *via* cyclisation to form intermediate **57** with the loss of hydrogen sulfide giving the oxadiazoles **(58a-e)**.



58a R= C_6H_5
58b R= 2-Thienyl-
58c R= 4-HO-C_6H_4-
58d R=4-Cl-C_6H_4-
58e R= 4-H_3CO-C_6H_4-

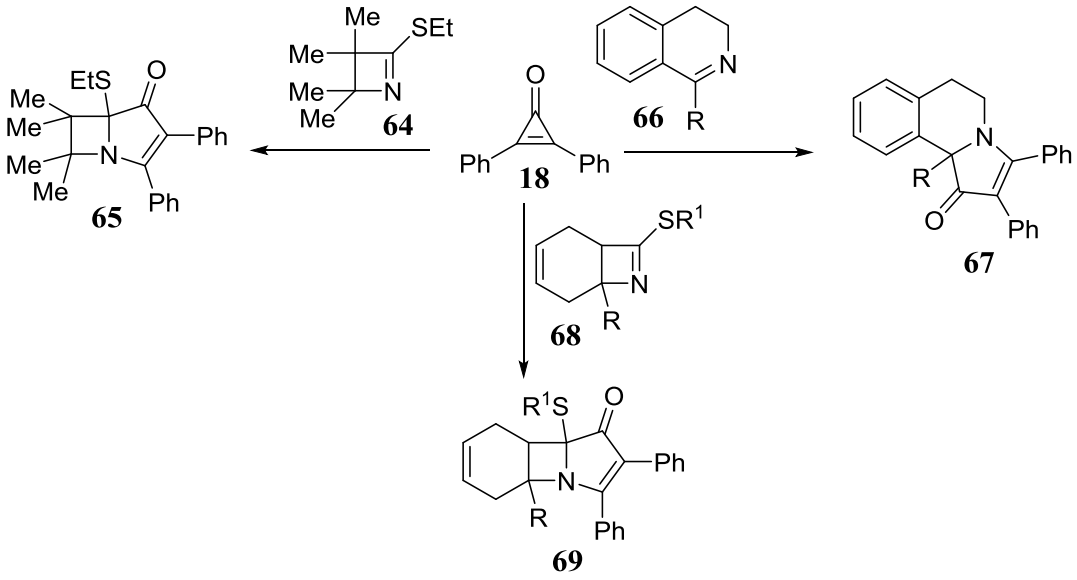
Scheme 1.7: Synthesis of pyrrolo[2,1-*b*]1,3,4-oxadiazoles using DPCP.

1974, Eicher[5c] studied the rectivity of diphenylcyclopropenone with acyclic imines to give the pyrrolidinone products **63** *via a* formal [3+2] cycloaddition reaction. The mechanism for this reaction as shown below in **Scheme 1.8.**



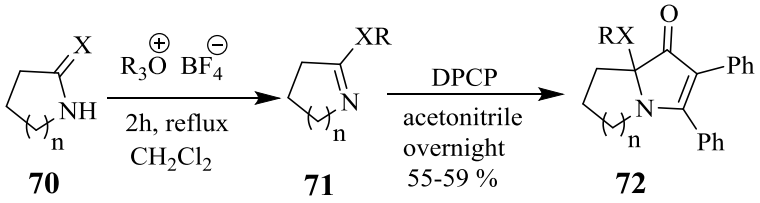
Scheme 1.8: Reactivity of DPCP with acyclic imine.

After this Eicher,[5d] Heimgartner,[5g] Yoshida[5f] and smalley and Hemming[5k] have further explored the reactivity of diphenylcyclopropenone with cyclic imines such as **64, 66** and **68** to give the pyrrolidinone ring containing products **65, 67** and **69** *via a* formal [3+2] cycloaddition reaction as shown in **Scheme 1.9.**



Scheme 1.9. A formal [3+2]-cycloaddition reaction of DPCP with cyclic imines.

The Hemming group continued earlier work in the field and has investigated the reactions of diphenylcyclopropenone with 4-, 5-, and 6-, membered ring cyclic imines **71** to give the pyrrolizidines, indolizidines and pyrroloazepines **72 (Scheme 1.10).**[29] One of the aims of this thesis was to extend this work to get some pyrrolizidines, indolizidine, pyrroloazepine and other heterocyclic pyrrolo natural product core structures.



Scheme 1.10: Synthesis of heterocyclic pyrrolo natural compounds.

1.5. Importance of pyrrolizidine, indolizidine and pyrroloazepine alkaloids

Polyhydroxylated pyrrolizidines, such as hyacinthacine A_1/A_2[30-31] (**73a-b)** and hyacinthacines B_1/B_2[32] (**74a-b) (Figure 1.8)**[28b] are important in biological studies where they have gained attention as glycosidase inhibitors. Glycosidases play vital roles in different kinds of diseases, for example, in various cancers, diabetes and viral infections such as AIDS.[33] Also, there are non-polyhydroxylated pyrrolizidines, such as jenamidines **75**, which inhibit leukaemia cell lines at clinically useful levels.[34]

Naturally occurring indolizidine alkaloids, such as indolizidine 223AB **76**, are secreted by the skin of the frog species dendrobatidae.[35] These kinds of compounds have gained attention as inhibitors of nicotinic receptor-channels and as potential leads in the search for treatments for Alzheimer's disease and other neurological disorders.[36] Polyhydroxylated indolizidine heterocycles, for example swainsonine **77,** are interesting as glycosidase inhibitors, antitumour, antiviral, immunoregulatory, and antidiabetic agents.[37] The pyrroloazepine nucleus is present in the stemona alkaloids, for example, stenoamide **78**, which have been used as treatments for a range of respiratory diseases.[28b]

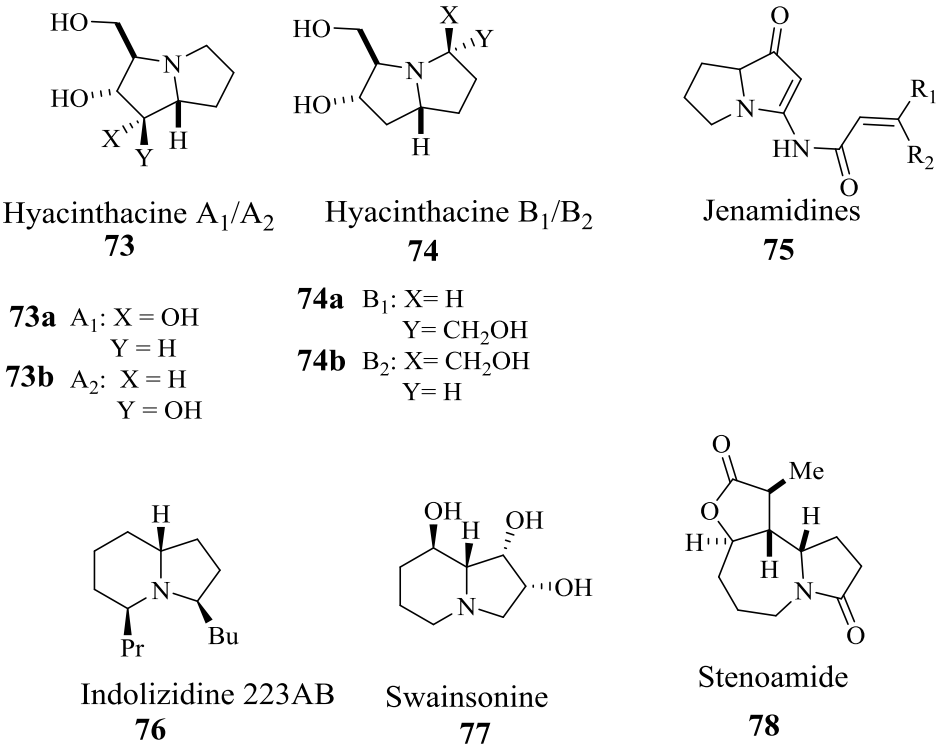
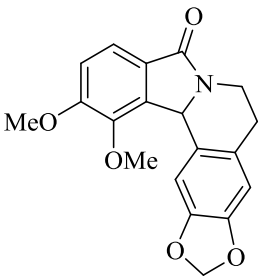


Figure 1.8: Heterocyclic pyrrolo natural compounds.

1.6. Pyrrolo-isoquinoline alkaloids

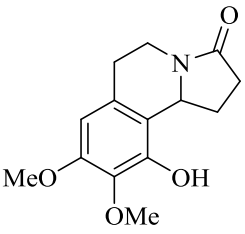
Due to the presence of isoquinoline and tetrahydroisoquinoline heterocycles as a basic unit in a wide range of naturally occurring alkaloids, these compounds have got considerable attention in the field of biological science.[38] For example, nuevamine[39] **79,** is a naturally occurring alkaloid which was isolated from Berberis darwinii Hook.



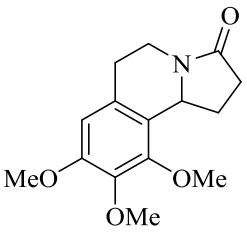
79

Nuevamine

In 1968, Kapadia *et al.*[40] were the first that isolated pyrroloisoquinoline alkaloids such as peyoglutam **80** and mescalotam **81** from the peyote cactus.

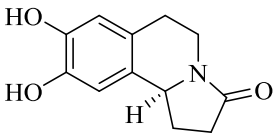


80



81

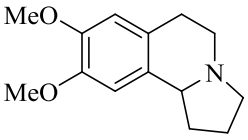
Wang and co-workers isolated the tricyclic lactam trolline alkaloid **82** from Trollius chinensis.[41]



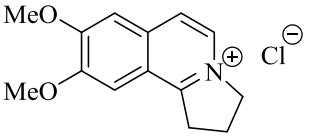
82

Trolline alkaloids showed antibacterial activity against respiratory bacteria such as Klebsiella pneumoniae, Staphylococcus aureus, Staphylococcus pneumonia and also found reasonable antiviral activity against influenza viruses A and B.[41b]

Zhang and co-workers in 2002, isolated two isoquinoline alkaloids crispine A **83** and crispine B **84** during photochemical studies of the plant carduus crispus[42] and these compounds have showed antitumor properties.[43]

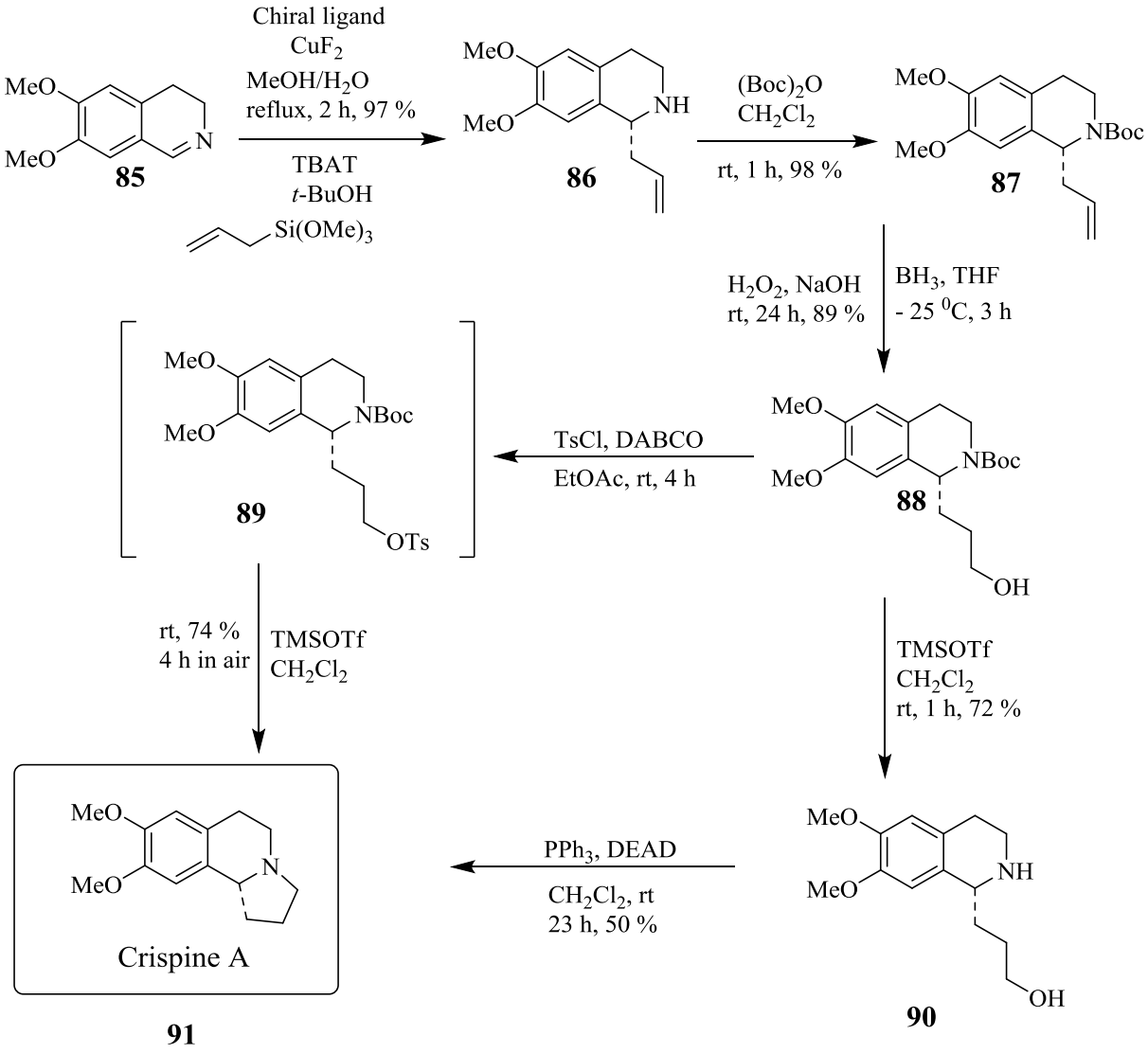


83



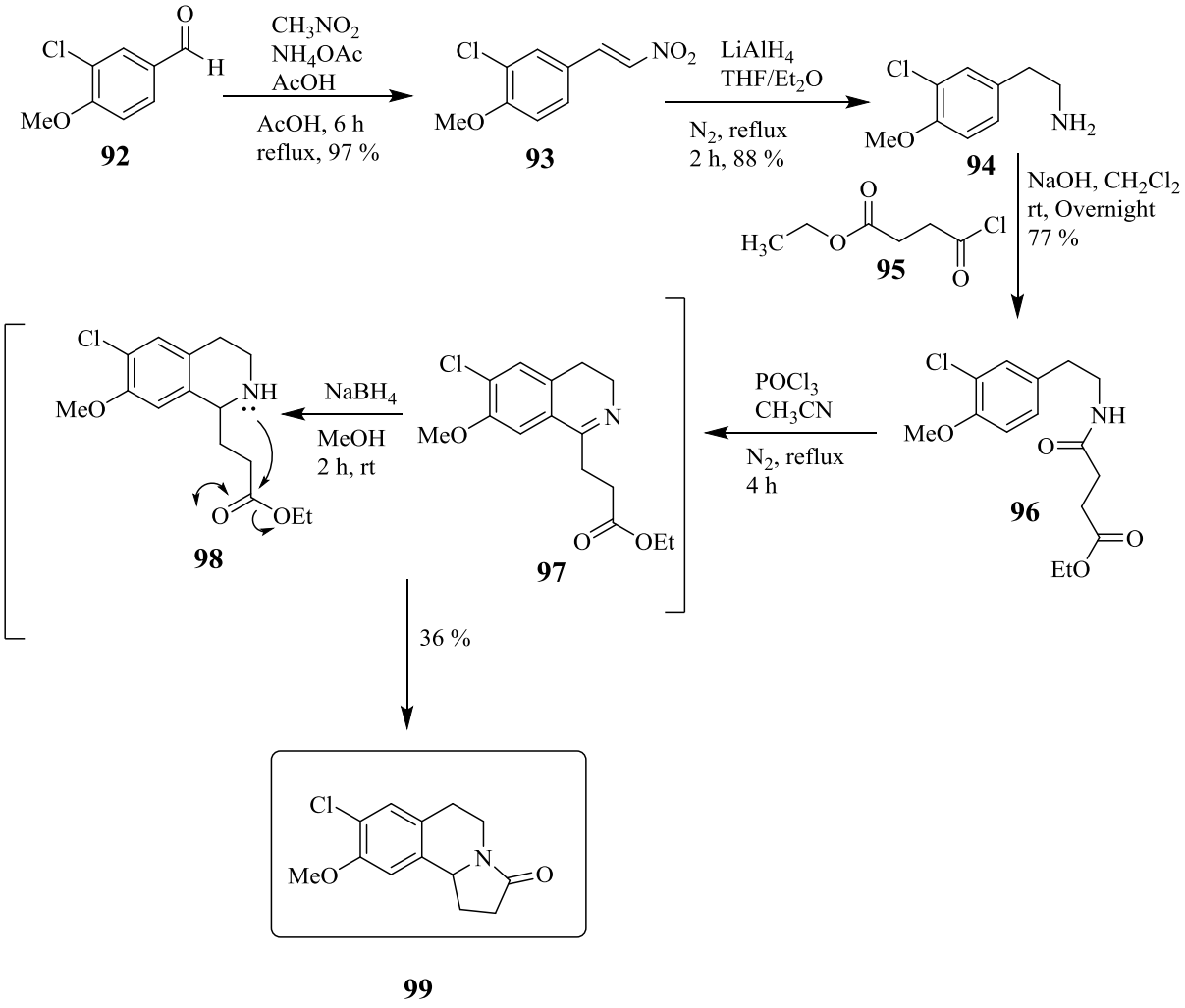
84

In 2011, M. Miyazaki *et al.*[44] synthesised enantiopure Crispine A using 6,7-dimethoxy-3,4-dihydroisoquinoline **85** as a starting material **(Scheme 1.11).**



Scheme 1.11: Synthesis of isoquinoline alkaloids.

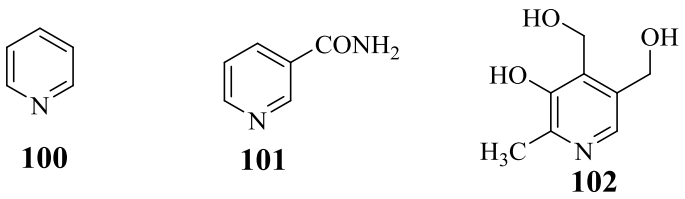
In 2012, L.Moreno *et al*. synthesised the pyrrolo[2,1-*a*]isoquinolin-3-one alkaloid **92** which has potential as an antimicrobial agent **(Scheme 1.12)**.[45]



Scheme 1.12: Synthesis of pyrrolo-isoquinoline derivatives.

1.7. Pyridines

As well as pyrrolo-based natural products, this thesis will also describe and build upon a new pyridine synthesis that was developed in the group. Pyridines are basic heterocyclic compounds which are structurally similar to benzene ring containing compounds, where one CH group of the benzene ring is replaced with a nitrogen atom (see, for example, compounds **100**, **101** and **102**).[46]



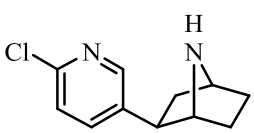
100 **101** **102**

Pyridine Niacin Pyridoxine

Figure 1.9: Pyridine and its derivatives.

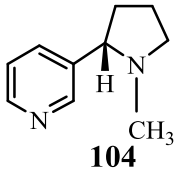
1.7.1. Biological roles of pyridines

The derivatives of pyridine play a vital role in biological chemistry[47] due to their applications in the pharmaceutical industry, agrochemical industry, natural product chemistry, and as well in materials science.[48] Many enzymes use the pyridine nucleotide (NADP) **105** in living organisms where it has significant importance in oxidation-reduction processes.[49] Naturally occurring pyridine alkaloids include epibatidine **103** which was isolated from the skin of the Ecuadorian frog *Epibatidores tricolor* and is a potent analgesic,[50] and nicotine **104** which is well known as the major active component of tobacco **(Figure 1.10)**.[46,50-51] Pyridoxine (vitamin B6) **102** plays a key role in the production of red blood cells.



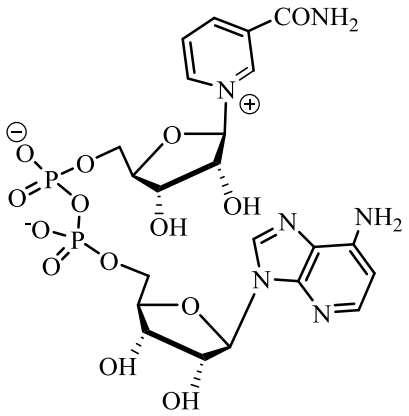
103

Epibatidine



104

Nicotine



Pyridine nucleotide

105

Figure 1.10: Pyridine natural products.

The synthetic derivatives of pyridine are playing vital roles as therapeutic agents. For example, pyridoxime **106** as an antidote for poisoning by organophosphates, sulphapyridine **107** is an antibacterial agent, A_3 adenosine receptor antagonist **108** is an antiinflammatory and antiasthmatic agent, 5- HT_{1A} receptor agonist **109** is an antidepressant agent, and the endothelin pyridine derivative **110** designed for the treatment of pain, inflammation, asthma, hypotension, heart failure and hypertension **(Figure 1.11)**.[46, 52-55]

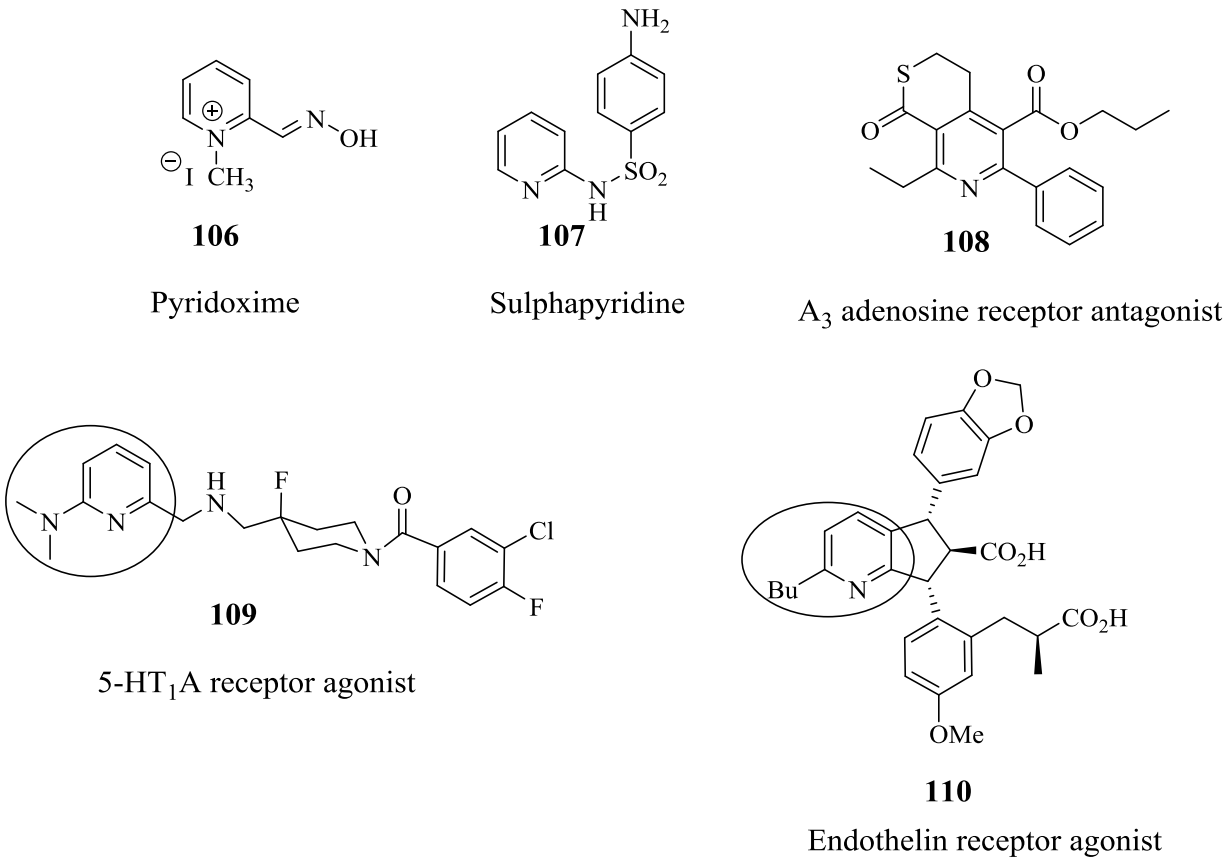


Figure 1.11: Pyridine drugs in the pharmaceutical industry.[46, 52-55]

The derivatives of pyridine are also utilized as herbicides, fungicides and bactericides that have significant importance in the field of agriculture **(Figure 1.12)**.[46, 55-57]

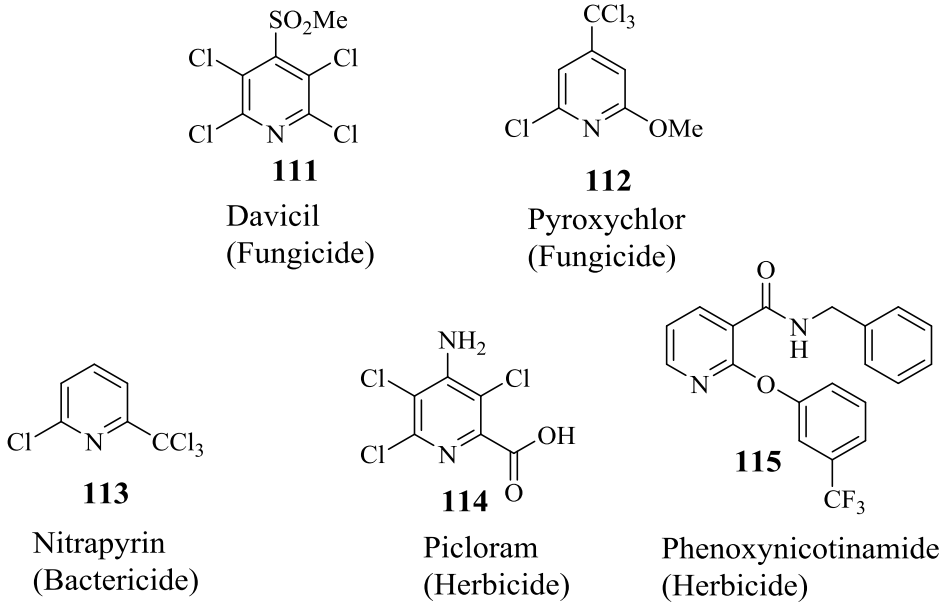


Figure 1.12: Pyridine derivatives in the field of agrochemicals.

1.7.2. Synthesis of pyridines

Anderson was isolated the pyridine base from bone oil but the correct structure of pyridine was not proposed until 1869.[58-59] Condensation methods have become the most common way to synthesise many pyridines by the reaction of amines with carbonyl compounds. Other methods for the preparation of the pyridine core are defined by the number of atoms in each fragment contributing to the pyridine ring, as shown in (**Figure 1.13)**.[46]

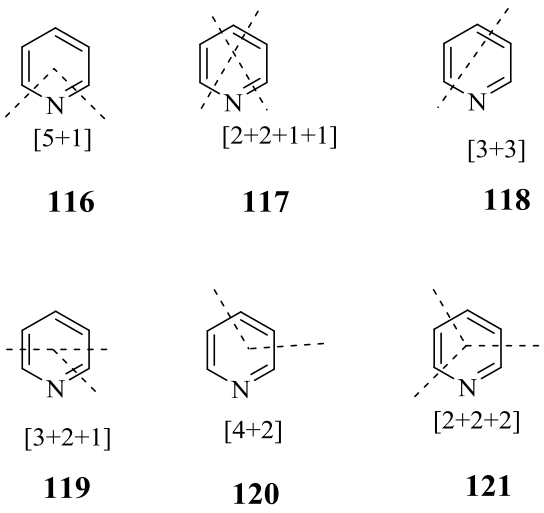
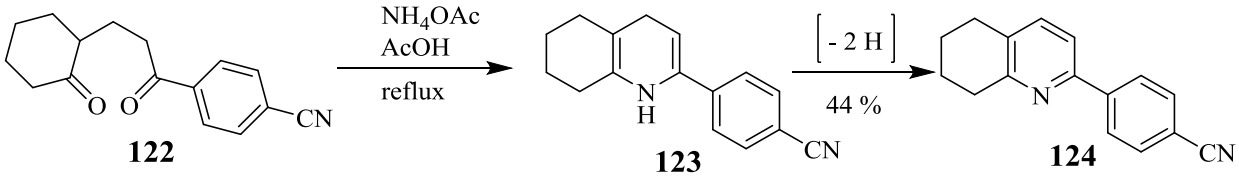


Figure 1.13: Approaches for preparations of pyridine cores.

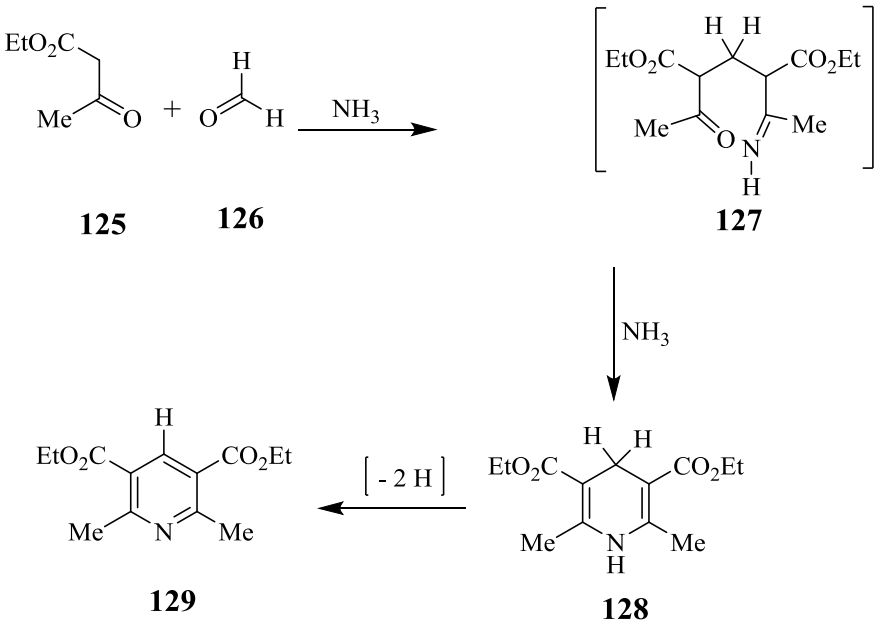
Ammonia (NH_3) is the most used nitrogen source for the synthesis of many pyridines,[60] including [5+1] condensation with 1,5-dicarbonyl compounds, as shown in **(Scheme 1.13)**.[61]



Scheme 1.13: Synthesis of pyridine *via* [5+1] condensation.

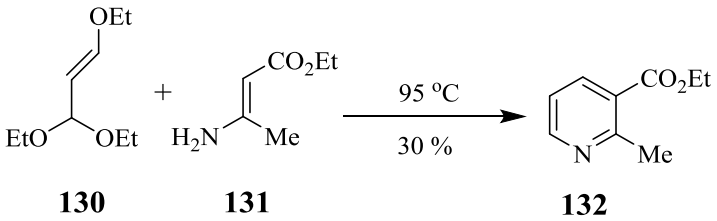
In 1882, Hantzsch introduced a [2+2+1+1] condensation method for the synthesis of the pyridine core, where ammonia is also used as a source of nitrogen. Symmetrical pyridines were synthesised by this methodology in which ammonia reacted with formaldehyde **126** and

two equivalents of ethyl 3-oxobutanoate **125** to give the target pyridine **129** after aromatisation of the isolable intermediate dihydropyridine **128 (Scheme 1.14)**.[62]



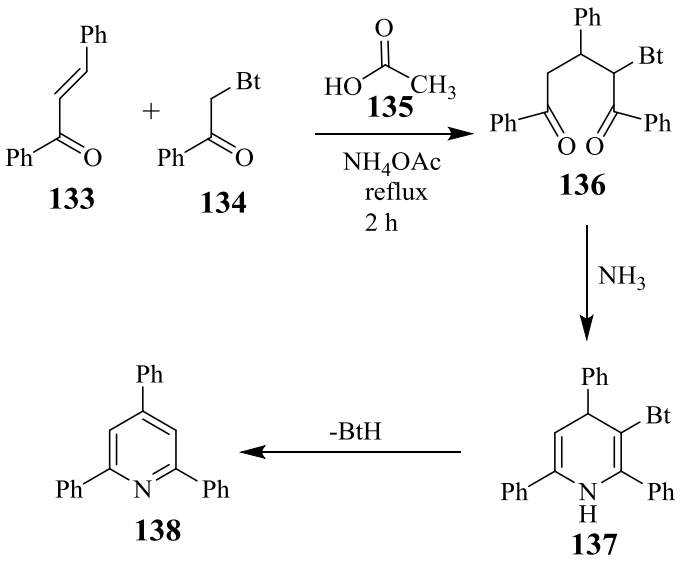
Scheme 1.14: Synthesis of pyridine *via* Hantzsch method.

The [3+3] condensation process has become useful to synthesise unsymmetrical pyridines from starting materials that are easily available **(Scheme 1.15)**.[63]



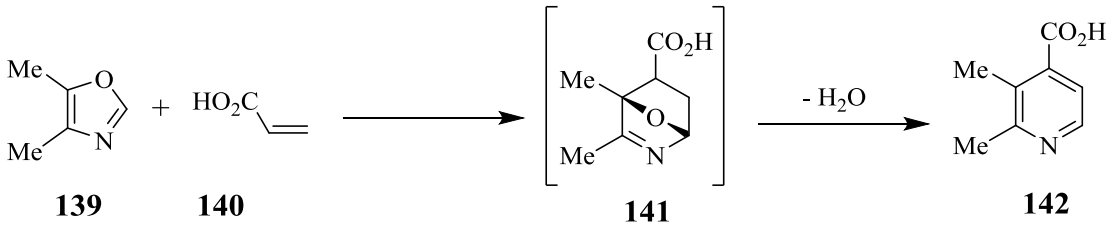
Scheme 1.15: Synthesis of pyridine *via* [3+3] condensation process.

Amongst all the preparative approaches for pyridine cores, the [3+2+1] approach is the most frequently used. In 1999, Katritzky *et al.* prepared tri-substituted pyridines in good yields using [3+2+1] approach by the reaction of α-benzotriazolyl ketone **134** with α,β-unsaturated compound **133** to construct a 1,5-dicarbonyl intermediate **136** which finally gave the target pyridine **138** *via* aromatization of intermediate amide **137** *via* lost of benzotriazole (BtH) **(Scheme 1.16)**.[64]



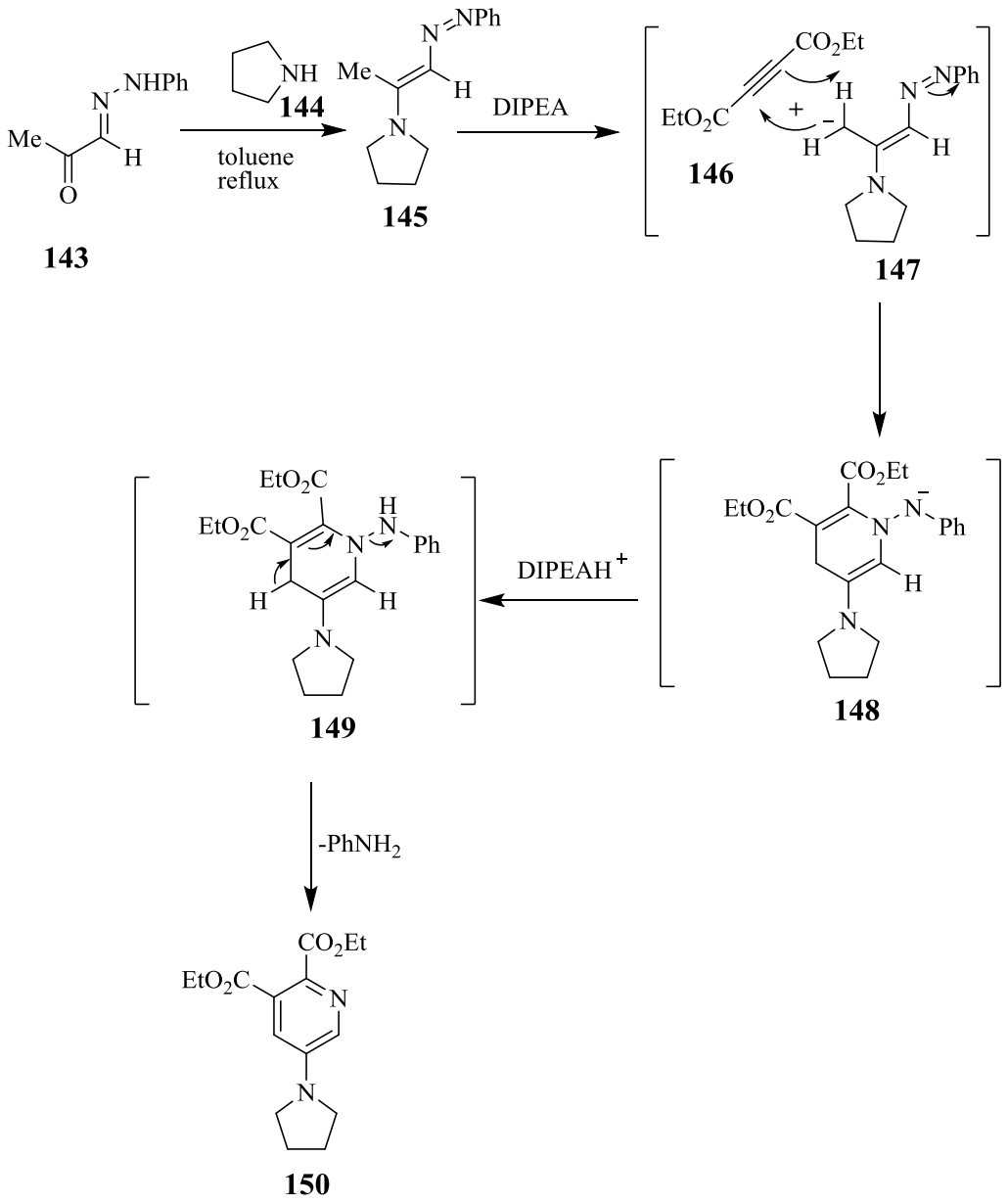
Scheme 1.16: Synthesis of triphenylpyridine *via* [3+2+1] approach.

Methods that do not rely on a cycloaddition process for the preparation of pyridines are of particular interest in the thesis. Such a reaction was developed by Kondrat'eva and Huan in 1965 which involved the addition of a dienophile to an oxazole **139** where the subsequent extrusion of H_2O gives the substituted pyridine **(Scheme 1.17)**.[65]



Scheme 1.17: Synthesis of pyridine *via* oxazole**.**

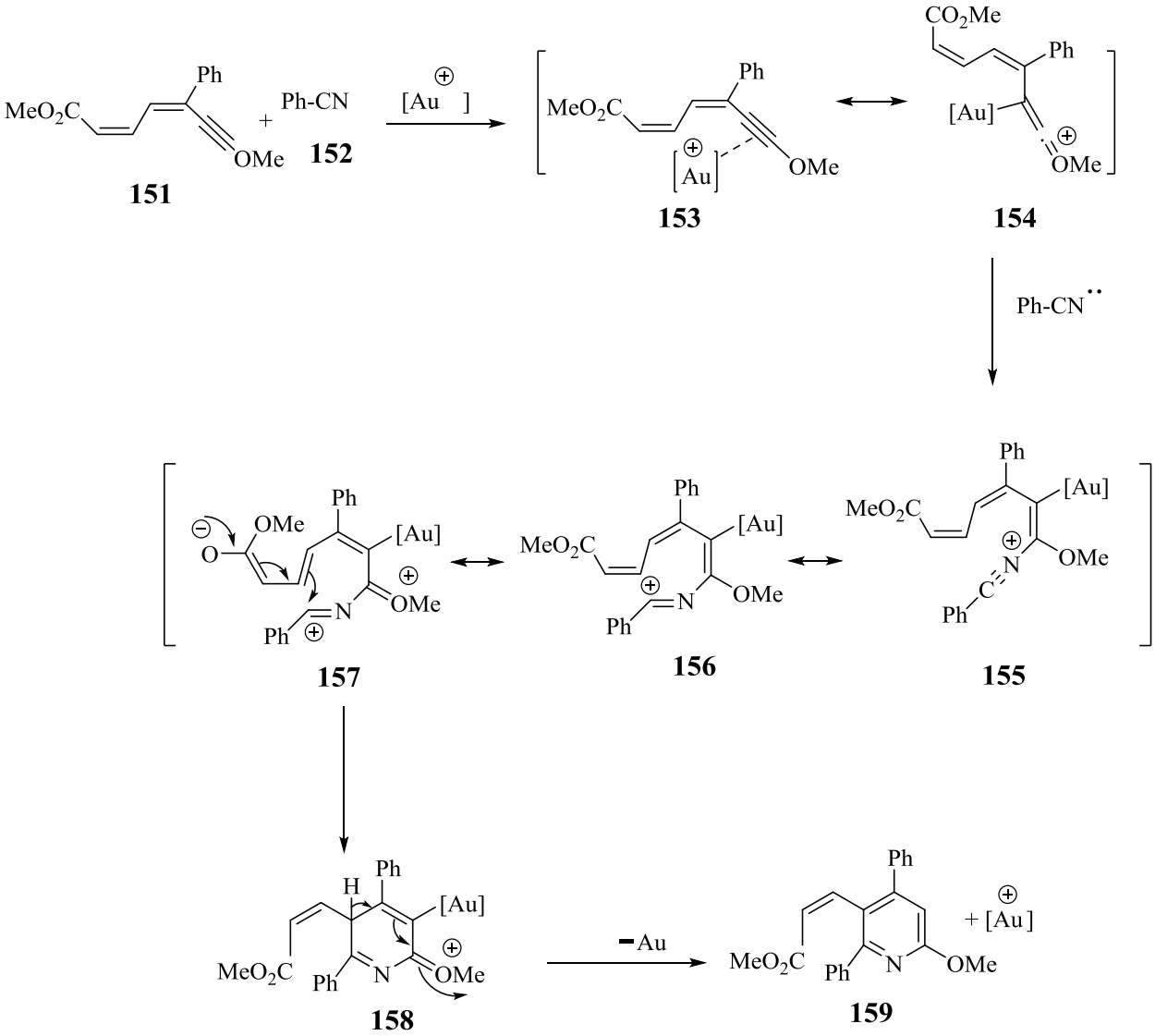
In 2010, D. Coffinier *et al.*[66] has studied a new cycloaddition approach using azoenamines with acetylenedicarboxylates. The synthesis of the pyridine started by the reaction of the keto hydrazone **143** with pyrrolidine **144** as starting materials in toluene to form azoenamine **145** in quantitative yields. Addition of DIPEA and then treatment of compound **145** with diethyl acetylenedicarboxylate **146** gave dihydropyridine **149** which then formed the desired pyridine compound **150** *via* loss of aniline **(Scheme 1.18)**.



Scheme 1.18: Synthesis of subsituted pyridine from azoenamine.

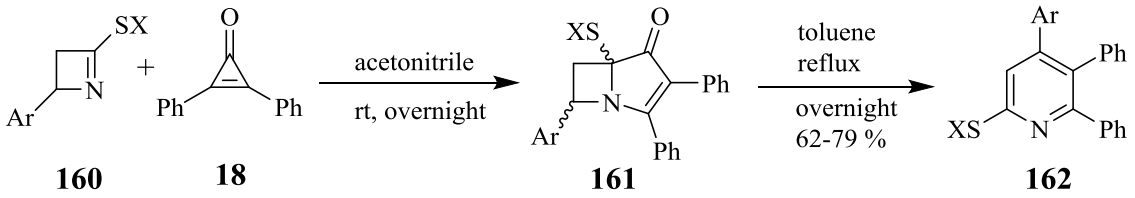
In 2008, Barluenga *et at.*[67] described the first example of a catalysed intermolecular hetero-dehydro-Diels-Alder reaction that occurs between dienyne **151** and nitrile **152** in the presence of a gold catalyst. The mechanism of this reaction involved intermediate **153** through coordination between gold and the triple bond of the 1,3-diene-5-yne which converted into **154** due to resonance. Complex **154** was reacted with benzonitrile giving the species **155** due to regioselective nucleophile attack of the nitrile. The intermediate **155** resonates to **156** and

then into **157** followed by rearrangement that led to the formation of dihydropyridine **158** which then decomplexes to give the target pyridine **159 (Scheme 1.19)**.[67]



Scheme 1.19: Synthesis of tetra-substituted pyridine.

In 2011, Hemming *et al*. developed a strategy for the synthesis of pyridines **162 (Scheme 1.29)**[8] *via* a [2+2]-cycloreversion of the adduct **161** obtained from the reaction between 4-aryl-1-azetine **160** and readily available diphenylcyclopropenone **18**. This process will be discussed in more detail later as it forms part of the discussion of this thesis.

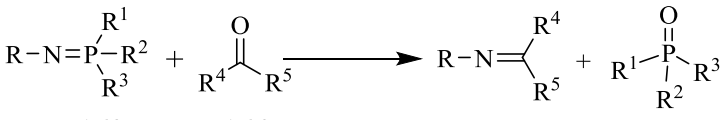


160 **18** **161** **162**

Scheme 1.20: Synthesis of pyridines from cycloadducts.

1.8. The Staudinger-aza-Wittig reaction

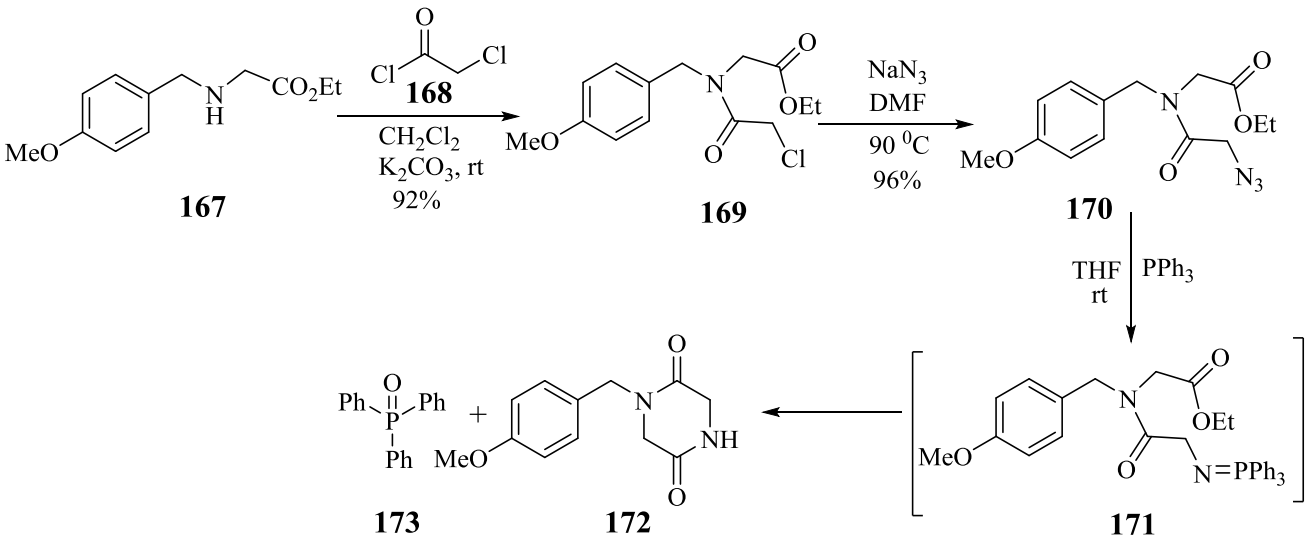
The aza-Wittig reaction has become a useful tool for the synthesis of heterocyclic compounds containing *C=N* double bonds.[68] The aza-Wittig reaction is used for the synthesis of cyclic imines by the reaction of iminophosphoranes **163** with carbonyl compounds to construct *C=N* double bond under mild reaction conditions **(Scheme 1.21)**.[69] Later in this thesis the construction of *C=N via* this route is used to produce cyclic imines for cyclopropenone additions and is also explored with cyclopropenone as the ketones **164**.



163 **164** **165** **166**

Scheme 1.21: The aza-Wittig reaction.

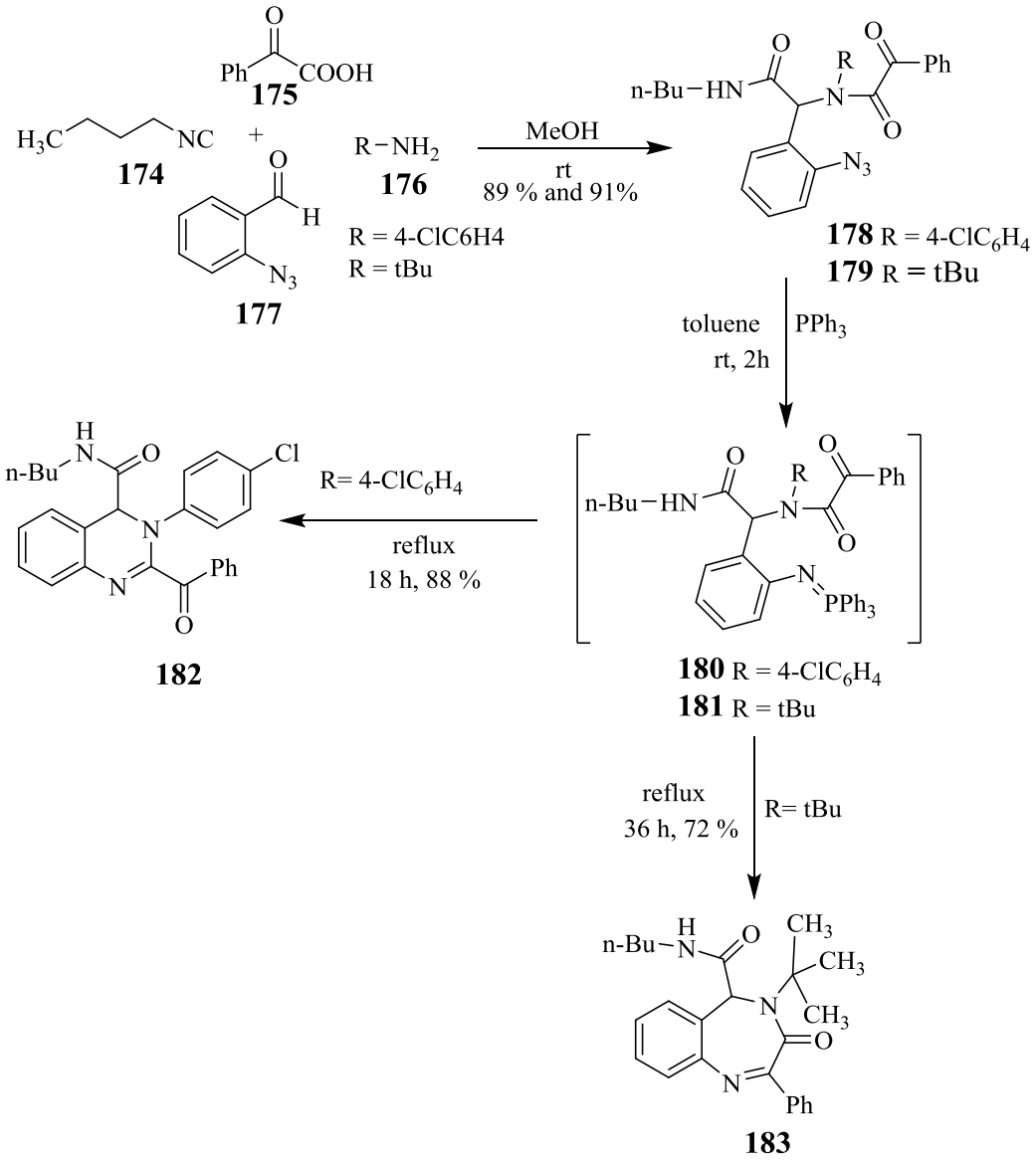
The first synthesis of an iminophosphorane **163** was reported by Staudinger in 1919 by the reaction of triphenylphosphine with an alkyl azide.[70] These iminophosphoranes[71] are used as reagents and intermediates in organic synthesis,[68] as precursors for the aza-Wittig reaction and for the construction of heterocyclic natural products.[72] For example, Majumdar *et al.*[73] have developed a strategy to synthesis piperazine-2,5-dione derivatives *via* intramolecular aza-Wittig reaction **(Scheme 1.22)**. The synthesis of piperazine-2,5-dione was carried out by the reaction of amino ester **167** with chloroacetyl chloride to give compound **169** which converted into **170** with the treatment of sodium azide. The azide group containing compound **170** was reacted with PPh_3 to obtain iminophosphorane **171** which finally cyclised to give the 1-benzylpiperazine-2,5-dione **172** *via* intramolecular aza-Wittig reaction **(Scheme 1.21)**.



Scheme 1.22: Synthesis of piperazine-2,5-dione derivatives *via* intramolecular aza-Wittig reaction.

The piperazine-2,5-diones are important due to the presence of this ring in natural products[74] with biological activities[75] such as antiviral,[76] antifungal,[77] antitumour,[78] antithrombic[79] and antibacterial.[80]

In 2015, Zhong *et al*.[81] developed a methodology to synthesis 2-acylquinazolines and 3*H*-1,4-benzodiazepine-3-ones *via* Ugi 4C/Staudinger/aza-Wittig reaction **(Scheme 1.23)**.



Scheme 1.23: Synthesis of 2-acylquinazolines and 3*H*-1,4-benzodiazepine-3-ones *via* Ugi 4C/Staudinger/aza-Wittig reaction.

In this synthesis, the reaction of 4-chloroaniline or *tert*-butylamine **176** with azidobenzaldehyde **177** gives an intermediate that was converted to Ugi 4C product **178** or **179** respectively with the treatment of n-butyl isocyanide **174** and benzoylformic acid **175**. The azide-containing compound **178** or **179** was reacted with PPh_3 in toluene and heated for 2 h to give the intermediate iminophosphorane **180** or **181** which was further heated and transformed into the corresponding dihydro-quinazoline **182** and 3*H*-1, 4-benzodiazepine-3-

ones **183 (Scheme 1.23)**, that are interesting in medical science due to their biological activities.[81-82]

1.9. 1,2,4-Oxadiazoles

Another heterocycle of interest in this thesis (see discussion) is the 1,2,4-oxadiazole. Oxadiazoles represent an important class of five-membered heterocycles, and exist in three different regioisomeric forms as 1,2,4-oxadiazole **184**, 1,2,5-oxadiazole **185** and 1,3,4-oxadiazole **186** which contain two nitrogen atoms, two carbon atoms and one oxygen atom.[83]

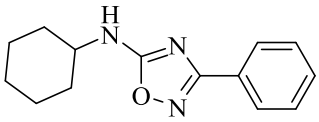
184

185

186

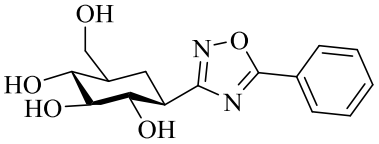
1.9.1. Medicinal roles for 1,2,4-oxadoazoles

1,2,4-Oxadiazoles are often used as an amide or ester bioisostere, and they are well known in medicinal chemistry.[84-96] These oxadiazoles have different biological activities such as anticancer,[85] anti-inflammatory,[86] immunosuppressive,[87] antidiabetic,[88] antimicrobial and antioxidant,[89] antihyperglycemic,[90] antitrypanosomal[91], anti-HIV agents[92] and Alzheimer's disease,[93] some examples of which are shown in **(Figure 1.14)**.



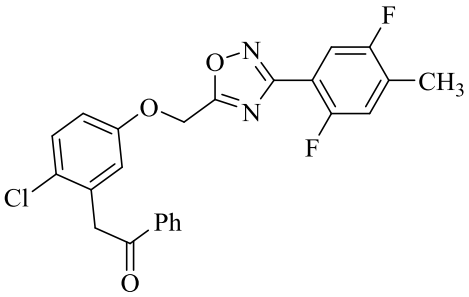
187

Antiinflammatory agent[86]



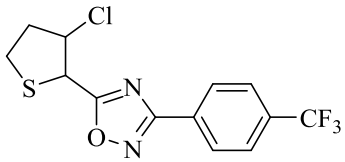
188

Antidiabetic agent[94]



189

Antimicrobial Agent[95]

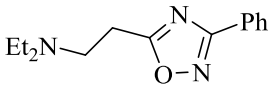


190

Anticancer agent[96]

Figure 1.14: Importance of 1,2,4-oxadiazoles.

Derivatives of 1,2,4-oxadiazoles are also useful for DNA interaction[97] and inhibiting bacterial infections.[98] They also play an important role in materials chemistry, such as polymers,[99] liquid crystals,[100] luminescent materials[101] and corrosion inhibitors.[102] 1,2,4-Oxadiazole ring containing compounds also show interesting fungicidal and larvicidal properties.[103] There are also several drug molecules **(Figure 1.15)**, where the 1,2,4-oxadiazole is the main component, for example, antitussive drugs such as perebron **191** and Libexin **192**, the serotonin agonist **193** which is used for treatment of migraine, and L-690548, **194**, for Alzheimer's disease.[104]



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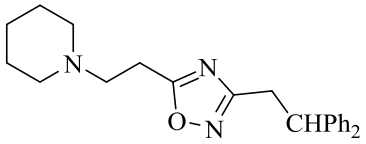

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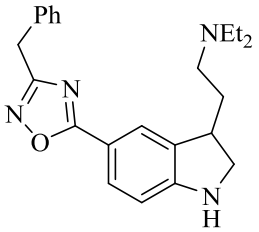

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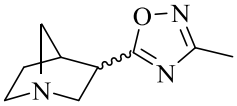
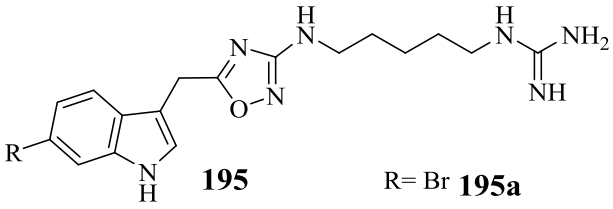


194

Figure 1.15: Drugs of 1,2,4-oxadiazoles.

Recently, Carbone and his colleagues[105] have isolated two indole alkaloids, Phidianidines A **195a** and B **195b** from the marine opithobranch mollusc *phidiana militaris* that contain the 1,2,4-oxadiazole as the basic core unit, the first natural products with a 1,2,4-oxadiazole ring.



195 R= Br **195a**, H **195b**

They also described that phidianidines **195a** & **195b** showed high cytotoxicity against both high proliferating tumour cells and embryonic cells such as fibroblasts and myoblasts in *in vitro* assays.

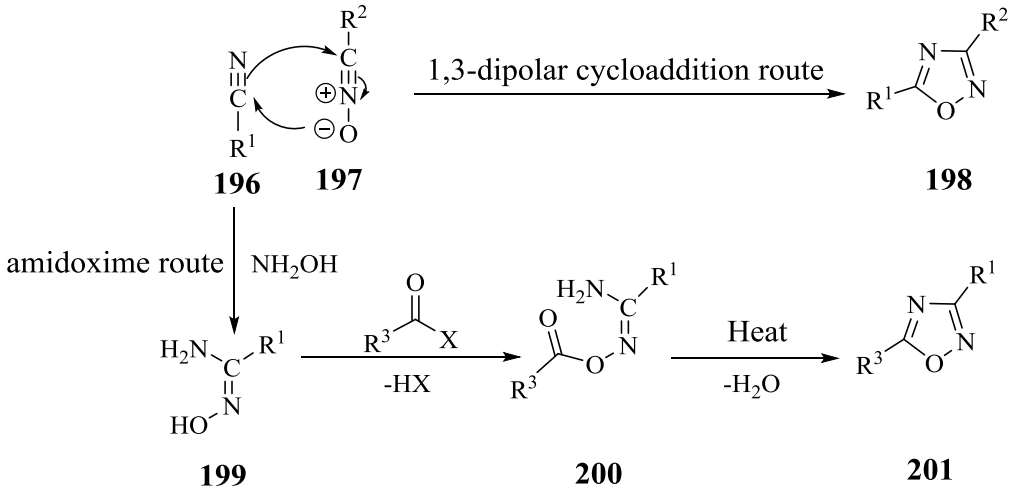
1.9.2. Synthetic methods for 1,2,4-oxadiazoles

There are two common routes amongst the known methodologies for the synthesis of 1,2,4-oxadiazoles.

i) **1,3-dipolar cycloaddition methodology**

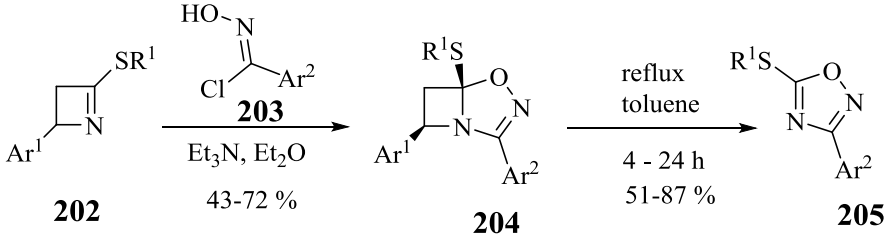
ii) **Amidoxime methodology**

In the first methodology, the nitrile **196** undergoes a 1,3-dipolar cycloaddition with the nitrile oxide **197** to obtain the required 1,2,4-oxadiazoles **198** depending upon the substitution groups of nitrile and nitrile oxide. In the second route, the 1,2,4-oxadiazoles **201** are obtained by reactions of different carboxylic acid derivatives with amidoximes **199** which are easily synthesised from nitriles **196** by the reaction of these with hydroxylamine hydrochloride **(Scheme 1.24)**.[99]



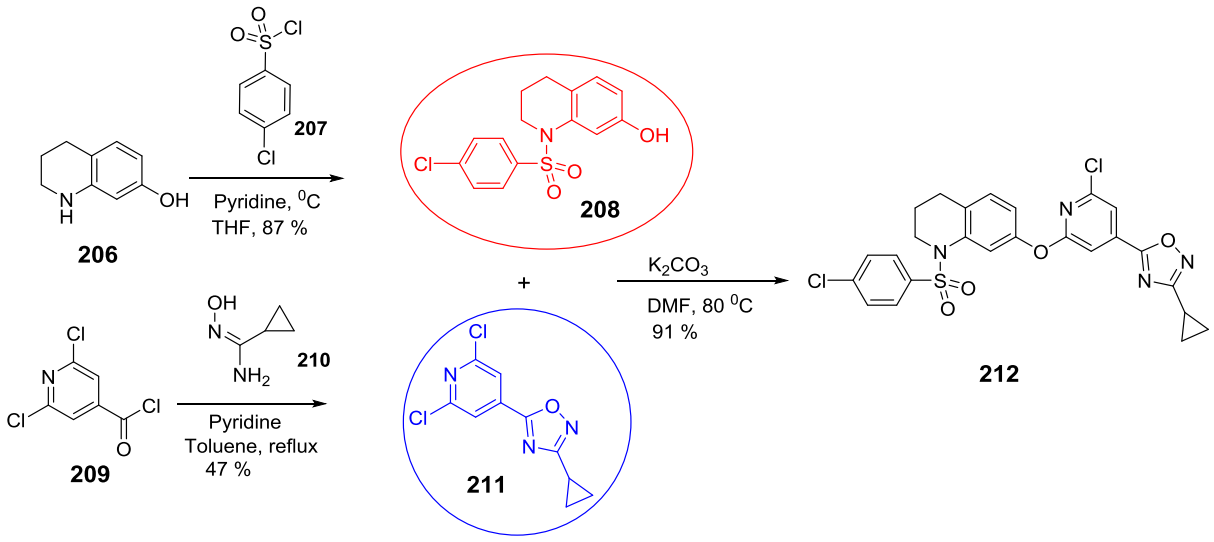
Scheme 1.24: Synthesis of 1,2,4-oxadiazoles.

In 2013, the Hemming group synthesised a series of 1,2,4-oxadiazoles using 1,3-dipolar cycloadditions between 1-azetines and nitrile oxides. They used different substituted 4-membered ring cyclic imines **202** with nitrile oxides to give the corresponding cycloaddition products which were heated in toluene to obtain the 1,2,4-oxadiazoles **205** using [2+2]-cycloreversion of intermediate **204** in good yields **(Scheme 1.25)**.[106]



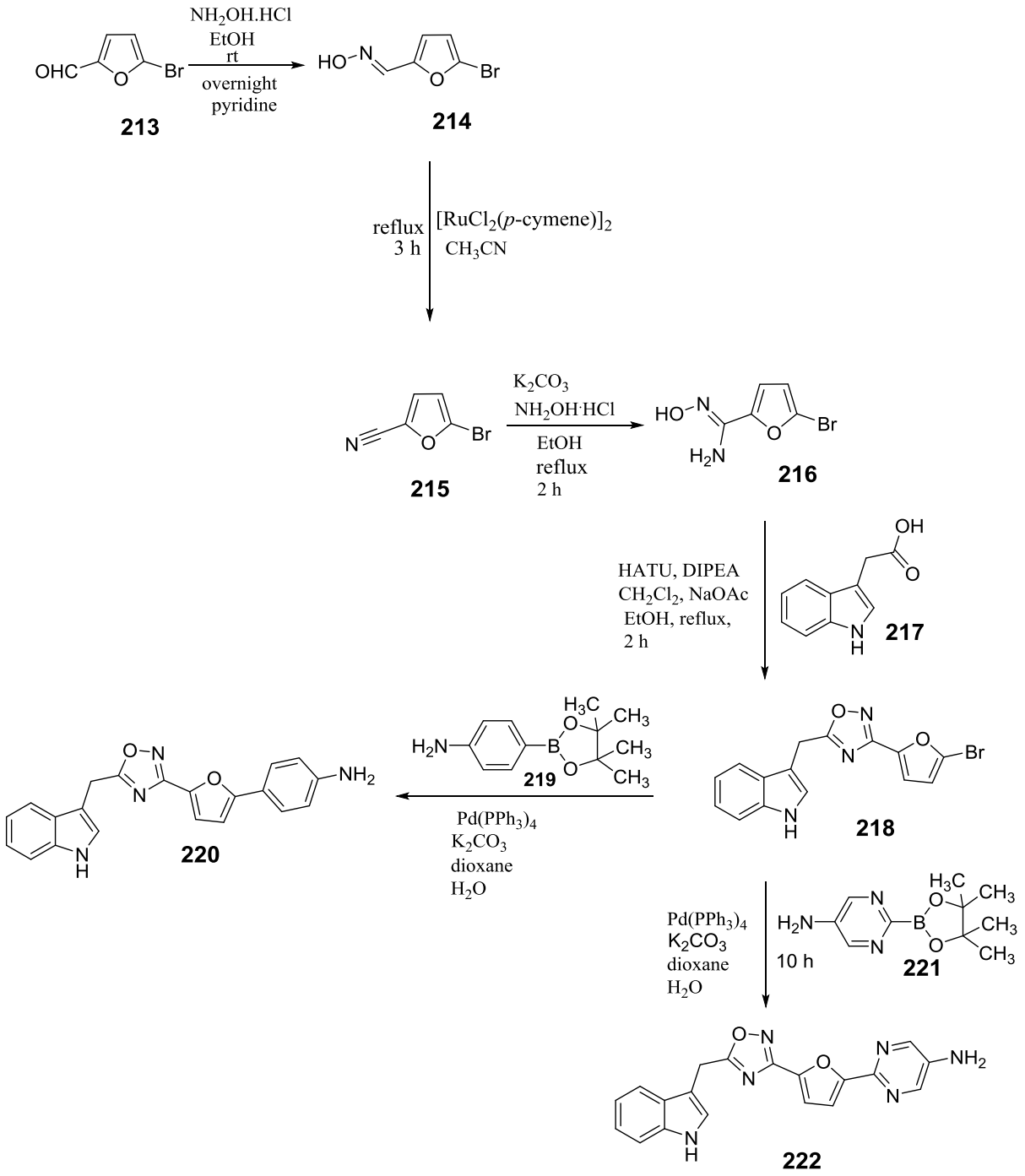
Scheme 1.25: Synthesis of 1,2,4-oxadiazoles.

In 2014, Y. Wang *et al.*[107] synthesised 1,2,4-oxadiazole (**212, Scheme 1.26)** as a novel gpr119 agonist that is a class of human G protein-coupled receptor. The compound **212** was made by treatment of tetrahydroquinoline-7-ol **208** with 2,6-dichloropyridin-4-yl)-1,2,4-oxadiazole **211**. The oxadiazole **211** was obtained from isonicotinoyl chloride **209** and amidoxime **210 (Scheme 1.26)**.



Scheme 1.26: Synthesis of 1,2,4-oxadiazole ring containing heterocyclic compound.

In 2015, C. S. Jiang *et al.*[108] synthesised a series of indole-based 1,2,4-oxadiazole derivatives and assayed them for neuroprotective effects against $A\beta_{25\text{-}35,}$ hydrogen peroxide and oxygen-glucose deprivation-induced neurotoxicity in SH-SY5Y cells, **Scheme 1.27** shows the synthesis.



Scheme 1.27: Synthesis of indole-base-1,2,4-oxadiazoles.

The work started with the preparation of 1,2,4-oxadiazoles **220** and **222** by the reaction of commercially available 5-bromo-2-furaldehyde **213** with hydroxylamine hydrochloride in ethanol to give aldoxime **214** in good yield (90 %) which was then converted into the required nitrile compound **215** using dichloro(*p*-cymene)ruthenium(II) dimer. The synthesis was

continued by addition of hydroxylamine hydrochloride to nitrile **215** to obtain the amidoxime intermediate **216** and after that the compound **216** was treated with indole-3-acetic acid **217** to give the key intermediate 1,2,4-oxadiazole **218**. Finally, oxadiazole intermediate **218** was reacted with different boronic acid pinacol esters **219** and **221** to give the targeted novel indole-based 1,2,4-oxadiazoles **220** and **222** derivatives as neuroprotective agents **(Scheme 1.25)**, based upon the marine-derived natural products **195a** and **195b** (please see above on p. 37).

Chapter 2

Results and discussion

2.1. Aims of the discussion

The first aim of this research was to use cyclopropenones in organic synthesis as shown below **(Figure 2.1)**. The synthesis of cyclopropenones and cyclic imines will also be discussed, along with a discussion of how these species react together.

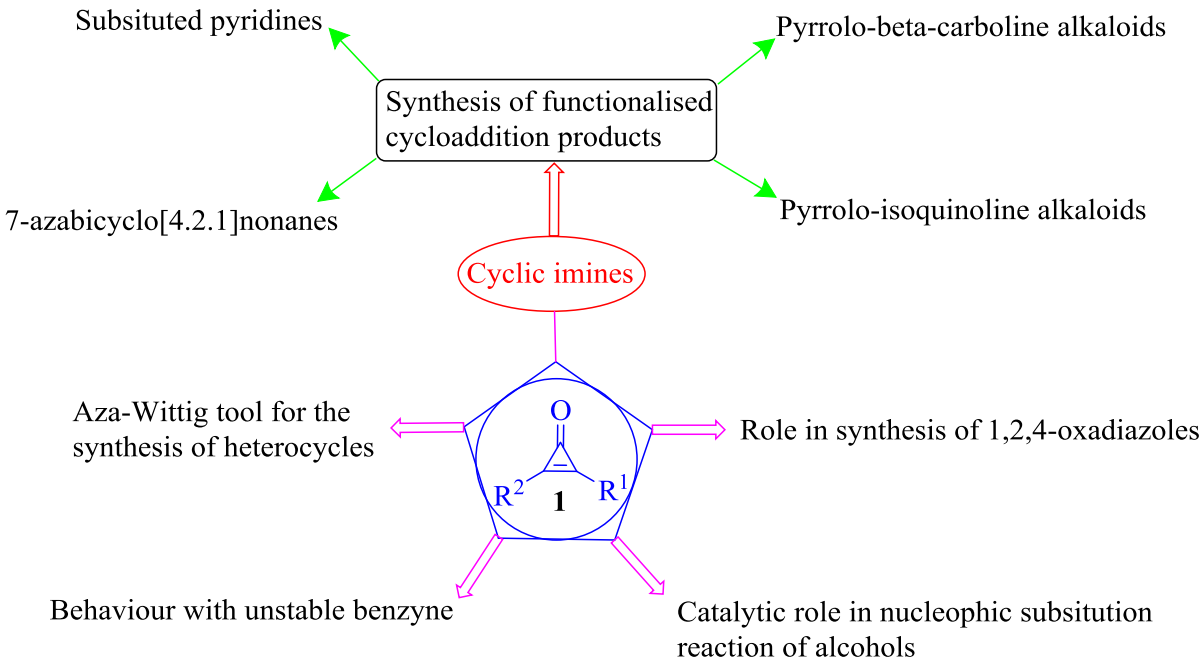


Figure 2.1: Roles of cyclopropenone in organic synthesis.

The imines used include rings that give access to pyrrrolo-β-carbolines and pyrrolo-isoquinolines. The imines used also include 1-azetines and it will be shown that these reactions gave rise to a range of products including pyridines, benzoisoquinolines, 7-azabicyclo[4.2.1]nonanes and 1,2,4 oxadiazoles. **Figure 2.2** summarises the general process to be explored.

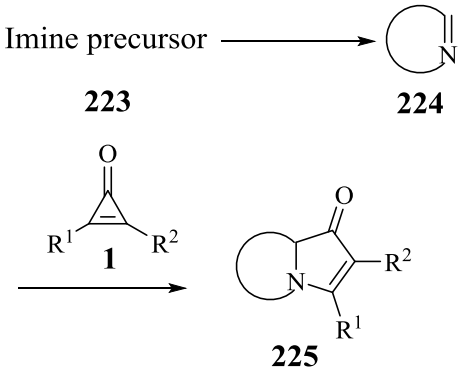


Figure 2.2: Reactivity of cyclic imine with cyclopropenone.

The next aim of this research **(Figure 2.3)** was to use cyclopropenones such as diphenylcyclopropenone as a catalyst for the bromination of alcohols to give bromides **227** and for the coupling of amidoximes **228** with carboxylic acids **229** for the synthesis of a series of 1,2,4-oxadiazoles **230**.

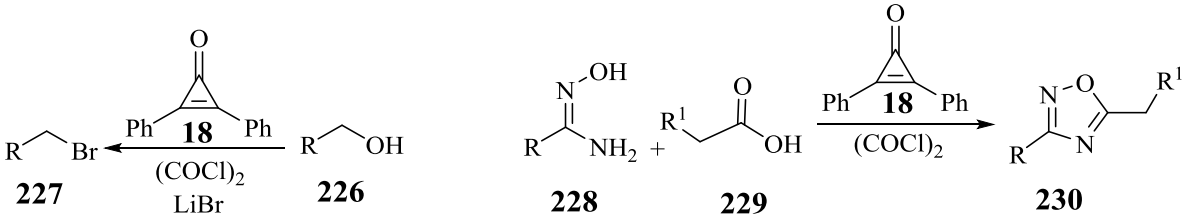
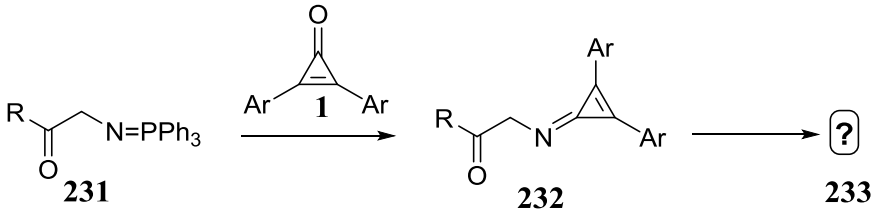


Figure 2.3: DPCP as catalyst.

The reaction of cyclopropenones was also explored with azides *via* conversion of the azides into iminophosphoranes **231** followed by aza-Wittig reaction with the cyclopropenone.



Scheme 2.4: Aza-Wittig reaction of cyclopropenones.

Finally, the synthesis of the natural product 3-*O*-[(*E*)-(2-oxo-4-(*p*-tolyl)but-3-en-1-yl] kaempferol **236** will be discussed.

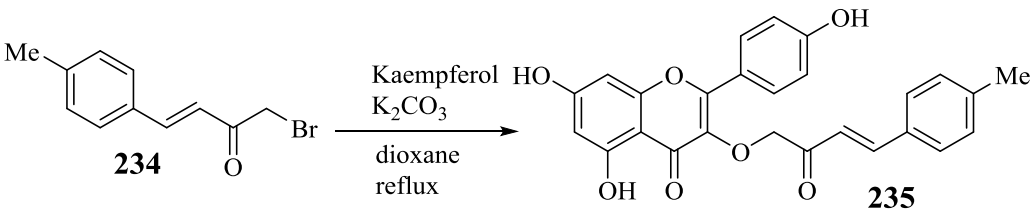
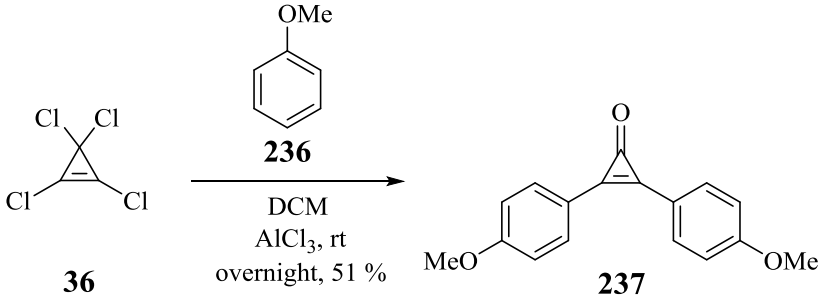


Figure 2.5: Synthesis and purification of natural product.

2.2. Synthesis of cyclopropenones

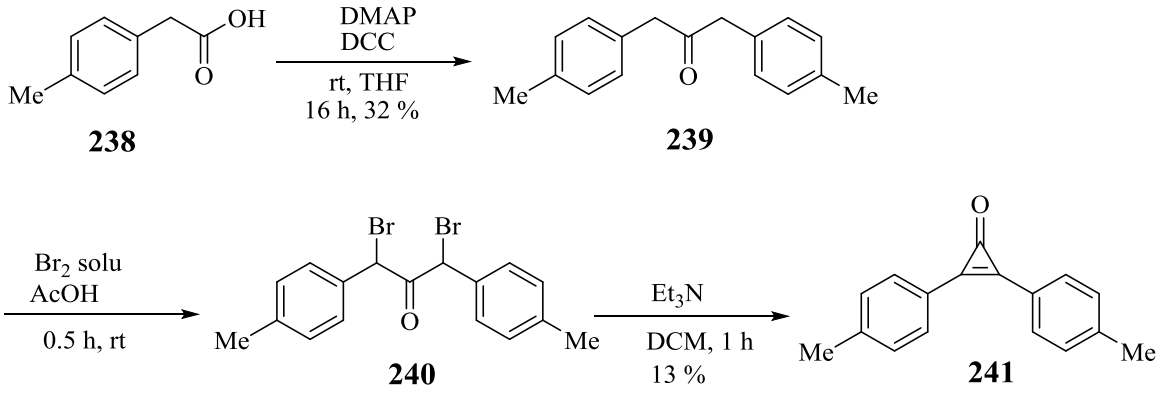
The initial reactions undertaken here involved the synthesis of dianisylcyclopropenone (DACP) **237** and ditolylcyclopropenone (DTCP) **241** following the published literature.[23, 109] The dianisylcyclopropenone **237** **(Scheme 2.1)** was synthesised by treating tetrachlorocyclopropene with anisole in the presence of aluminium chloride in dichloromethane. The required compound **237** was obtained in 51 % yield.



Scheme 2.1: Synthesis of dianisylcyclopropenone.

The structure of required cyclopropenone **237** was assigned by ^{1}H, ^{13}C, DEPT-135, COSY and IR spectroscopy. The spectral data collected for compound **237** matched those reported in the literature.[23] The ^{1}H NMR spectrum recorded for cyclopropenone **237** showed four aromatic protons at 7.94 ppm as a doublet with coupling constant (J = 8.6 Hz) and the other four aromatic protons at 7.08 ppm with coupling constant (J = 8.6 Hz) whilst the singlet peak at 3.93 ppm represented the methoxy groups and confirmed the formation of dianisylcyclopropenone **237**. IR spectroscopy also showed an absorbance peak at 1842 cm^{-1} for C=O group which furthur helped to assign the structure of cyclopropenone.

The synthesis of ditolylcyclopropenone **241** started from *p*-tolylacetic acid as a starting material. Following a procedure by Lambert *et al*,[109] *p*-tolylacetic acid was reacted with *N,N'*-dicyclohexylcarbodiimide in the presence of 4-(dimethylamino)pyridine to give the required diaryl ketone **239** in 32 % yield. The compound **239** was treated with bromine solution in acetic acid to give the 1,3-dibromo-1,3-di-*p*-tolylpropan-2-one **240**. After that, the dibromoketone **240** was treated with triethylamine to obtain the desired cyclopropenone **(241, Scheme 2.2).**



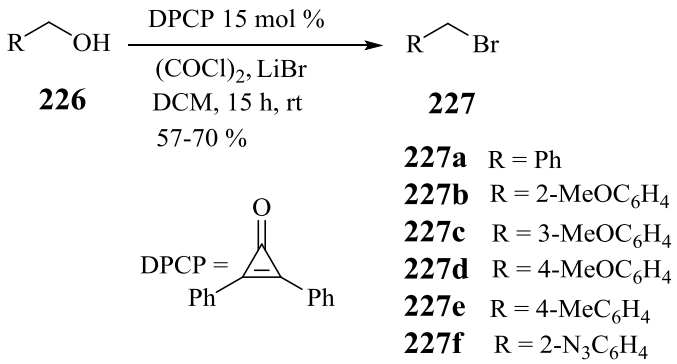
Scheme 2.2: Synthesis of ditolylcyclopropenone.

The proton and carbon spectra obtained for compounds **239** and **240** matched those already reported in the literature.[110] The ^{1}H NMR spectrum obtained for **241** showed four aromatic protons at 7.89 ppm as a doublet with (J = 8.1 Hz) and the other four aromatic protons at 7.40 ppm with coupling constant (J = 8.1 Hz) whilst the singlet signal at 2.49 ppm represented the methyl groups. The IR spectrum for compound **241** showed an absorbance peak at 1831 cm^{-1} for C=O group which confirmed the synthesis of ditolylcyclopropenone.

2.3. Diphenylcyclopropenone (DPCP) as catalyst

Lambert and co-workers have reported the catalytic synthesis of alkyl chlorides from alcohols using cyclopropenones as catalysts in the presence of activating reagent oxalyl chloride.[109] Denton *et al*.[10] also developed a method for the chlorination and bromination of alcohols under catalytic Appel conditions but there was a limitation caused by triphenylphosphine

oxide due to the problematic purification of desired product from it. To overcome this drawback, we aimed to combine these two processes in order to design a strategy for the catalytic bromination of alcohols using DPCP as catalyst in the presence of an activating reagent such as oxalyl chloride and a bromide source. Our findings are summarised in **Scheme 2.3.**



Scheme 2.3: Catalytic bromonation of alcohols using DPCP as catalyst.

Initially, benzyl alcohol was chosen and a catalytic amount 15 mol % of DPCP and then NaBr were added to the reaction mixture before the addition of oxalyl chloride solution in DCM over 5 h. The reaction was monitored by TLC but unfortunately it did not give the desired results. The reaction was repeated but this time LiBr was used and the reaction was followed by TLC. ^{1}H NMR analysis of the reaction mixture indicated a mixture of benzyl chloride and benzyl bromide. The proportion of benzyl bromide was improved by increasing the amount of LiBr but unfortunately the problem of a mixture was still seen. Benzyl bromide and benzyl chloride could not be separated due to very similar polarities on the TLC plate and so NMR (**Figure 2.6** & **Figure 2.7**) was used for analysis. Finally, the desired product benzyl bromide was obtained in pure form by increasing the addition time of the oxalyl chloride in dichloromethane over 15 h as shown in **Figure 2.6** and **Figure 2.7**.

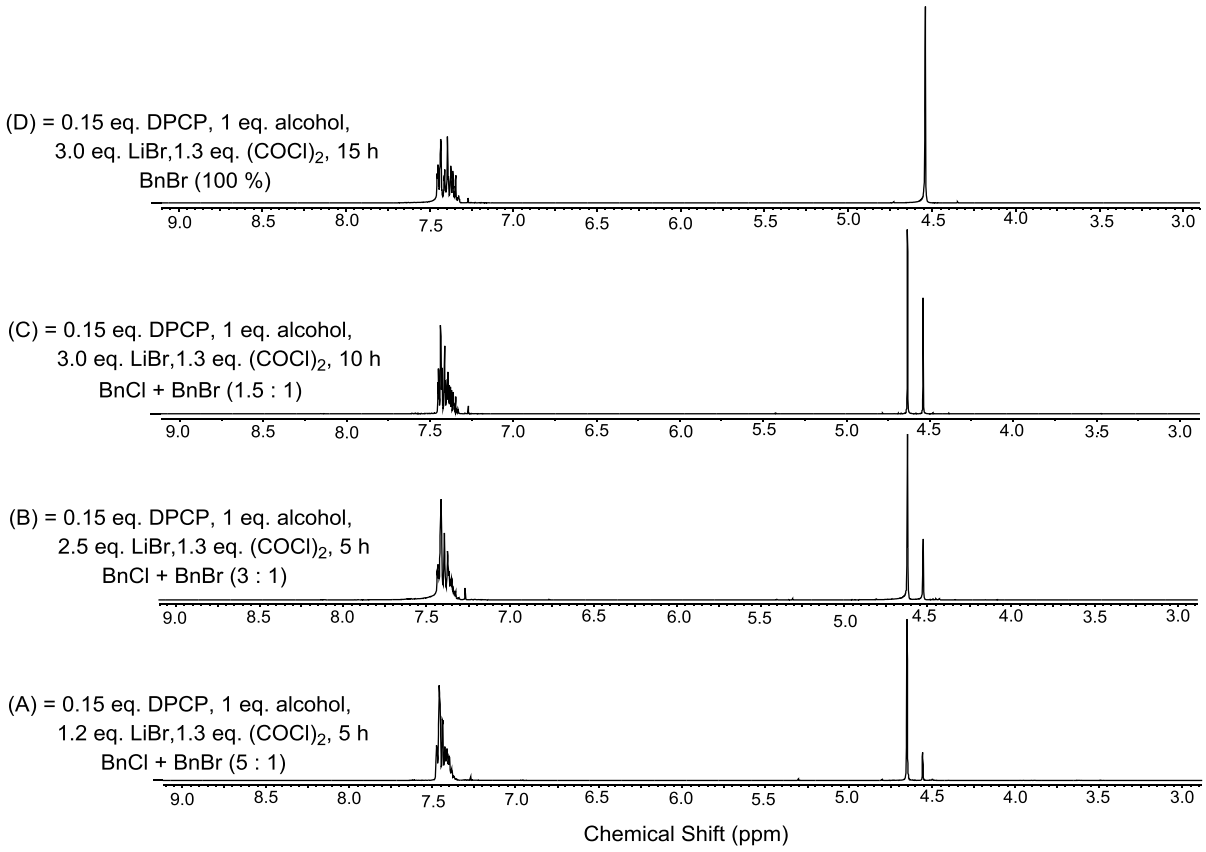


Figure 2.6: ^{1}H spectra for BnCl & BnBr.

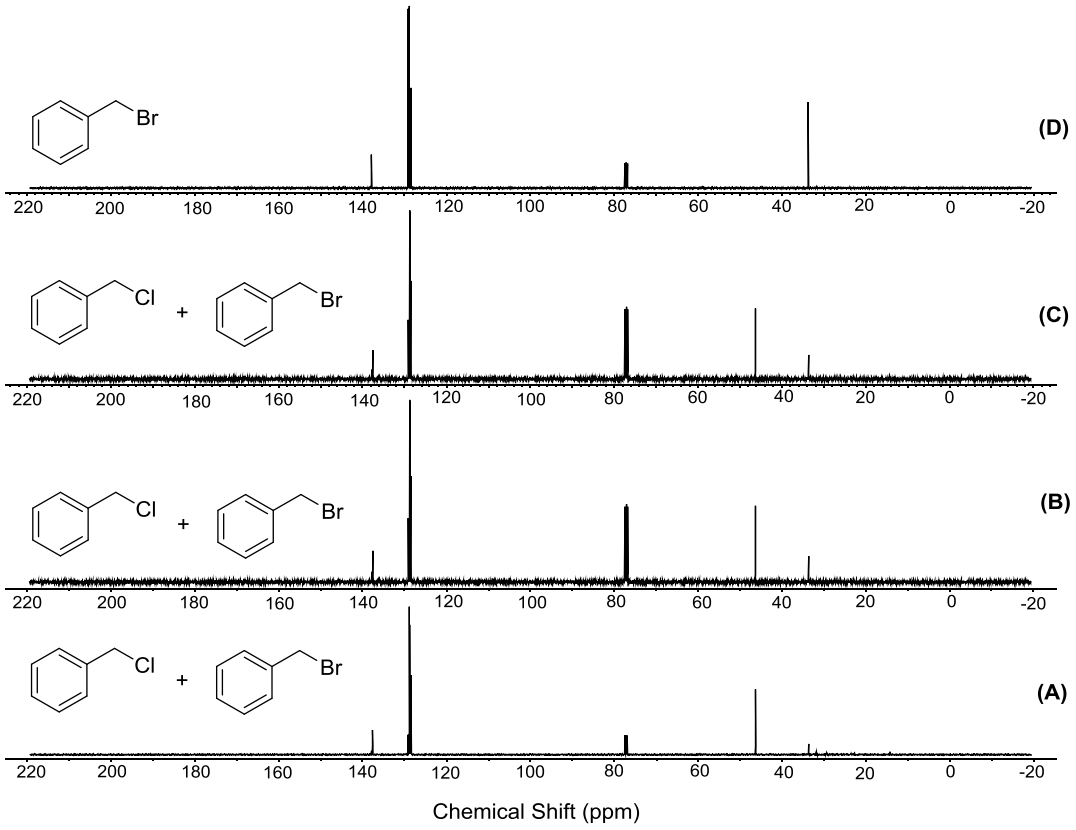


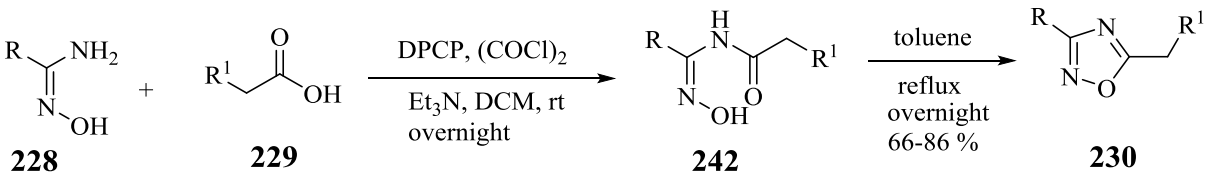
Figure 2.7: ^{13}C spectra for BnCl & BnBr.

This set of conditions was applied to 5 other benzyl alcohols to give the corresponding bromide products **(227b-f)** in good yields as described in **Scheme 2.3**. It should be noted that when the reaction was attempted in the absence of DPCP, no reaction was observed. 15 mol % of DPCP was found to be optimal.

The catalytic processes were also attempted in the presence of LiF instead of LiBr and with iodide sources but were unsucessful. Similar work in the Hemming group is underway to get the fluoro and iodo products but no further work was done for this thesis.

2.4. Synthesis of 1,2,4-oxadiazoles

Due to the importance of 1,2,4-oxadiazoles in the pharmaceutical industries as described in the introduction, our laboratory has had a long interest in the synthesis of 1,2,4-oxadiazoles. The synthesis of 1,2,4-oxadiazoles from amidoximes **228** and carboxylic acids **229** requires activation of the carboxylic acid. We wanted to know if we could use the known DPCP catalysed activation of carboxylic acids **229** to allow coupling to amidoximes **228** in order to make *N*-acyl amidoximes **242** and hence 1,2,4-oxadiazoles **230** as shown in **Scheme 2.4** below. In this project we focused on making 1,2,4-oxadiazoles with pyridyl substituent as these were proving to be interesting ligands in a collaborative project with a supramolecular research group.



228 **229** **242** **230**

228a R = 2-C_5H_4N
228b R = 2-$C_4H_3N_2$
228c R = 3-Me-2-C_5H_3N

(Amidoximes)

242a R = 2-C_5H_4N & R^1 = Ph
242b R = 2-C_5H_4N & R^1 = 4-MeC_6H_4
242c R = 2-C_5H_4N & R^1 = 4-$MeOC_6H_4$
242d R = 2-C_5H_4N & R^1 = 4-ClC_6H_4
242e R = 2-$C_4H_3N_2$ & R^1 = Ph
242f R = 2-$C_4H_3N_2$ & R^1 = 4-MeC_6H_4
242g R = 2-$C_4H_3N_2$ & R^1 = 4-$MeOC_6H_4$
242h R = 3-Me-2-C_5H_3N & R^1 = Ph
242i R = 3-Me-2-C_5H_3N & R^1 = 4-MeC_6H_4
242j R = 3-Me-2-C_5H_3N & R^1 = 4-MeO-C_6H_4
242k R = 3-Me-2-C_5H_3N & R^1 = 4-ClC_6H_4

***N*-acyl amidoximes**

229a R^1 = Ph
229b R^1= 4-MeC_6H_4
229c R^1= 4-$MeOC_6H_4$
229d R^1= 4-ClC_6H_4

(Acids)

230a R = 2-C_5H_4N & R^1 = Ph
230b R = 2-C_5H_4N & R^1 = 4-MeC_6H_4
230c R = 2-C_5H_4N & R^1 = 4-$MeOC_6H_4$
230d R = 2-C_5H_4N & R^1 = 4-ClC_6H_4
230e R = 2-$C_4H_3N_2$ & R^1 = Ph
230f R = 2-$C_4H_3N_2$ & R^1 = 4-MeC_6H_4
230g R = 2-$C_4H_3N_2$ & R^1 = 4-$MeOC_6H_4$
230h R = 3-Me-2-C_5H_3N & R^1 = Ph
230i R = 3-Me-2-C_5H_3N & R^1 = 4-MeC_6H_4
230j R = 3-Me-2-C_5H_3N & R^1 = 4-$MeOC_6H_4$
230k R = 3-Me-2-C_5H_3N & R^1 = 4-ClC_6H_4

(1,2,4-oxadiazoles)

Scheme 2.4: Synthesis of 1,2,4-oxadiazoles.

The reaction was started by the treatment of diphenylcyclopropenone (DPCP) with oxalyl chloride and then adding a mixture of acid **229** and triethylamine to the reaction mixture and then adding amidoxime **228** to the mixture to produce *N*-acyl amidoximes **242** which were furthur heated to reflux overnight in toluene to obtain the desired 1,2,4-oxadiazoles **230a-k** in good yields. This is shown later in **Figure 2.10**. Compounds **230a-k** were fully characterised by NMR and MS. For example, the ^{1}H NMR analysis of 1,2,4-oxadiazole **230b (see Figure 2.8)** showed the disappearance of the amide and hydroxyl groups peaks in the recorded ^{1}H NMR spectrum of *N*-acyl amidoxime **242b** which indicated the formation of the carbon-oxygen bond of the 1,2,4-oxadiazole by the removal of H_2O. The carbon spectrum for target compound 1,2,4-oxadiazole showed the CH_2 signal at 3.82 ppm and methyl group at 2.35 ppm. The spectrum also showed 5-quatenary peaks at 179.0, 168.2, 146.3, 137.3 and 130.2 ppm, respectively and six aromatic CH proton peaks between 150.3 - 123.1 ppm which helped to assign the structure of 1,2,4-oxadiazole **230b.**

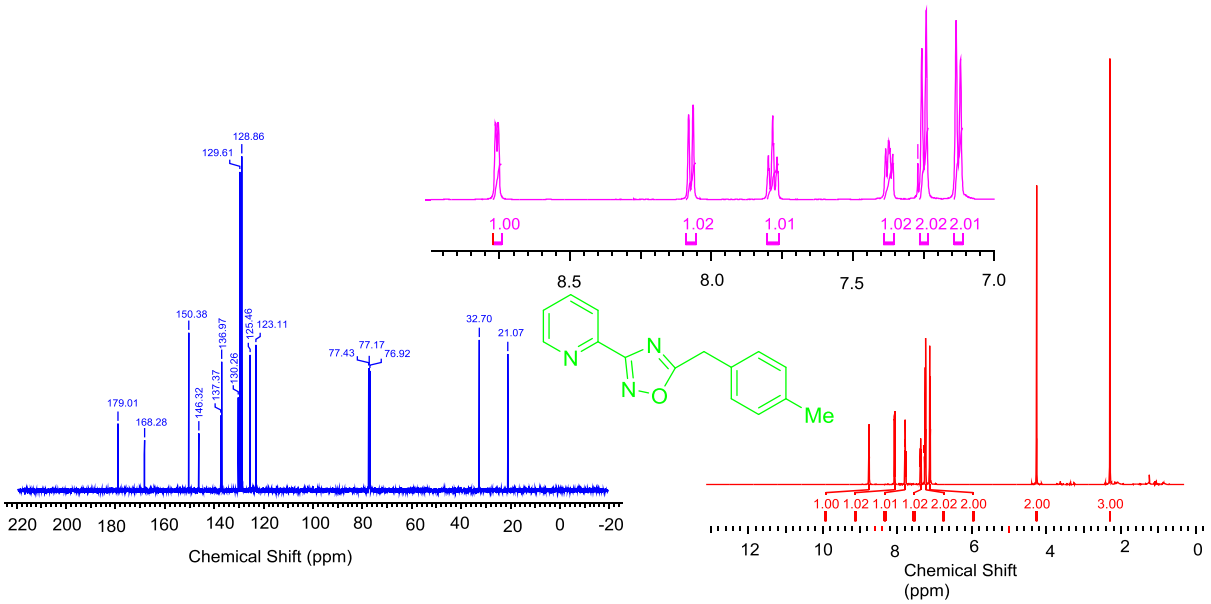


Figure 2.8: ^{1}H and ^{13}C spectra of 1,2,4-oxadiazole.

The IR spectrum also showed the disappearance of absorbance peaks for hydroxyl group at 3469 cm^{-1}, for amide bond (NH) at 3301 cm^{-1} and for the carbonyl group at 1740 cm^{-1}, respectively. Finally, MS confirmed the synthesis of 1,2,4-oxadiazole **230b**. Similarly, other 1,2,4-oxadiazoles were characterised as described for the synthesis of 1,2,4-oxadiazole **230b.**

Figure 2.9 shows how the *N*-acylamidoximes are formed from the carboxylic acid and $(COCl)_2$ with DPCP as catalyst. It is found that amidoximes could be coupled to carboxylic acids at room temperature by using 1.1 equivalents of $(COCl)_2$ in the presence of 1.0 equivalent of DPCP. In this process the DPCP reacts with $(COCl)_2$ to form a 1,1-dichlorocyclopropene and then a cyclopropenium ion with enhanced nucleophilicity. **Figure 2.10** shows an alternative mechanism involving ketene **247**.

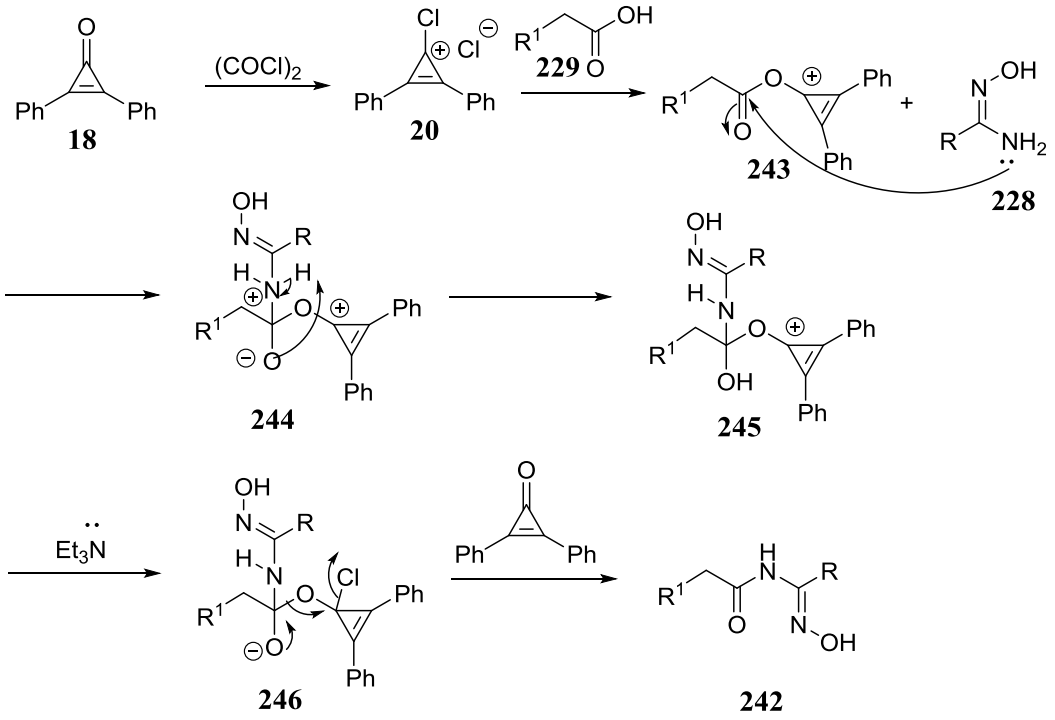


Figure 2.9: Suggested mechanism (A) for the synthesis of *N*-acyl amidoximes.

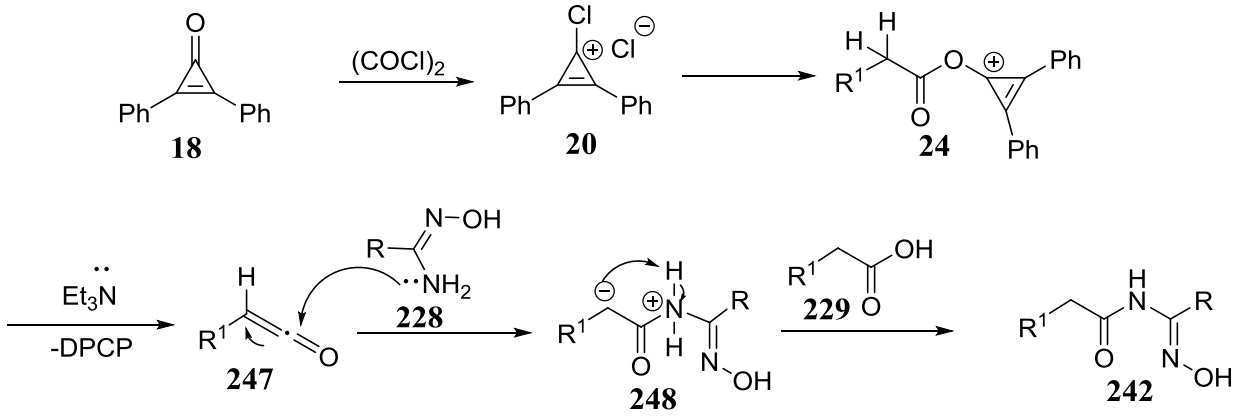


Figure 2.10: Suggested mechanism (B) for the synthesis of *N*-acyl amidoximes.

The suggested mechanism[111] for the synthesis of the 1,2,4-oxadiazole involves the dehydration and cyclisation to obtain the desired 1,2,4-oxadiazole as shown in **Figure 2.11.**

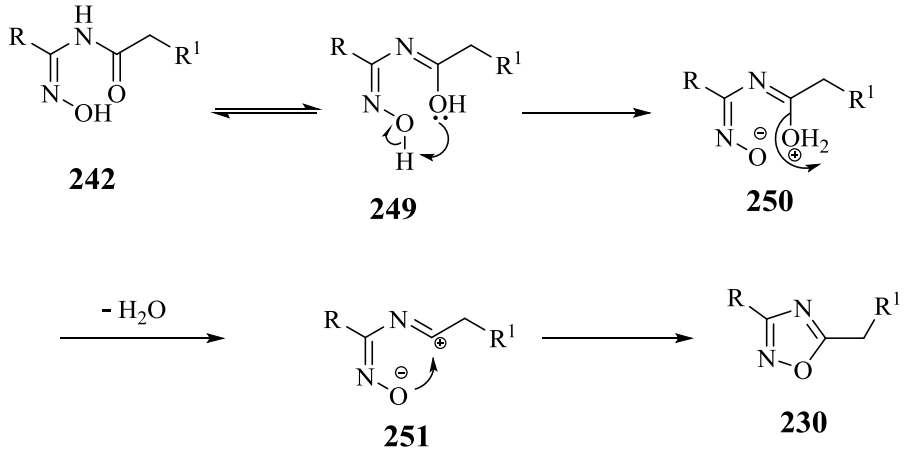


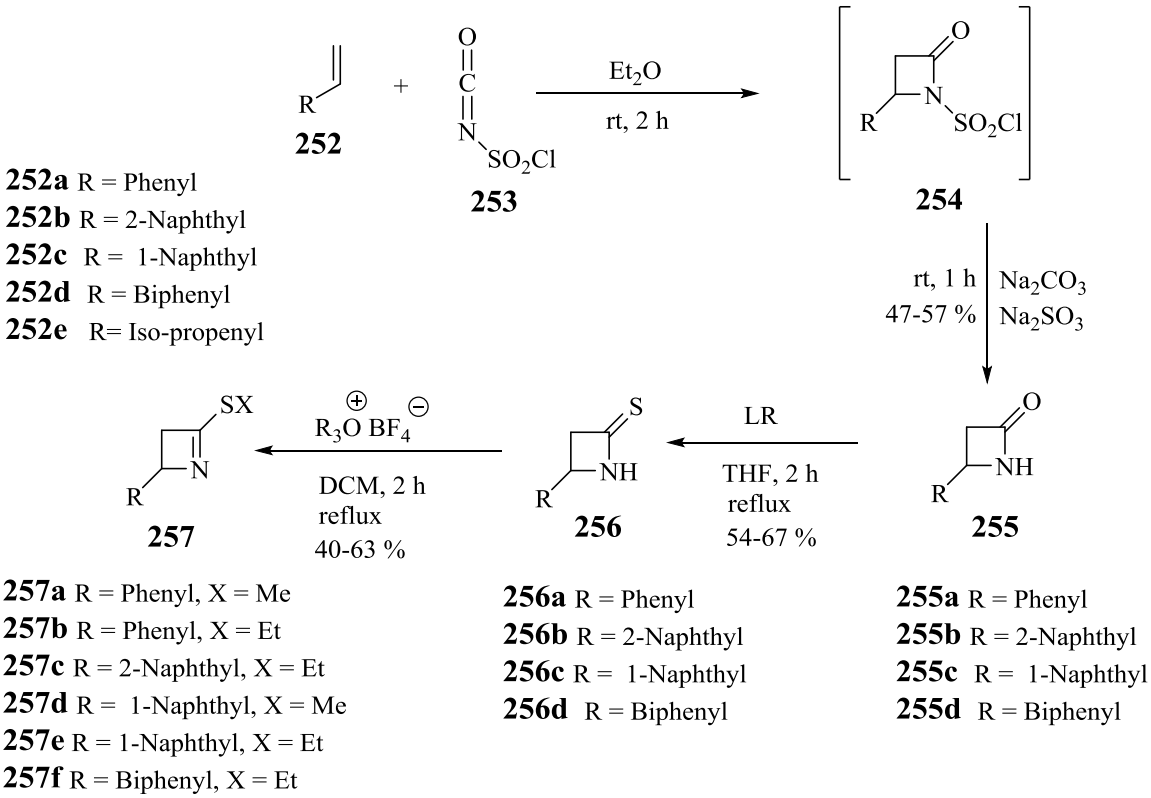
Figure 2.11: Suggested mechanism for synthesis of 1,2,4-oxadiazole.

The synthesis of 1,2,4-oxadiazoles using benzoic acid and its derivatives was attempted but unfortunately the desired results were not obtained. This reaction was noted to fail at the first step i.e. the amide bond formation between the amidoxime and carboxylic acid. This is interesting because it might suggest that the coupling method proceeds *via* the ketene type intermediate **(see Figure 2.10)** and this is being explored elsewhere in the Hemming group. Again, when the acylation of the amidoxime was attempted with no DPCP present, no reaction was observed.

2.5. Synthesis of 1-azetines

The next part of this work was to look at the reactions of cyclopropenones with imines commencing with 1-azetines. The first step towards the synthesis of 1-azetines involved the synthesis of 4-aryl-azetidinones. According to a published procedure [8] commercially available styrene, 2-vinylnaphthalene, 1-vinylnaphthalene and 4-vinylbiphenyl were reacted with chlorosulfonyl isocyanate **253** producing the corresponding chlorosulfonyl β-lactams **254** using a [2+2] cycloaddition approach. After this, the chlorosulfonyl group was removed using sodium carbonate and sodium sulfite to give the corresponding 4-aryl-1-azetidine-2-ones **255a-d**. The second step towards synthesis of 1-azetines involved the preparation of thiolactams by the reaction of Lawesson's reagent (LR) with the corresponding lactam in

THF. These reaction mixtures were heated at reflux for 2 h to get the required thiolactams **(256a-d, Scheme 2.5)**.



Scheme 2.5: Synthesis of 4-aryl-1-azetidines.

The proposed mechanism[68, 70] involved in the thionation process is shown below. The ylidic intermediate obtained due to the breakage of the sulfur-phosphorus bond during the reflux process is the reactive species, and behaves as a sulfur nucleophile towards the lactam carbonyl **(Figure 2.12).**

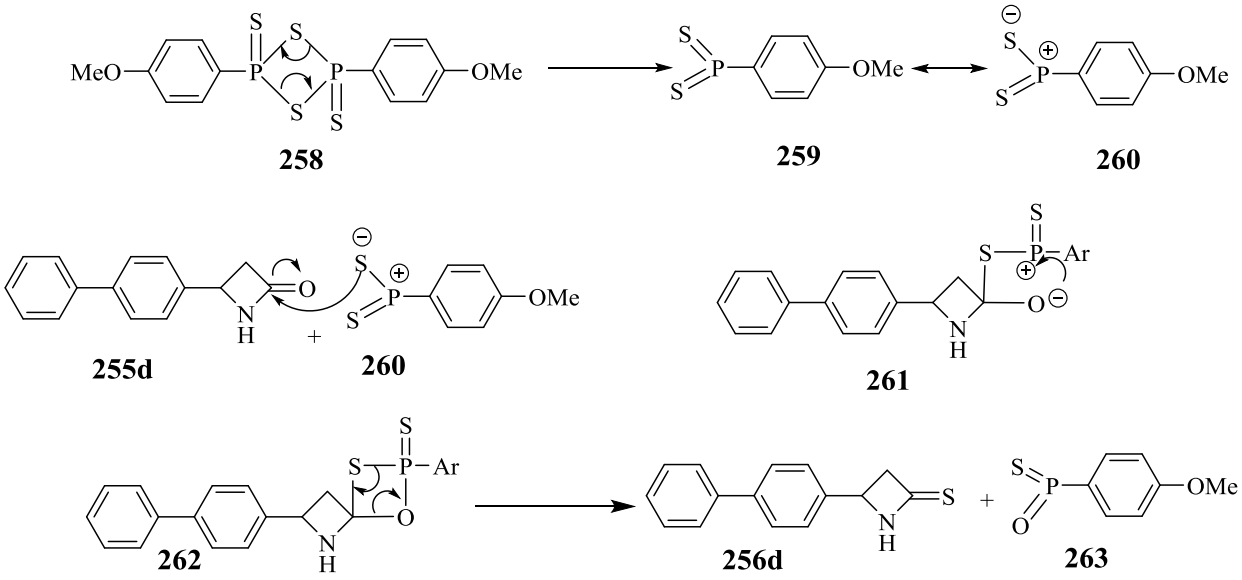


Figure 2.12: Mechanism inovoled for the synthesis of thiolactam.

The final step in the synthesis of 1-azetines involved the alkylation of thiolactams with Meerwein's reagents (trimethyl or triethyloxonium tetrafluoroborate) in dichloromethane. These reaction mixtures were stirred for 1 h at room temperature and then at reflux for 1 h. These reaction mixtures were worked up using 50 % aqueous potassium carbonate to give the desired 1-azetines **257a-d**.

The proposed mechanism for the synthesis of the 1-azetines involves an attack from the thiolactam sulfur to triethyl oxonium tetrafluoroborate due to the presence of electron-pair on the nitrogen atom. The carbonate work-up deprotonates the iminium intermediate.[112]

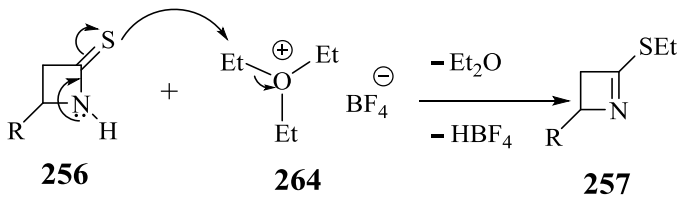


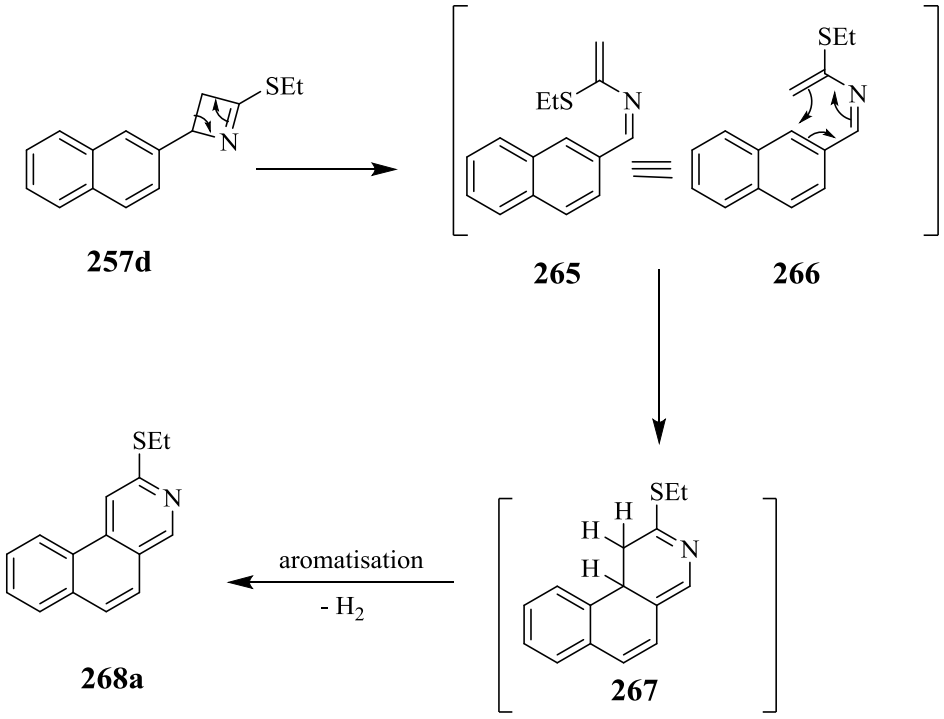
Figure 2.13: Mechanism involved for synthesis of cyclic imines.

All compounds gave consistent spectroscopic data. For example, the ^{1}H NMR spectrum obtained for phenylazetidinone **255a** showed a broad singlet signal for the amide proton at

6.15 ppm, a doublet of doublets (J = 5.3 Hz and 2.3 Hz) at 4.75 ppm for the CH proton of the 1-azetidinone ring and a multiplet of peaks for the phenyl protons between 7.42 - 7.30 ppm. The proton peaks for the methylene group of the 1-azetidinone ring appeared as a doublet of doublets of doublets *(J* = 14.9, 5.3 and 2.3 Hz) at 3.47 ppm and a doublet of doublets (J = 14.9 and 2.3 Hz) at 2.92 ppm. The ^{13}C NMR spectrum contained for phenylazetidinone **255a** showed a carbon peak for the C=O group at 168.0 ppm, four carbon signals for the phenyl ring at 140.2, 128.9, 128.3 and 125.7 ppm, a carbon peak for CH at 50.4 ppm and the carbon signal for CH_2 at 48.1 ppm, respectively. The ^{1}H NMR spectra obtained for 4-aryl-1-azetidin-2-thiones **256a-d** showed a broad singlet signal for the amide proton around 8.19 – 8.52 ppm, a doublet of doublets for the CH proton of 1-azetine ring and multiplet peaks for the aromatic protons. The signals for the methylene group of the 1-azetine ring showed as a doublet of doublets of doublets and a doublet of doublets. The ^{13}C NMR spectra recorded for these azetidinthiones **256a-d** showed a characteristic signal for the quatenary carbon (S=C) at 204.5 ppm, signals as expected for the aromatic rings, a carbon peak for CH between 56.5 – 59.1 ppm and methylene signal between 51.2 – 56.5 ppm. The ^{1}H NMR spectra of 1-azetines **257a-d** showed the disappearance of the amide NH bond and the emergence of proton signals for the methyl and ethyl groups in the recorded spectra of 1-azetines **257a-d**, which confirmed the preparation of these 4-membered cyclic imines. Similarly, In the ^{13}C spectra recorded for 1-azetines **256a-d**, the disappearance of the distinctive signal of the quatenary carbon (C=S) and the emergence of carbon signals for the carbon atoms of C=N and ethyl or methyl groups were diagnostic.

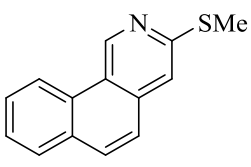
Interestingly, when 4-ethyllthio-2-(2′-naphthyl)-1-azetine **257c** was synthesised from the corresponding thiolactam 4-(2′-naphthyl)-1-azetidine-2-thione **256b** and left overnight rather than used immediately, the 1-azetine was not the isolated product, but underwent rearrangement to give the benzoisoquinoline **268a,** as shown in **Scheme 2.6**. Further

investigation of this reaction was carried out and benzoisoquinoline could be isolated in good yields (73 %) after storage of the sample of crude. 1-azetine **257c** in $CDCl_3$ for one week. It is possible that 1-azetine **257c** was converted into the benzoquinoline *via* the vinylic imine **265** as an intermediate **(see Scheme 2.6)** using a [2+2] ring opening then 6π-electrocyclisation and aromatization by loss of hydrogen.[113] The structure of benzoisoquinoline **268a** was supported by NMR spectroscopy and MS spectrometry.



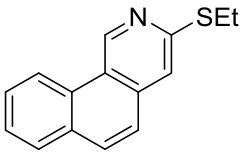
Scheme 2.6: Proposed mechanism for benzoisoquinolines.

The 1-azetines **257d** and **257e** behaved in the same manner and gave the benzoisoquinolines (**268b** & **268c**-see experimental).



268b

87 % yield



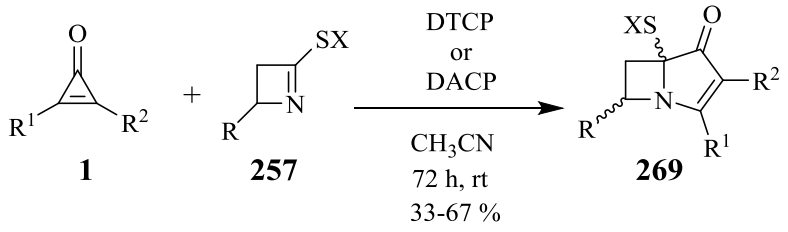
268c

78 % yield

The phenyl and biphenyl 1-azetines **257a**, **257b** and **257f** did not form the analogous isoquinolines and were noted to be pure when formed from the corresponding thiolactams.

2.6. Synthesis of cycloadducts with 1-azetines

The synthesis of cycloadducts **269** proceeded by the reaction of cyclopropenones **1** with different 1-azetines **257** in acetonitrile as shown in **Scheme 2.7**. These reaction mixtures were stirred at room temperature for 24 h and gave the desired compounds **269a-f** as shown in **Table 2.1.**



Scheme 2.7: Synthesis of cycloadducts.

Table 2.1: Formation of cycloaddition products

Entry	Product	R	R^1/R^2	X	yield (%)
1	**269a**	Phenyl	4-MeC_6H_4	Me	65
2	**269b**	Phenyl	4-MeC_6H_4	Et	67
3	**269c**	Phenyl	4-$OMeC_6H_4$	Me	42
4	**269d**	Phenyl	4-$OMeC_6H_4$	Et	39
5	**269e**	Naphthyl	4-MeC_6H_4	Et	42
6	**269f**	Naphthyl	4-$MeOC_6H_4$	Et	33

The proposed mechanism[28b] involves the electron donating thioalkyl group stimulating the nucleophilic attack from the azetine nitrogen to cyclopropenone **1** to give the intermediate **270 (Figure 2.14)** which then undergoes an intramolecular attack on the electrophilic carbon to form the cycloaddition compounds.

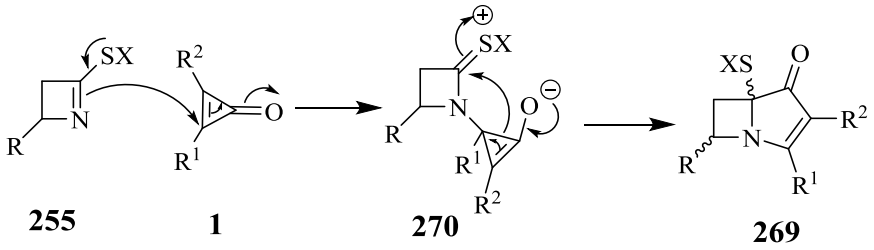
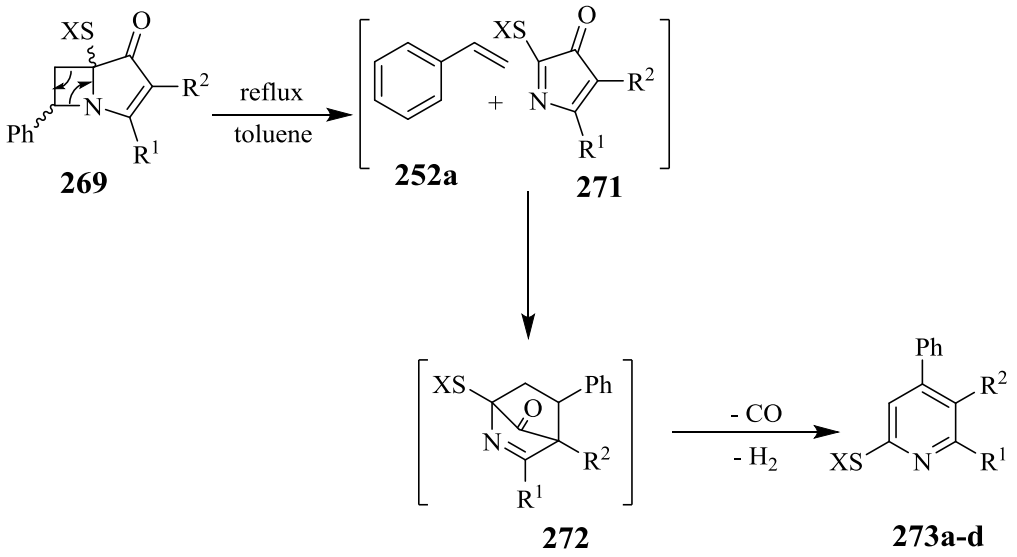


Figure 2.14: Mechanism for a formal [3+2] cycloaddition reaction.

The title compounds **269a-f** were characterized by NMR and IR analysis and mass spectrometry. The ^{1}H NMR spectrum obtained for cycloadduct **269a** showed a mixture of diastereomers. The methyl groups of **269a** were observed at 2.31, 2.22, 2.17, 2.11, 2.02 and 1.97 ppm, respectively which confirmed the mixture of diastereomers. The proton peak for the CH of the 4-membered ring of one diastereomer appeared as a multiplet peak between 5.46 – 5.44 ppm, whilst the proton peak for the CH of the other diastereomer was observed as a doublet of doublets at 4.15 ppm. The four methylene proton signals of both diastereomers appeared as doublet of doublets at 3.06 ppm, a multiplet peak between 2.93 - 2.83 ppm and a doublet of doublets at 2.38 ppm, respectively. The aromatic proton peaks of both diastereomers appeared between 7.53 - 6.66 ppm. The ^{13}C NMR spectrum recorded for **269a** showed two carbon signals for the C=O groups at 202.7 and 202.5 ppm for the two diastereomers, respectively. The ^{13}C spectrum also showed two carbon peaks for the 4-membered ring CH at 66.4 and 65.9 ppm whereas the carbon peaks for the confirmed CH_2 appeared at 34.5 and 31.2 ppm. The structure of compound **269a** was also confirmed with mass spectrometry MS $(ESI)^{+}$ 412.2 and consistent HRMS. The IR spectrum recorded for **269a** showed an absorbance peak at 1675 cm^{-1} for C=O group.

2.7. Synthesis of pyridines from cycloadducts

The chemistry of the cycloaddition products **269a-d** was explored by heating them at reflux in toluene. Pyridines **273a-d** were formed in reasonable yields **(see Table 2.2)** after complete consumption of starting materials by indication of TLC **(Scheme 2.8).**



Scheme 2.8: Synthesis of pyridines.

The proposed mechanism[8] involved the formation of a styrene **252a** and azacyclopentadienone **271** by [2+2] cycloreversion in the first step and then a regioselective [4+2] hetero Diels-Alder cycloaddition. The intermediate **272** gave the pyridines **273a-d** by chelotropic extrusion of carbon monoxide and aromatization *via* loss of hydrogen. In previous work, the aromatic R^1 & R^2 groups were limited to phenyl, so this work has extended the scope of the reaction, by showing that other diaryl cyclopropenones can react.

Table 2.2: Formation of pyridines

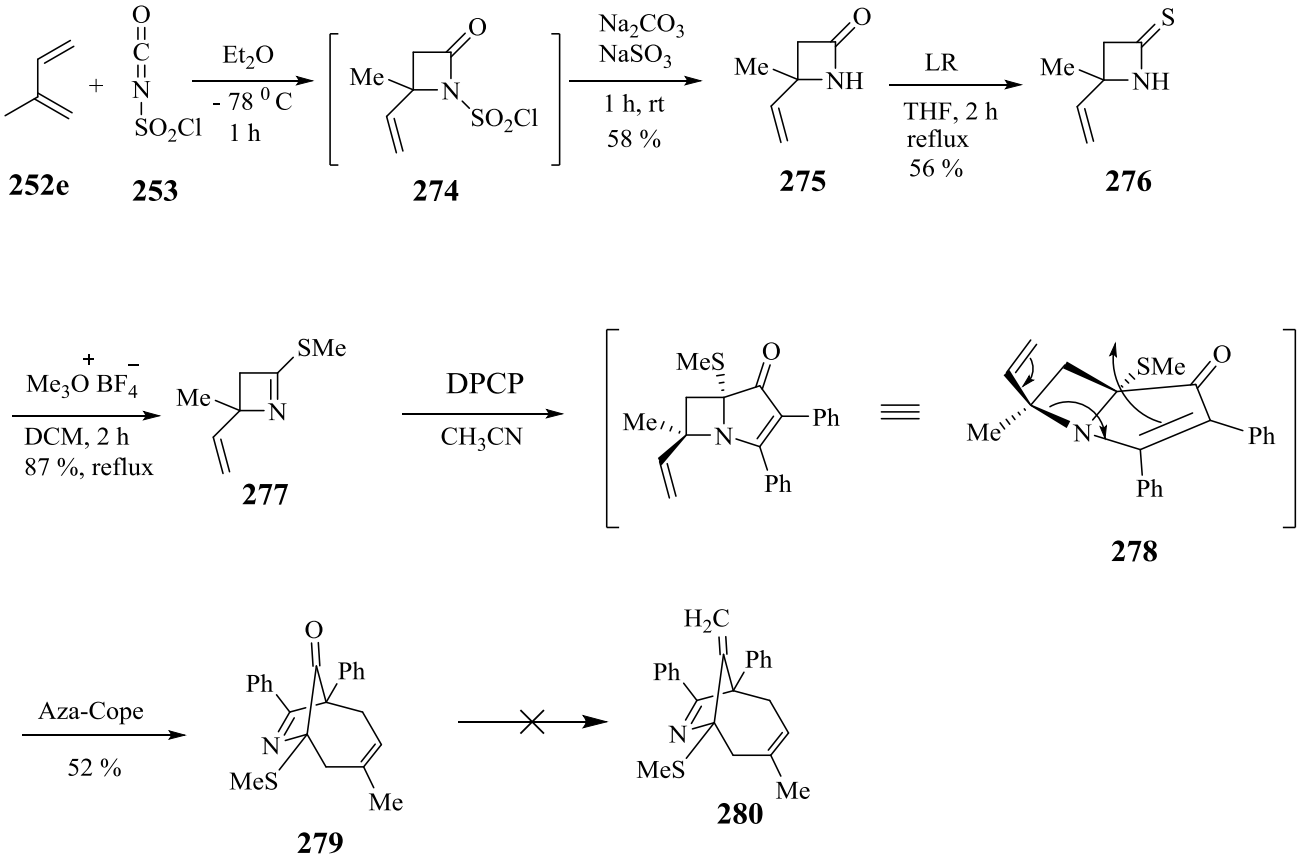
Entry	Product	R^1/R^2	X	yield (%)
1	**273a**	4-MeC_6H_4	Me	58
2	**273b**	4-MeC_6H_4	Et	61
3	**273c**	4-$MeOC_6H_4$	Me	67
4	**273d**	4-$MeOC_6H_4$	Et	55

The ^{1}H NMR spectrum for pyridine **273a** showed the disappearance of the carbonyl signals at 202.7 and 202.5 pm which had been present in the spectrum recorded for cycloadduct **273a** and the emergence of a pyridine proton as a singlet at 7.09 ppm. In addition, the spectrum showed the proton signals of three methyl groups at 2.57, 2.21 and 1.15 ppm, respectively. Eight protons of the two substituted aryl groups and five protons of the phenyl group appeared between 7.20 – 6.65 ppm and helped confirm the synthesis of the pyridine. The ^{13}C spectrum for compound **273a** showed the carbon peaks of the three methyl groups at 21.2, 21.1 and 13.3 ppm, respectively. All aromatic CH and quaternary carbons were also present. The structure of compound **273a** was confirmed through MS $(ESI)^+$: m/z [M+1] 382.2 and consistent HRMS. Similarly, the structural data of the other pyridines **273b-d** was consistent with the proposed structures.

2.8. Synthesis of 7-azabicyclo[4.2.1]nonane from a 4-vinyl-1-azetine

The preparation of a 4-methyl-4-vinyl-1-azetidin-2-one **275 (Scheme 2.9)** was the initial step for the synthesis of 1-azetine **277**. According to a published procedure,[82] commercially available isoprene was reacted with chlorosulfonyl isocyanate producing the chlorosulfonyl β-lactam **274** *via* a [2+2] cycloaddition. After this, the chlorosulfonyl group was removed using sodium carbonate and sodium sulfite to give the target 4-methyl-4-vinyl-1-azetidin-2-one **275** which was converted to the thiolactam **276** in the presence of Lawesson's reagent (LR). The

next step involved the alkylation of the thiolactam with trimethyl oxonium tetrafluoroborate to give 2-methylthio-4-methyl-4-vinyl-1-azetine **277** which was used for the next step (cyclopropenone reaction) without purification. As per previous work in the group with ethyl analogue, it is found that this gave cycloadduct **278** which rearranged to 7-azabicyclo[4.2.1]nonane **279**, as a result of an aza-Cope [3,3]-sigmatropic rearrangement. The reaction confirmed previous work in the group,[28a] provided another example and gave some material whose chemistry could be explored, unfortunately compound **279** was formed to be unreactive (*i.e.* stable to heat & not convertable to **280** by Wittig reaction).



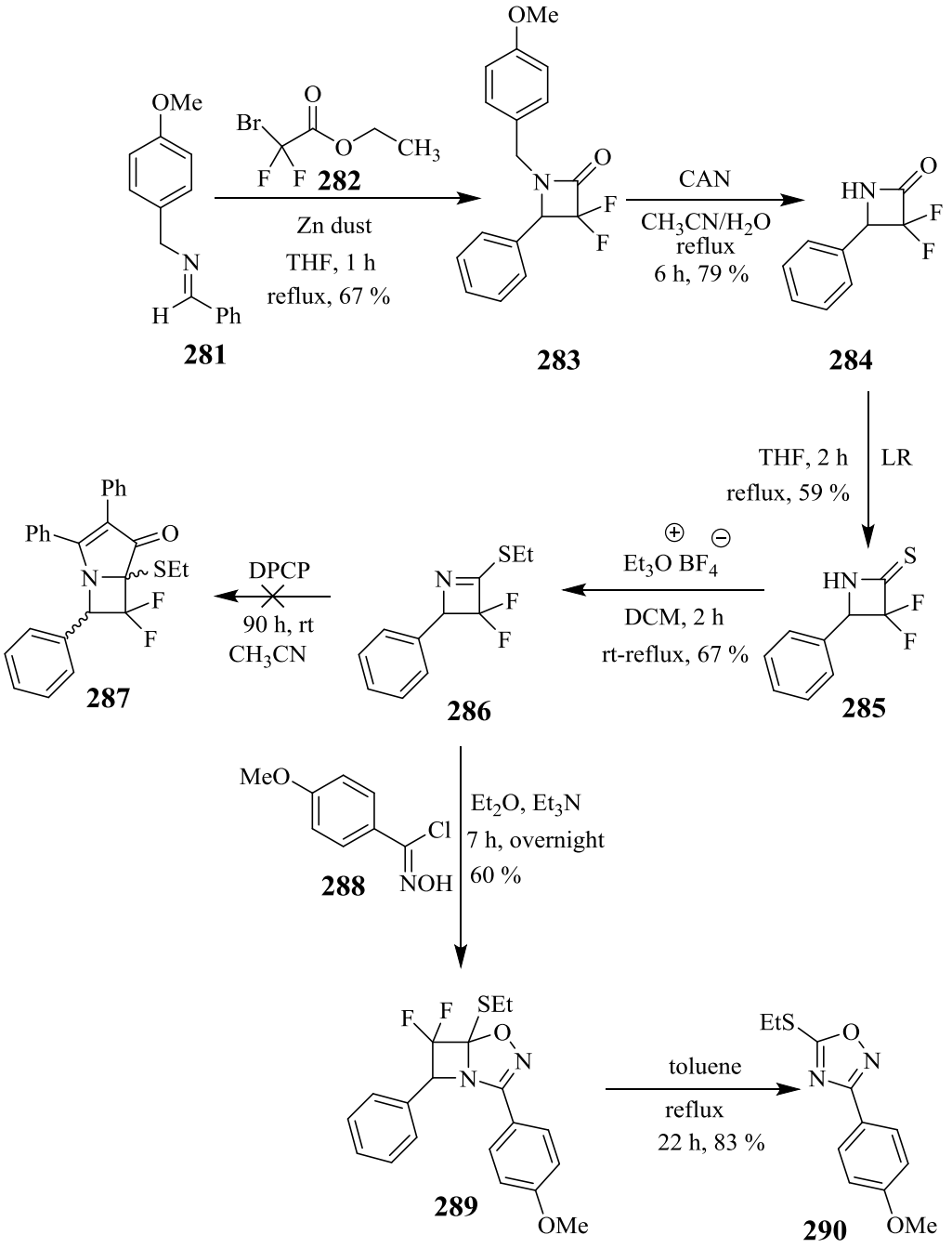
Scheme 2.9: Synthesis and suggested mechanism for the synthesis of **279**.

The ^{1}H NMR spectrum obtained for compound **279** showed signals for the four protons of the two methylene groups at 3.04, 2.90, 2.71 and 2.56 ppm and one signal at 5.32 ppm for CH of the alkene. The ^{1}H NMR spectrum also showed two peaks for the methyl groups at 2.03 and 1.65 ppm, respectively. The aromatic protons were observed between 7.57 - 7.06 ppm. The

number of carbons found in the ^{13}C NMR spectrum for compound **279** also matched with the structure.

2.9. Synthesis of F-containing cycloadducts and 1,2,4-oxadiazoles from a fluorinated 1-azetine

In order to see if fluorinated adducts of 1-azetines could behave in the same way as 1-azetines **257a-f**, a fluorinated 1-azetine was made. We hoped this would help us to further understand the pyridine mechanism suggested in **Scheme 2.8** above. Following a procedure adopted by Marcotte *et al*,[114] imine **281** was treated with ethyl bromodifluoroacetate **282** in the presence of freshly prepared zinc dust[115] to obtain the azetidinone **283.** Deprotection of the *p*-methoxybenzyl group of compound **283** with ceric ammonium nitrate (CAN) proceeded smoothly to give the required β-lactam **284**. After that, 3,3-difluoro-4-phenyl-1-azetidin-2-one **284** was reacted with Lawesson's reagent (LR) to produce the β-thiolactam **285** which was treated with triethyl oxonium tetrafluoroborate in dichloromethane to obtain 1-azetine **286**. The 4-ethylthio-3,3-difluoro-2-phenyl-1-azetine **286** was reacted with *p*-methoxyphenyl hydroximoyl chloride **288** to afford the 5-ethylthio-6,6-difluoro-2-(*p*-methoxyphenyl)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene **289** in 78 % yield. After that, the cycloadduct was heated in toluene to obtain the 1,2,4-oxadiazole **290**. Attempts were also made for the synthesis of cycloadduct **287** by the reaction of 4-ethylthio-3,3-difluoro-2-phenyl-1-azetine **286** with DPCP in acetonitrile at room temperature. This reaction was monitored by TLC and after 30 h there was shown a very slight indication of a new spot, yellowish in colour. Even after 90 hours, TLC revealed the dense spots of starting materials side by side with the faint new spot. Heating to reflux did not improve the reaction. No product could be isolated and the identity of the faint new spot could not be established.

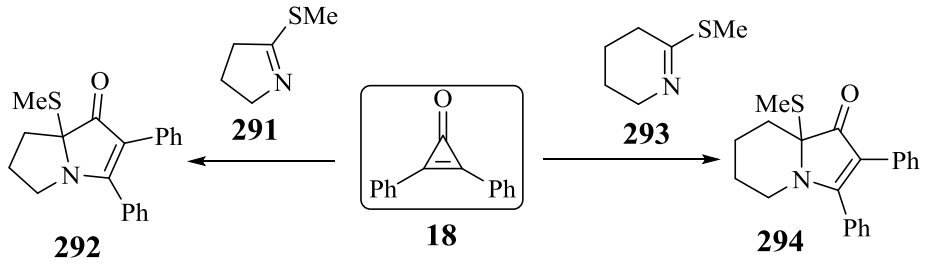


Scheme 2.10: Synthesis of cycloadduct and 1,2,4-oxadiazole.

The NMR data of 1,2,4-oxadiazole **290** was matched with that previously reported in the literature,[106] whereby our group had made the same compound from the corresponding non-fluorinated analogue.

2.10. Synthesis of cycloadducts from the reaction of 5 & 6-membered cyclic imines with diphenylcyclopropenone

The aim of this section of the work is to synthesise a range of cyclic imines in order to obtain the cycloadducts *via* a formal [3+2] cycloaddition route after treatment with cyclopropenones (DPCP, DTCP and DACP). 5-(methylthio)-3,4-dihydro-2*H*-pyrrole **291** and methylthio tetrahydropyridine **293** are five- and six-membered ring cyclic imines which were synthesised from their corresponding thiolactams following the published procedure in the literature.[28b, 113]

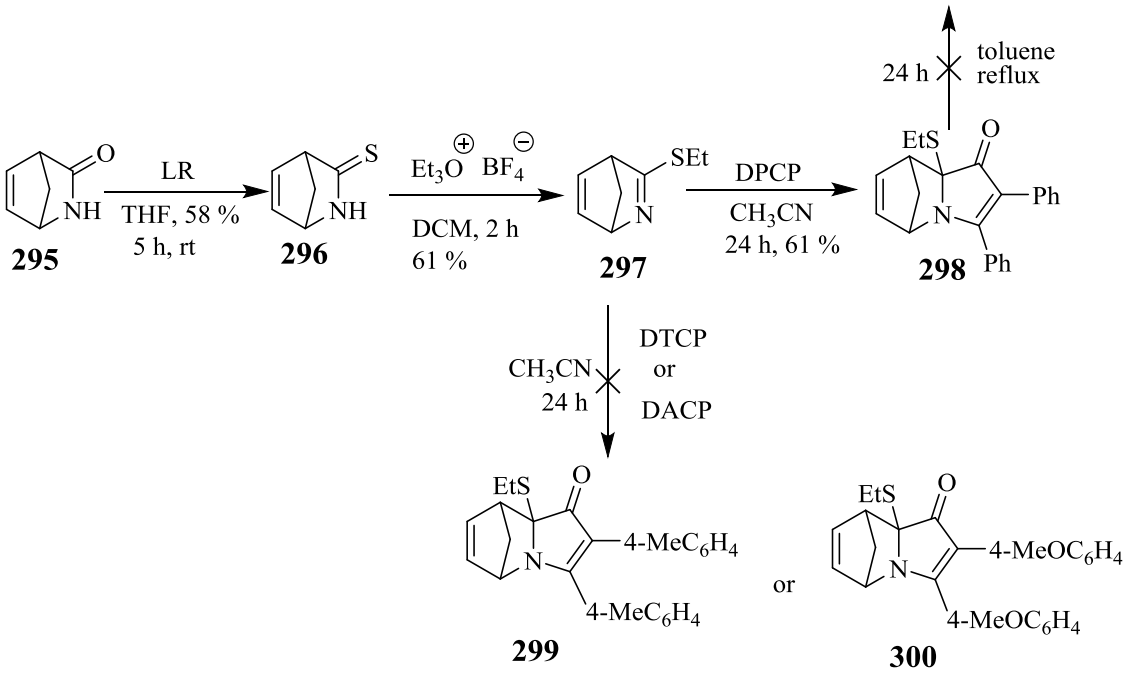


Scheme 2.11: A formal [3+2] cycloaddition reaction of DPCP.

The cyclic imines **291** & **293** were reacted with DPCP to obtain the pyrrolo-ring cycloadducts **292** and **294** and the data was matched with that previously reported by our group.[28b,113] Unfortunately cyclic imines **291** and **293** did not react with ditolylcyclopropenone or dianisylcyclopropenone and the starting materials were observed at the end of reactions.

A new cyclic imine, 3-ethylthio-2-azabicyclo[2.2.1]hept-2,5-diene **297**, was also synthesised from the commercially available lactam, 2-azabicyclo[2.2.2]hept-5-en-2-one **295**, which was converted to thiolactam **296** in the presence of Lawesson's reagent. The thiolactam was treated with triethyloxonoium tetrafluoroborate to give the azacycloheptadiene **297**. This cyclic imine was treated with cyclopropenones (DPCP, DTCP and DACP) in order to attempt to form the cycloadducts *via a* formal [3+2] cycloaddition reaction but unfortunately it gave only results with DPCP. The other cyclopropenones (DTCP and DACP) again showed no reaction and starting materials were recovered. However, the reactivity of the cycloadduct **298**

was explored by heating it in toluene. TLC showed no indication of reaction and only starting material **298** was observed by NMR analysis. It was hoped that compound **298** might undergo a retro [4+2] cycloaddition to generate the azacyclopentadienone seen above **(Scheme 2.8)**, but no evidence for this was seen.



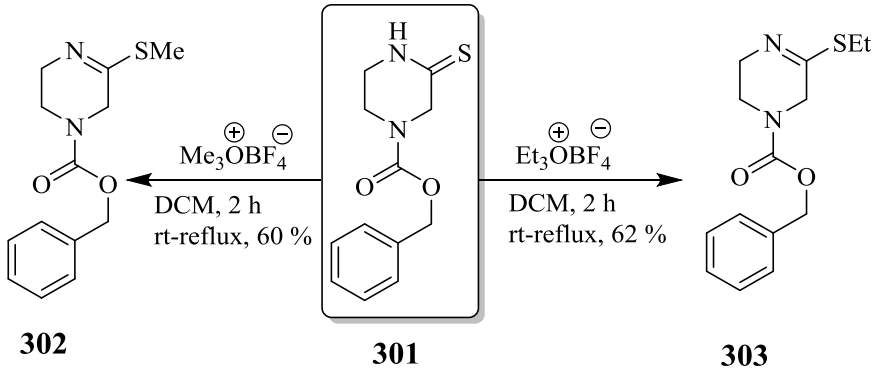
Scheme 2.12: Formal [3+2] cycloaddition reaction of azabicycloheptadiene.

The ^{1}H NMR spectrum obtained for azacycloheptadiene cycloadduct **298** showed the methyl group as a triplet at 1.34 ppm whilst the peak for methylene group attached to the methyl group appeared as a multiplet between 2.76 - 2.61 ppm. The CH directly attached to the nitrogen atom and the CH attached to the C-S appeared as multiplets between 4.01 - 3.94 and 3.41 - 3.39 ppm, while the two protons of the CH_2 group appeared as two sets of multiplets between 1.93 - 1.81 and 1.71 - 1.65ppm, respectively. The proton peaks of the alkene appeared as two sets of doublets of doublets at 6.69 and 6.50 ppm having coupling constants (J = 5.3 and 2.9 Hz). The spectrum also showed the signals of the two phenyl groups between 7.43 - 7.05 ppm. The ^{13}C NMR spectrum obtained for compound **298** showed the carbon signal for the C=O group at 201.0, two carbon peaks for CH_2 at 44.1 and 22.9 pm and the

carbon peak for CH_3 at 14.1 ppm. The assigned structure of the new compound **298** was also supported with the help of MS.

2.11. Reactivity of cyclic imines containing two heteroatoms in the ring with cyclopropenone

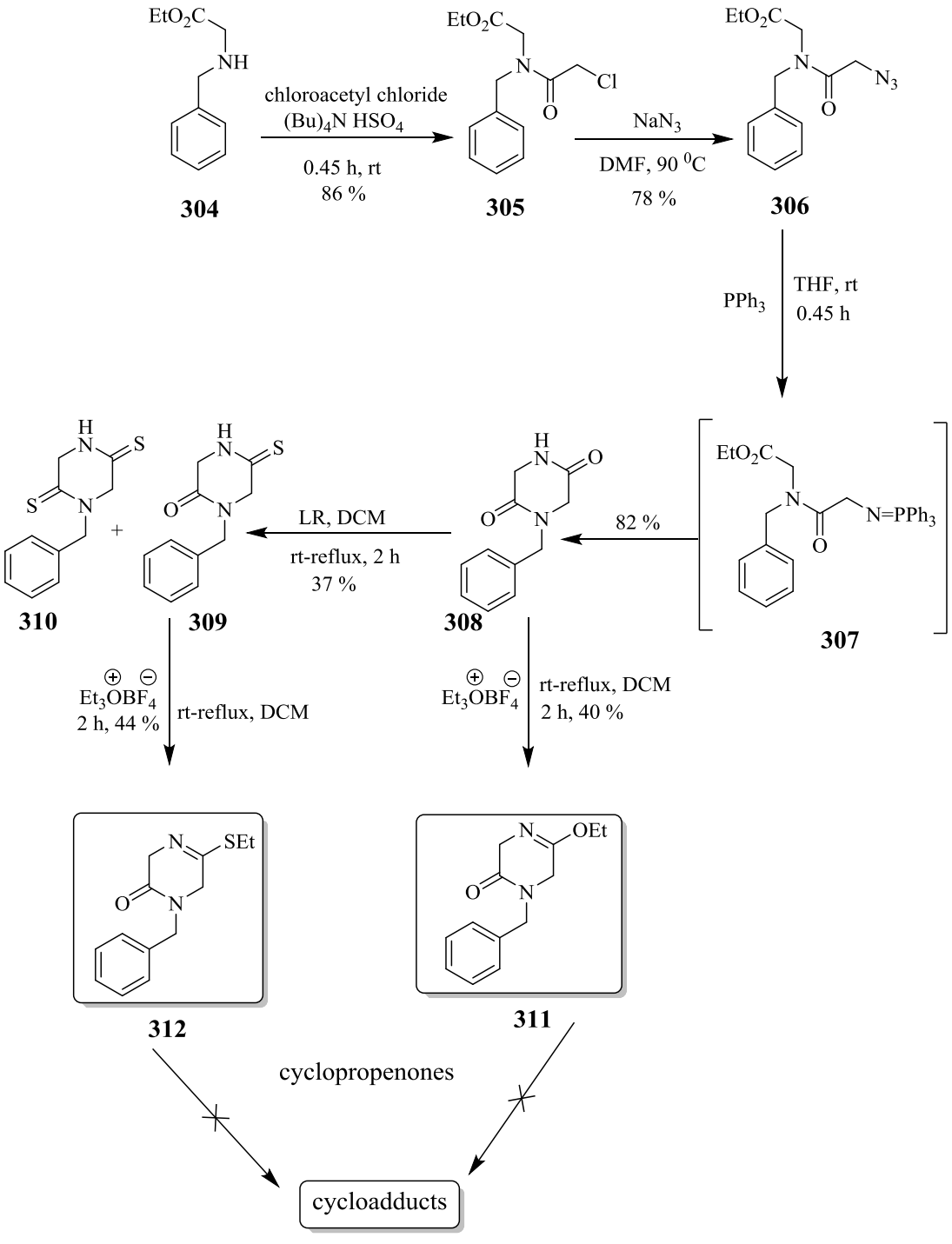
The synthesis of cyclic imines was obtained that contained another heteroatom. The cyclic imines **302** and **303** were synthesised from the commercially available lactam *via* convertion to the thiolactam **301**. These pyrazines were unreactive towards diphenylcyclopropenone, dianisylcyclopropenone or ditolylcyclopropenone under many different reaction conditions.



Scheme 2.13: Synthesis of cyclic imines.

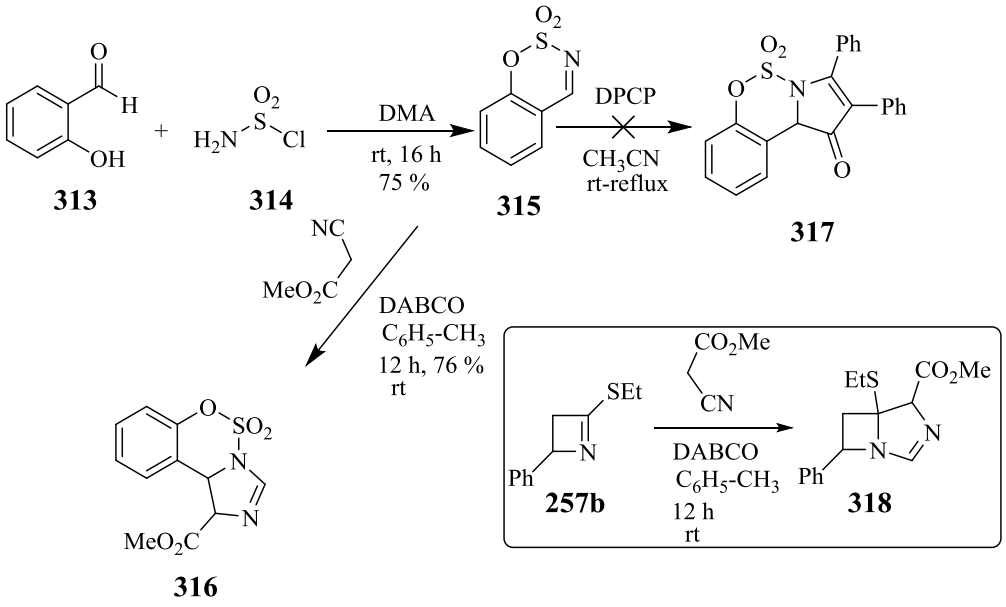
Also prepared as part of this investigation were the pyrazinones **311** and **312** as shown in **Scheme 2.14**. Looking at **Scheme 2.14**, the preparation of *N*-chloroacetyl-*N*-benzylglycine ethyl ester **305** was achieved by the reaction of chloroacetyl chloride with *N*-benzylglycine ethyl ester in the presence of tetrabutyl ammonium hydrogen sulfate and after that it was converted to *N*-azidoacetyl-*N*-benzylglycine ethyl ester **306**.[73] Azide **306** was reacted with triphenyl phosphine in wet THF to give the iminophosphorane as an intermediate which cyclised to give 1-benzylpiperazin-2,5-dione **308**. After that, the 1-benzylpiperazine **308** was thionated in the presence of Lawesson's reagent to obtain the thiolactam product **309.** The product 1-benzylpiperazin-2,5-dithione **310** was also obtained as a side product during formation of compound **309.** 1-Benzylpiperazin-2,5-dione **308** and 1-benzyl-5-thioxopiperazine-2-one **309** were converted to cyclic imines **311** & **312** after treatment with

triethyloxonium tetrafluoroborate. These pyrazinone cyclic imines were found to be unreactive towards DPCP, DTCP and DACP and only starting materials were recovered.



Scheme 2.14: Synthesis of cyclic imines and attempted synthesis for cycloadducts.

The benzoxathiazine **315** was synthesised and explored its reactivity. The synthesis of benzoxathiazine-2,2-dioxide **315** has been reported by Y. Liu *et al*[116a] by the reaction of salicylaldehyde **313** with freshly prepared sulfamoyl chloride **314** in DMA as shown in **Scheme 2.15**. The reaction was repeated and then attempted to react compound **315** with cyclopropenones. No successful reactions were observed. Guo *et al.*[116b] reacted compound **315** with isocyanoacetate to form the imidazoline **316.** The reaction of isocyanoacetate with 1-azetines **256b** was attempted under Guo's conditions but again observed no successful reactions, and were unable to form bicyclic **318**.



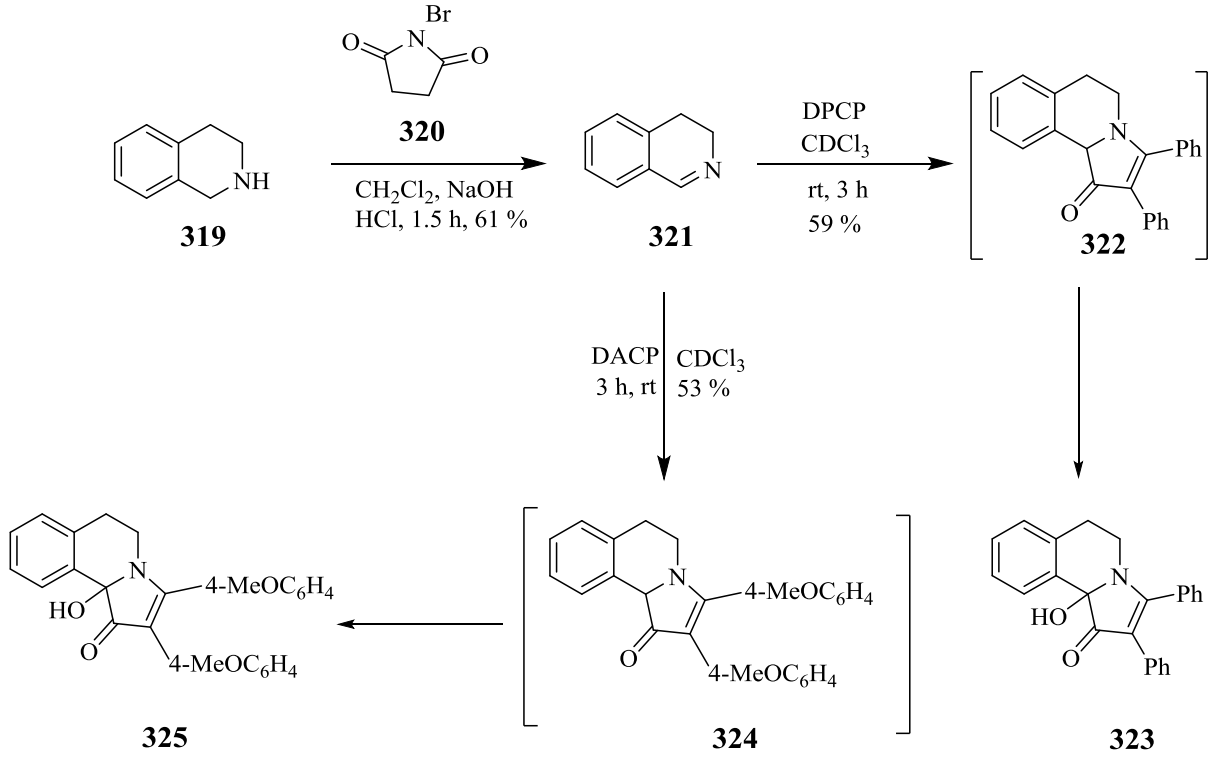
Scheme 2.15: Synthesis of benzoxathiazine and its attempted reactions.

2.12. Synthesis of pyrrolo-isoquinoline alkaloids from the reactions of cyclopropenones with 3,4-dihydroisoquinolione cyclic imines

Next we decided to look at some benzo-fused cyclic imines. As shown in **Scheme 2.16**, the first step was the reaction of 1,2,3,4-tetrahydroisoquinoline **319** with *N*-bromosuccinimide followed by treatment with 30 % sodium to obtain the target 3,4-dihydroisoquinoline **321** after loss of HBr.[117] After this, diphenylcyclopropenone was reacted with 3,4-dihydroisiquinoline **321.** The reaction mixture was monitored by TLC and even after 10

minutes, the starting cyclic imine and cyclopronenone had disappeared and a new spot emerged on the TLC plate. After this, the solvent was removed under reduced pressure but unfortunately no product could be identified. The same reaction was repeated but this time the reaction was performed in deuterated chloroform and followed by ^{1}H NMR analysis.

The expected product **322** could not be seen but it was clear that a very similar product had formed. After 3 h in Deuterated chloroform, this new product could be isolated and was identified as the hydroxy compound **323** formed in 50 % yield. DACP behaved the same and reacted with imine **321** to give compound **325** in 53 % yield.

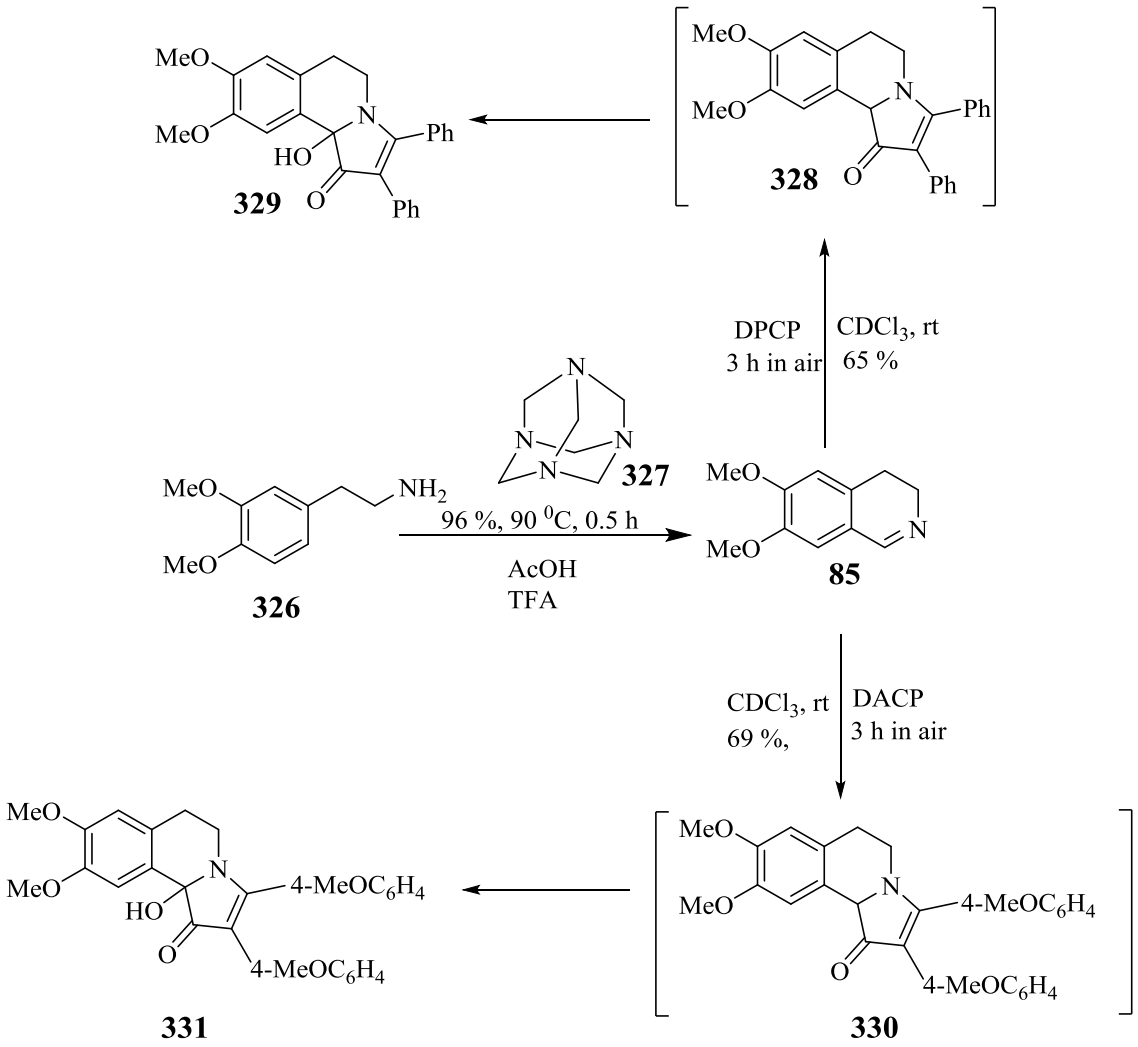


Scheme 2.16: Synthesis of pyrrolo-isoquinoline derivatives.

The ^{1}H NMR spectrum for compound **323** showed all 14 aromatic protons between 8.07 - 6.91 ppm. The proton signals of the methylene next to nitrogen showed as two sets of doublets of doublets at 3.82 and 3.78 ppm with the other methylene group showing one proton at 3.54 ppm and the other as a multiplet between 2.63 - 2.47 ppm overlapping with the OH. The ^{13}C NMR spectrum recorded for compound **323** showed a signal for the C=O group

at 198.1 ppm, two carbon signals for CH_2 at 40.7 and 29.3 ppm, respectively. The carbon spectrum also revealed ten carbon peaks for CH and eight for quatenary carbon including the alcohol at 85.7ppm which helped to determine the structure of **323**. The structure of compound **323** was also established through MS(ESI)$^+$: *m/z* [M + H] 354.1 and consistent HRMS which confirmed the additional oxygen atom. The IR spectrum further helped to assign the structure with the OH at 3256 cm^{-1}. The data of compound **325** was characterised in a similar way and all data was consistent with the structure of compound **325**, including the diagnostic OH.

In order to get some further examples of this process, the 6,7-dimethoxy-3,4-dihydroisoquinoline **85** was synthesised according to the published procedure[44] as shown in **Scheme 2.17**. The reaction behaviour of this cyclic imine **85** was determined to be similar to 3,4-dihydroisoqinoline with both diphenylcyclopropenone and 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **(Scheme 2.17)**. It was again noted that the products had an OH at the bridgehead rather than the expected H and **(Figure 2.15)** proposes a mechanism.[5, 29] The mechanism proposes that the hydroxy pyrrole **336** readily picks up O_2 to form hydroperoxide **337**[29] which can then cleave to give the observed product **329**.



Scheme 2.17: Synthesis of pyrrolo-isoquinoline.

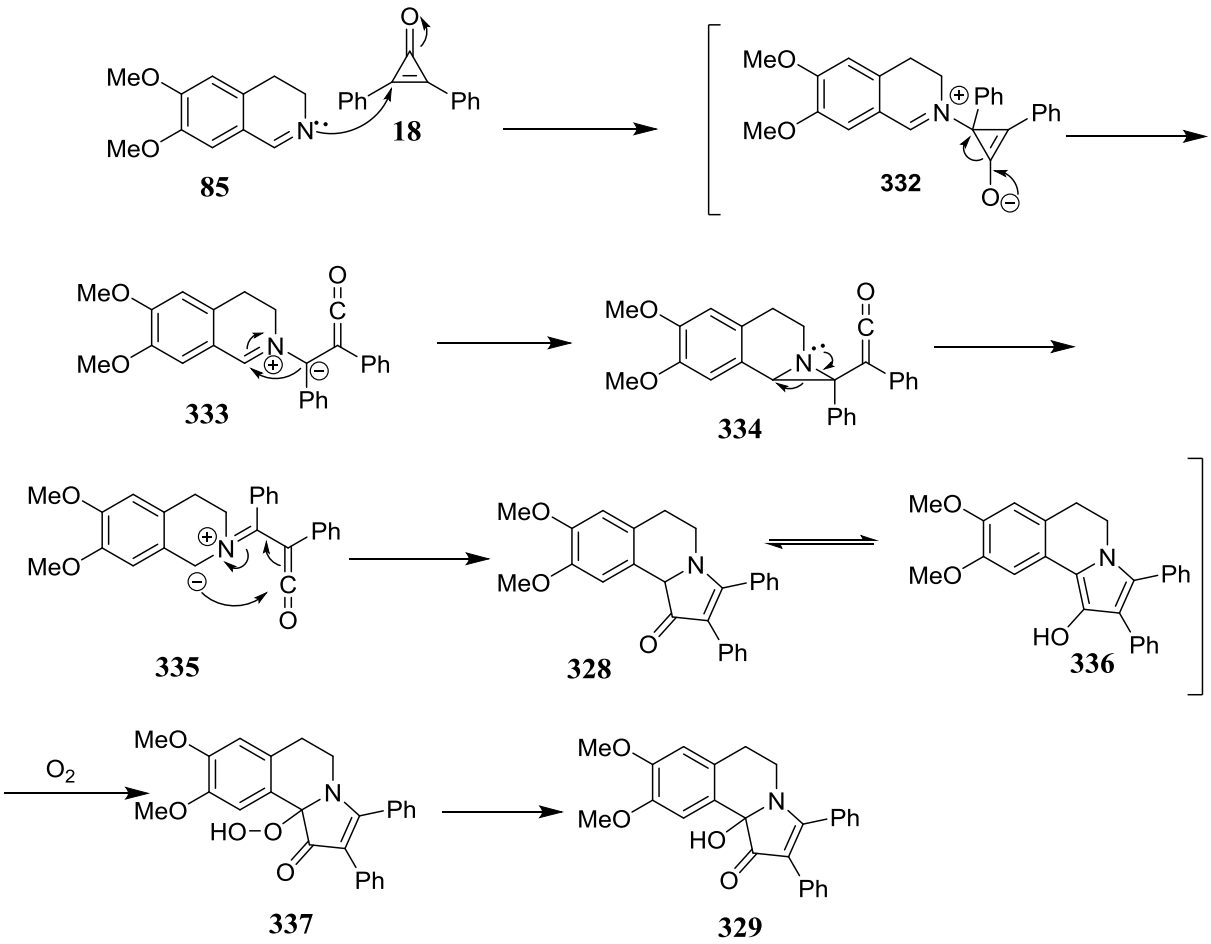
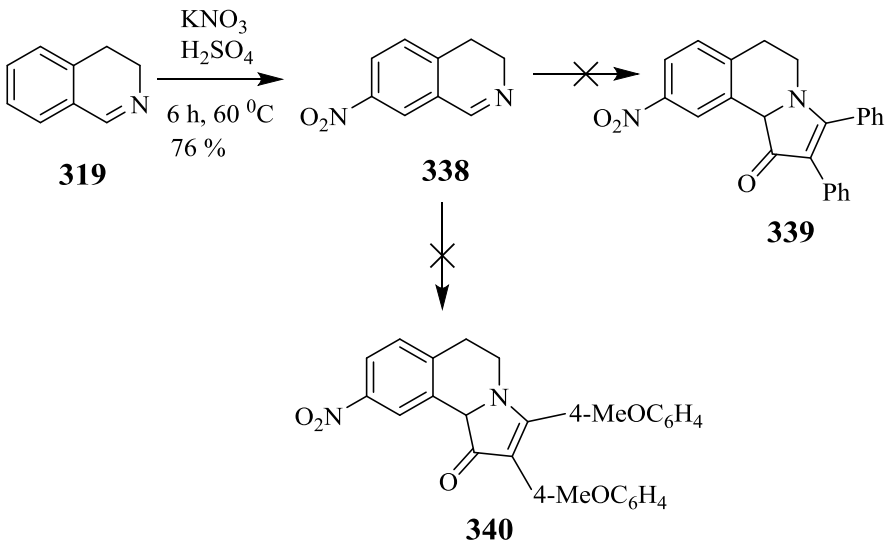


Figure 2.15: Proposed mechanism for formation of the pyrrolo isoquinolines with OH group.

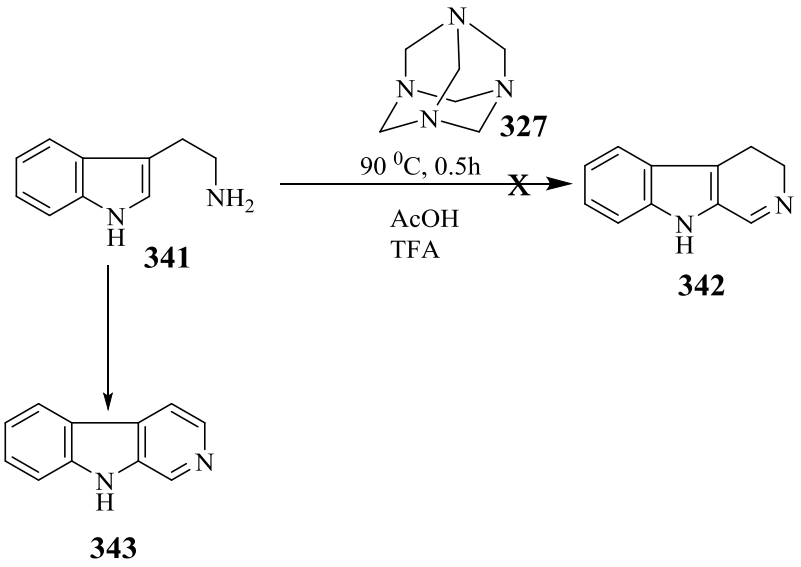
7-Nitro-3,4-dihydroisoquinoline **338** was synthesised using KNO_3 with 3,4-hydroisoquinoline **338**.[117] However, when diphenylcyclopropenone, dianisylcyclopropenone or ditolylcyclopropenone were mixed with cyclic imine 7-nitro-3,4-dihydroisoquinoline **338**, no reaction was observed. It may be the case that the electron rich **85** promotes reaction but the electron poor **338** stops it.



Scheme 2.18: Synthesis of isoquinoline imine and its attempted cycloaddition reactions.

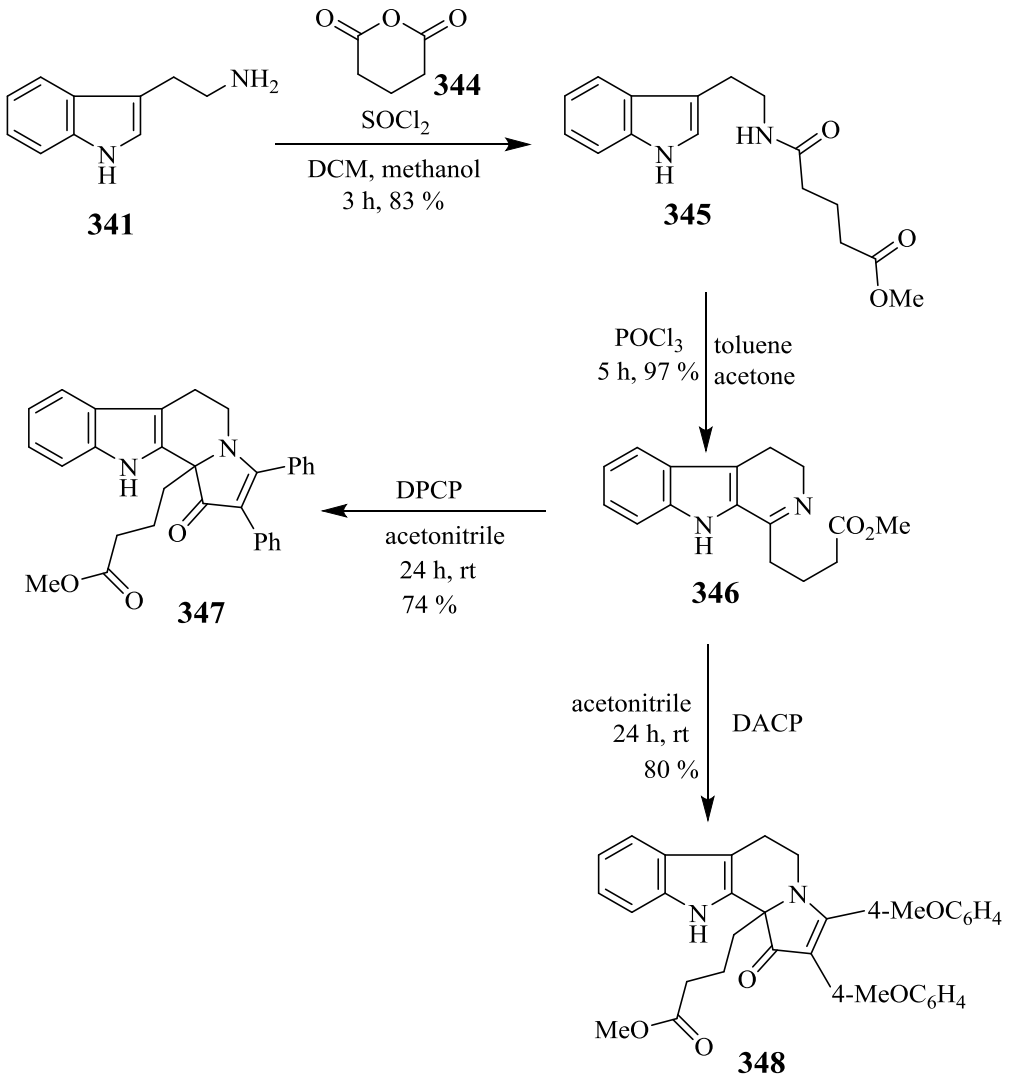
2.13. Synthesis of pyrrolo-indoles from the reactions of cyclopropenones with 3,4-β-carboline cyclic imines

β- and γ-carboline alkaloids are interesting targets due to their biological roles and potential in medicinal chemistry.[118,119] With this in mind, we were interested in the synthesis of these indole scaffolds. Pictet Spengler condensation is a common route for the synthesis of indole and isoquinoline alkaloids,[120] and so we used a route based on this for the attempted synthesis of cyclic imine **342.** However, the formation of 9*H*-pyrido[3,4-*b*]indole **343** was observed instead of the desired cyclic imine **342**. Compound **343** is known in the literature[121] and is not useful for our cycloaddition studies because aromatic C=N systems do not react.



Scheme 2.19: Attemted synthesis for 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole cyclic imine.

In order to make an imine that would be suitable for a formal [3+2] cycloaddition reaction, we used tryptamine **341** and converted it into the amide **345** by reaction with glutaric anhydride **346**. Bischler-Napieralski ring closure[122] then gave the known imine **346**. Compound **346** was then treated with the cyclopropenones DACP, DPCP and DTCP, respectively. DPCP and DACP showed successful reactions and gave the cycloadducts **347** and **348** which were isolated in 74 % and 80 % yield, respectively. DTCP did not react. Imine **346** was chosen because it was available from trypamine **341** as shown in **Scheme 3.20** and because it has a substituent that would block the brigehead OH formation seen in **Schemes 2.15** and **2.16**, above.



Scheme 2.20: Synthesis of pyrrolo-indole alkaloids.

The mechanism involved for the synthesis of cyclic imine **346** is as shown in **Figure 2.16**[122] and the proposed mechanism for the formation of cycloaddition product **347** has already been discussed above (p73).

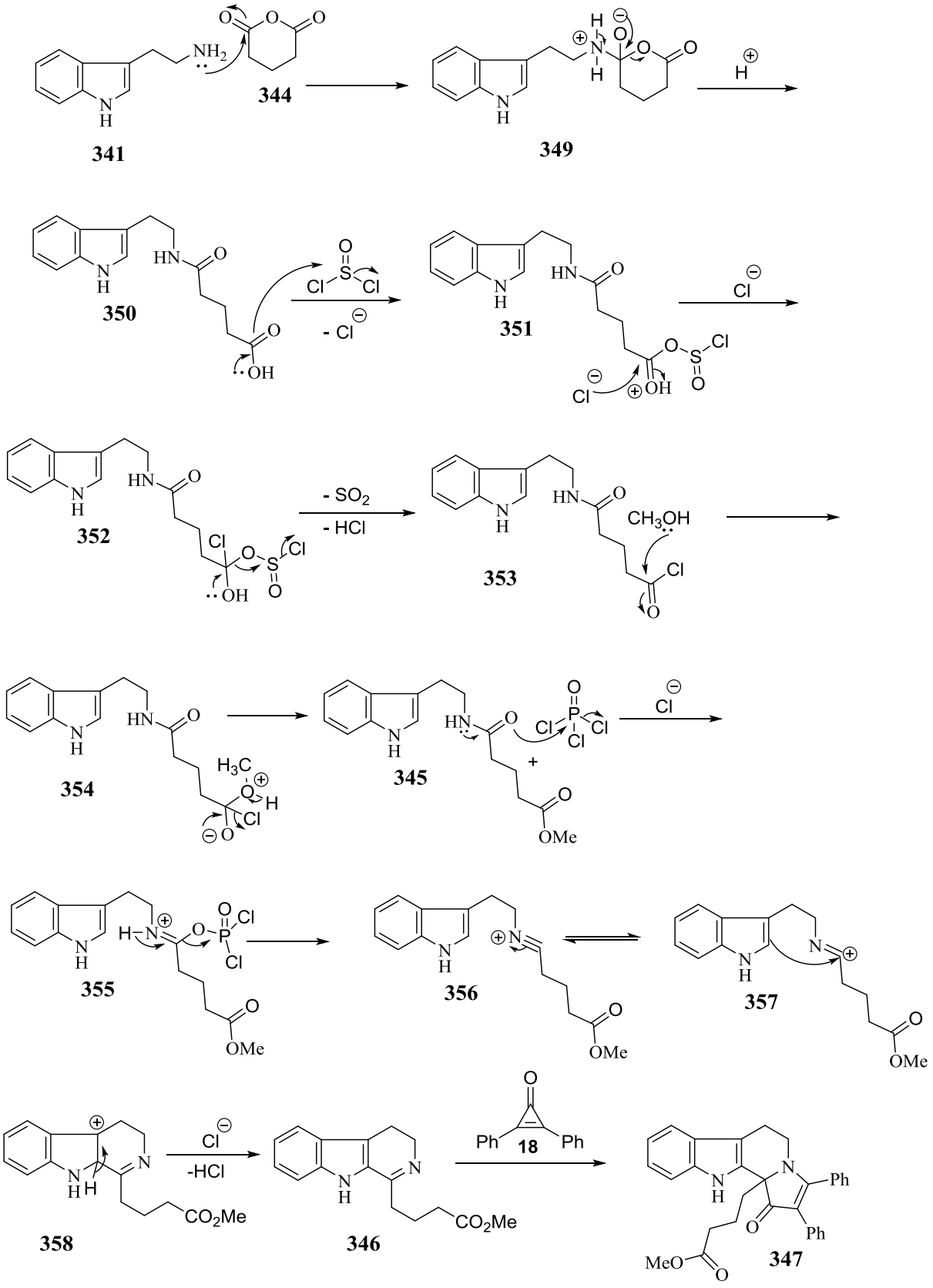
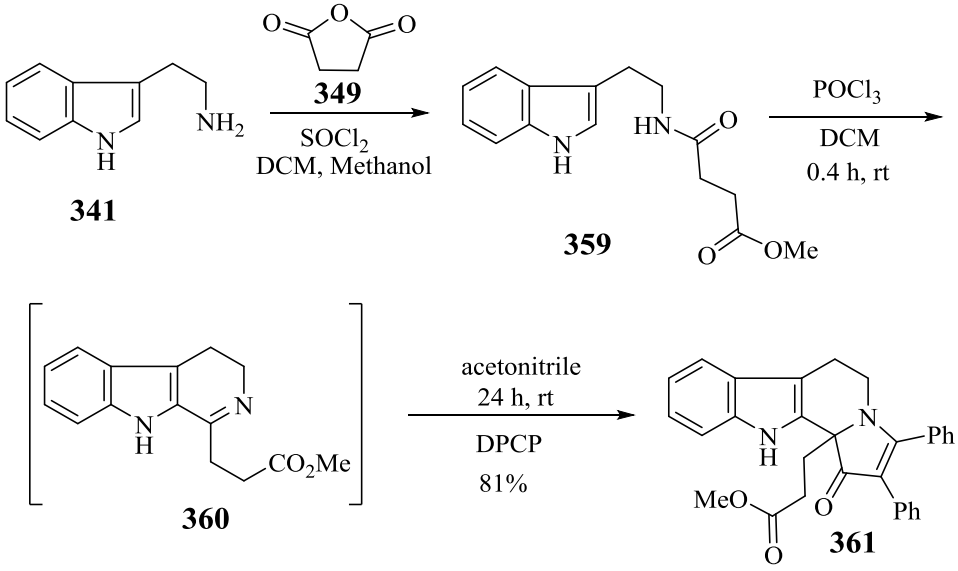


Figure 2.16: Mechanism for the synthesis of cyclic imine **346**.

The data for amide **345** and cyclic imine **346** are matched with that previously reported in the literature.[122] The structure of compound **347** was confirmed by analytical techniques. The ^{1}H NMR spectrum of **347** showed the presence of the indole (NH) at 8.97 ppm and the other aromatic protons between 7.55 - 7.05 ppm. The ^{1}H spectrum for compound **347** also revealed the methylene (CH_2) signals and methoxy peak towards the upfield region of the spectrum. The ^{13}C NMR spectrum for this product also showed the methylene peaks at 41.6, 36.7, 33.7, 22.3 and 19.1 ppm and the methoxy group at 69.9 ppm. A total of 11 quaternary carbons including the two carbonyls and the bridgehead sp^3 carbon were seen along with the expected number of aromatic CH signals. The IR spectrum also showed the absorbance peaks for the amine and carbonyl groups which are consistent with the structure of compound **347**. The structure of **347** was also consistent with data obtained from high resolution mass spectrometry.

The tryptamine **336** was also reacted with succinic anhydride **349** in the presence of thionyl chloride to produce the amide ester **359** which was converted into imine **360** and reacted with DPCP to give the cycloadduct **361**. The structure of the compound **361** was confirmed by analytical techniques.



Scheme 2.21: Synthesis of pyrrolo-indole derivative.

The ^{1}H NMR spectrum for compound **361** showed a signal for the indole NH proton at 9.27 ppm and signals between 7.56 – 7.11 ppm for the fourteen aromatic protons. The peaks corresponding to eight methylene protons were found between 4.09 – 2.44 ppm and a singlet peak depicted the OCH_3 protons at 3.76 ppm in the proton spectrum of **361 (Figure 2.17).**

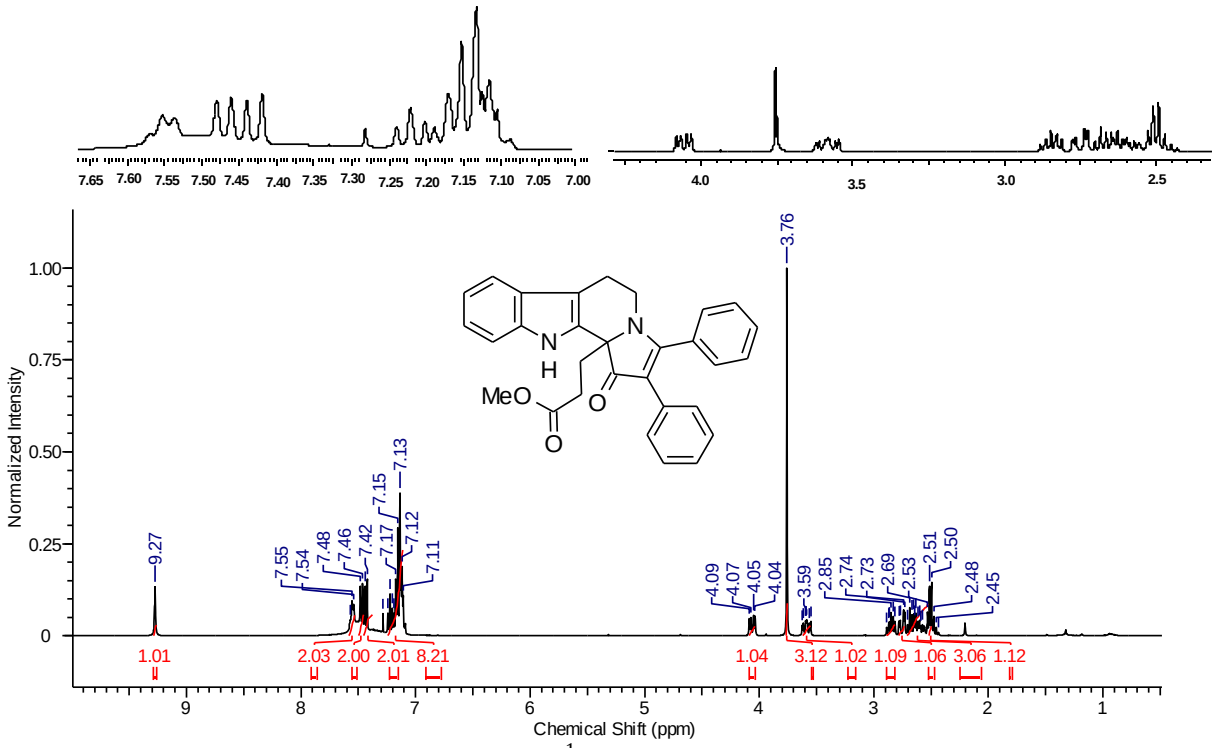


Figure 2.17: ^{1}H spectrum of **361**.

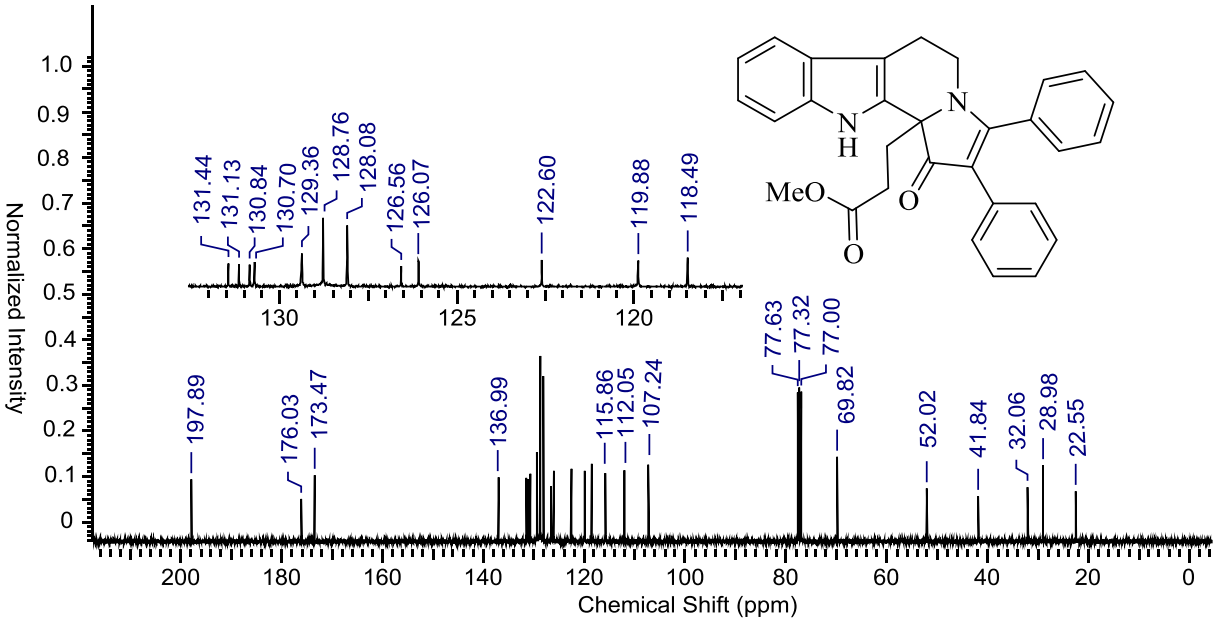
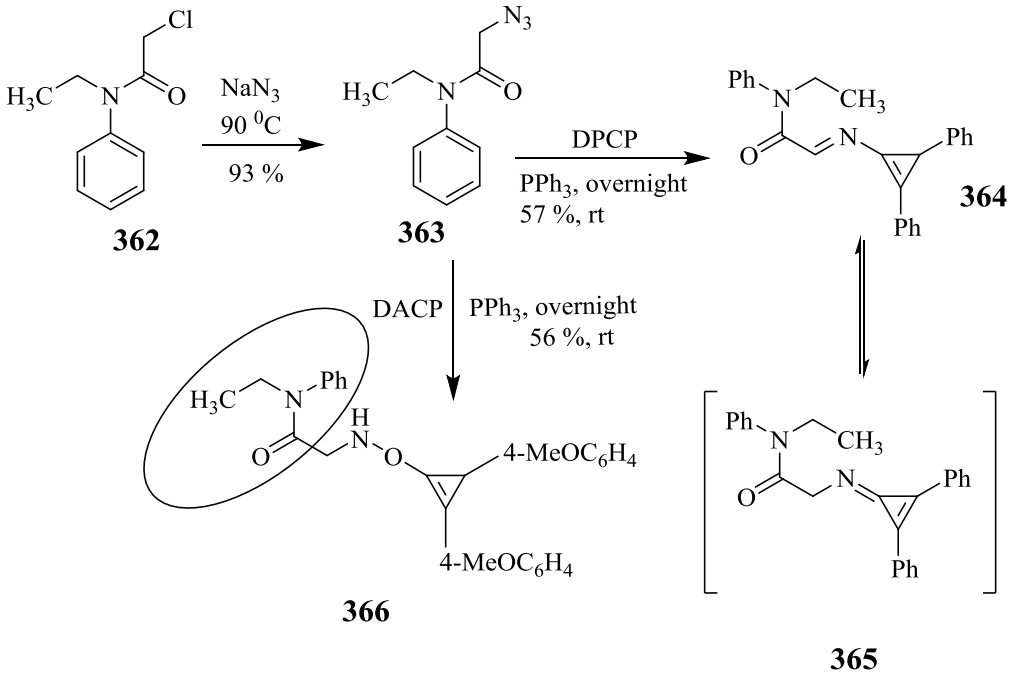


Figure 2.18: ^{13}C spectrum of **361**.

The ^{13}C NMR spectrum recorded for this compound **(Figure 2.18)** showed a signal at 52.0 ppm for the methyl peak of OCH_3, while the signals corresponding to the two carbonyl groups (C=O) were found at 197.8 ppm and 173.4 ppm, respectively. The carbon spectrum also revealed the four methylene carbon peaks at 41.8, 28.9 and 22.3 ppm, respectively. The ^{13}C spectrum recorded for this compound also showed the quaternary and aromatics peaks which are consistent with the structure of compound **361**. The structure of compound **361** was also confirmed by MS $(ESI)^+$: m/z [M+H] 463.2 and consistent HRMS. The IR spectrum recorded for compound **361** showed an absorbance peak at 3269 cm^{-1} for the N-H bond. The IR spectrum also showed an absorbance at 1744 cm^{-1} and at 1639 cm^{-1} for the ester and ketone carbonyl groups, respectively.

2.14. Reactivity of azide-terminal containing compounds with cyclopropenones

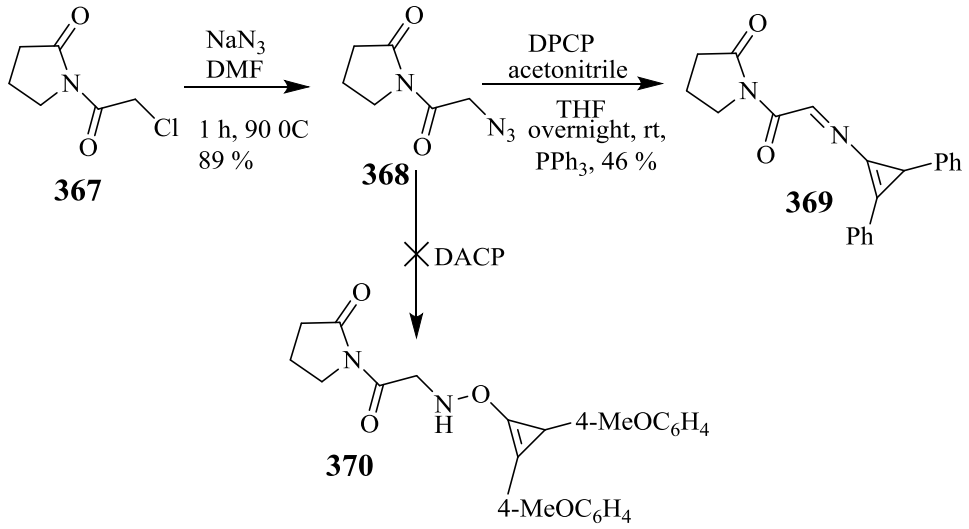
The aim of this part of the work was to combine our interest in cyclopropenones and imine formation by reacting cyclopropenones with iminophosphoranes using the aza-Wittig reaction. For this purpose, azide compounds were synthesised in order to give the required iminophosphorane intermediates after treatment with triphenylphosphine. For the azide synthesis, the initial step was the reaction of *N*-ethylaniline with chloroacetyl chloride in the presence of tetrabutylammonium hydrogen sulfate to give the 2-chloro-*N*-ethyl-*N*-phenylacetamide **362** which was converted to 2-azido-*N*-ethyl-*N*-phenylacetamide **363** after treatment with sodium azide **(Scheme 2.22)**. The iminophosphorane[73] intermediate was obtained after reaction of azido compound **363** with PPh_3 which was converted into the product **364** in the presence of diphenylcyclopropenone, which is a tautomer of the expected product **365**. When the iminophosphorane intermediate was treated with dianisylcyclopropenone, a different reaction was seen and the product was tentatively assigned the structure **366**, as discussed below.



Scheme 2.22: Reactivity of cyclopropenones with azide-terminal substrate.

The ^{1}H NMR signals for the CH_2 and CH_3 for the compound **364** were observed at 3.59 and 1.17 ppm, respectively. One proton peak for CH of **364** appeared as a singlet at 6.74 ppm, whilst the other sixteen CH protons were observed between 7.56 - 6.95 ppm. The ^{13}C NMR spectrum recorded for this compound showed a carbon signal for the C=O group at 155.4 ppm. The ^{13}C spectrum also showed a carbon peak for the CH_2 at 46.0 ppm whereas the carbon peak for CH_3 appeared at 12.9 ppm. Only one CH_2 was present-fully consistent with compound **364**. There were also observed eleven carbon peaks for CH and five quaternary carbons in addition to the C=O. The structure of compound **364** was also confirmed by mass spectrometry MS $(ESI)^+$: m/z [M+H] 367.2 and consistent HRMS. Finally, an IR spectrum recorded for **364** showed an absorbance peak at 1686 cm^{-1} for C=O group. The structural part of compound **366** which is shown in a circle **(Scheme 2.22)** was similar to compound **364** but DEPT135 analysis revealed an additional CH_2 group. One carbonyl, two OCH_3 and one CH_3 signals were present in the ^{13}C NMR spectrum of compound **366**. This spectrum also showed eight CH and seven quaternary carbon peaks plus the C=O group at 167.7 ppm. The assigned structure of compound **366** was also consistent with results obtained by mass spectrometry

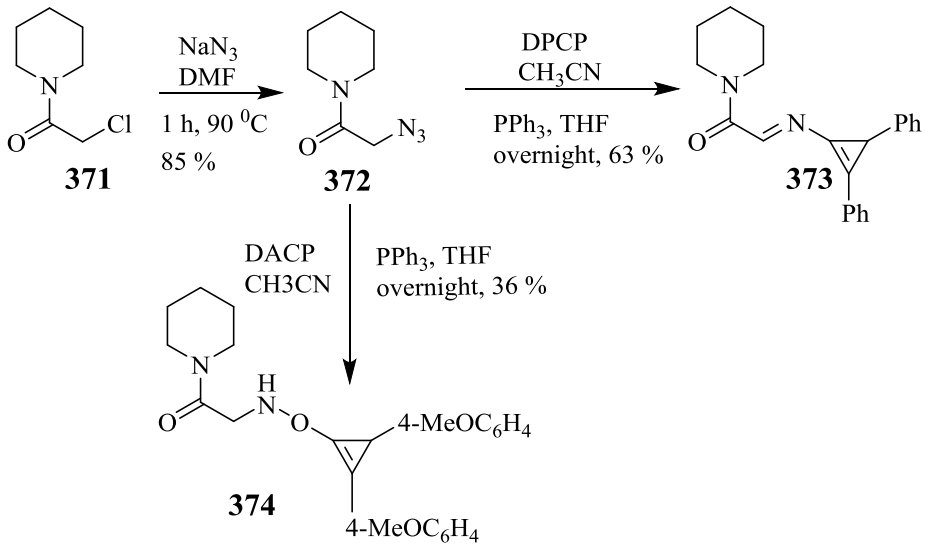
confirming the extra oxygen atom and IR analysis, which showed the NH at 3369 cm^{-1}. The suggested mechanism for the formation of compound **366** will be discussed later in this thesis. The formation of compound **366** and especially of the proposed structure **366** was unsual and so more examples were sought. So, as shown in **Scheme 2.23**, the 1-(2-chloroacetyl)pyrrolidin-2-one **367** was synthesised from 2-pyrrolidinone as starting material.[123] Following a procedure by Takeuchi *et al*,[124] 1-(2-chloroacetyl)pyrrolidin-2-one **367** was reacted with sodium azide in dry dimethylformamide to give the required azide **368**. After this, azide **368** was treated with triphenylphosphine in THF and then after 45 minutes, the intermediate iminophosphorane was reacted with diphenylcyclopropenone to give the predicted compound **369.** When the intermediate iminophosphorane was mixed with DACP, the reaction was complex and we could not identify any product **(eg 370)** from the reaction mixture.



Scheme 2.23: Reactivity of cyclopropenones with 1-(2-azidoacetyl)pyrrolidin-2-one.

Next, 2-chloro-1-(1-piperidyl)ethanone **371** was synthesised according to a published procedure,[73] then reacted with sodium azide to obtain the required compound **372** as shown in **Scheme 2.24**. After this, 2-azido-1-(1-piperidyl)ethanone **372** was reacted with triphenylphosphine and the iminophosphorane intermediate was reacted with diphenylcyclopropenone or dianisylcyclopropenone, respectively, to get the compounds **373**

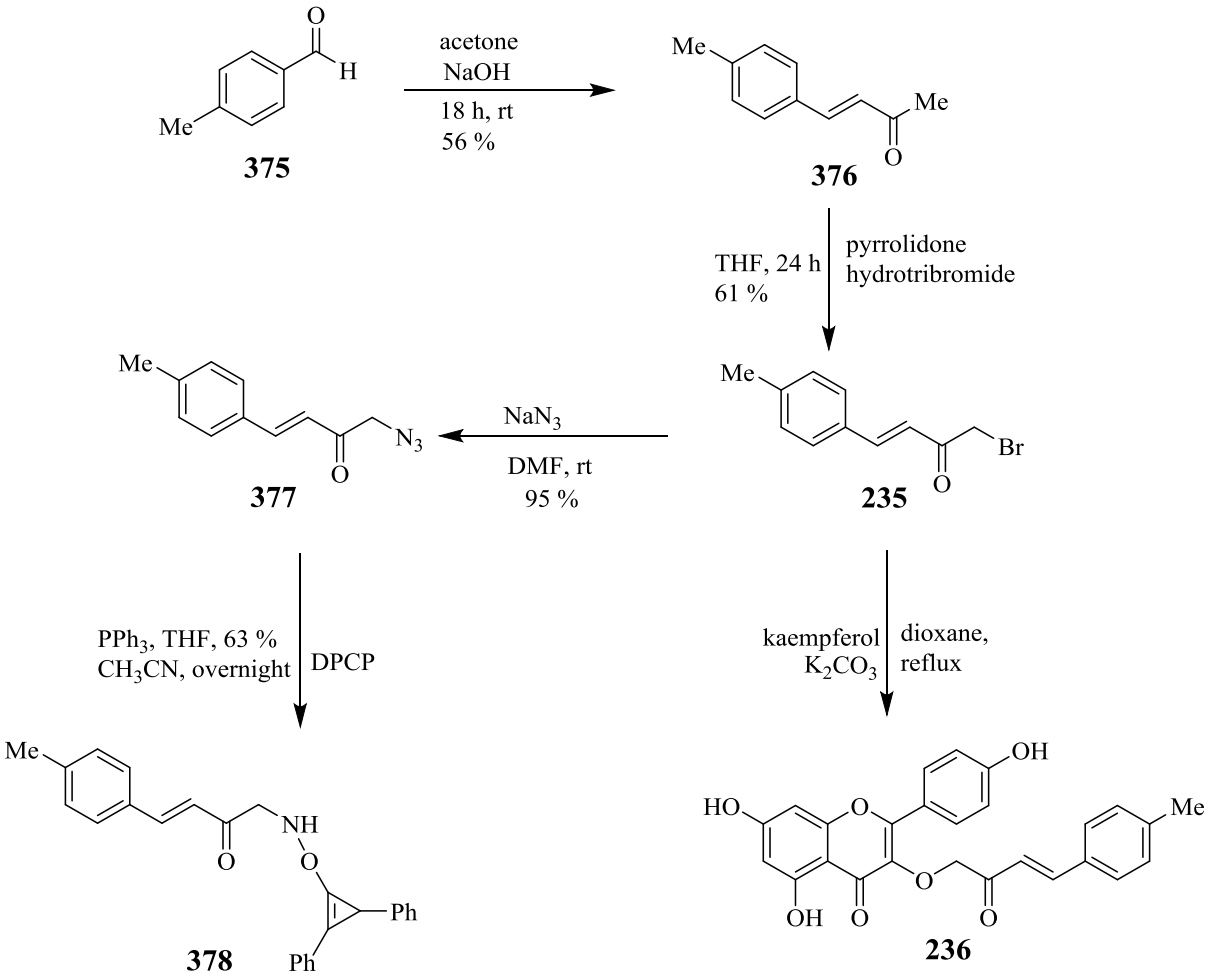
and **374**. In this process, both DPCP and DACP behaved exactly as per **Scheme 2.24**, giving the products **373** and **374**.



Scheme 2.24: Reactivity of cyclopropenones with 2-azido-1-(1-piperidyl)ethanone.

The data for compound **373** was straightforward. For compound **374**, the ^{1}H NMR showed the NH at 6.04ppm. The ^{13}C NMR showed the CH_2 that is next to the NH as well as the the correct number of CH and Cq signals. The data was consistent and so the tentative structure **374** is assigned. To get furthur examples and to help verify this unexpected reaction, (*E*)-4-(*p*-tolyl)but-3-en-2-one **376** was synthesised by the reaction of *p*-tolualdehyde **375** with acetone in a Claisen-Schmidt reaction.[125] Following a procedure by Babu *et al*,[126] α,β-unsaturated ketone **376** was reacted with pyrrolidone hydrotribromide in dry THF to give the (*E*)-1-bromo-4-(*p*-tolyl)but-3-en-2-one **235** as shown in **Scheme 2.25**. Compound **235** was reacted with sodium azide to obtain the required azido-compound **377** which was treated with triphenylphosphine in THF to obtain the iminophosphorane intertemediate. After 45 minutes, a solution of diphenylcyclopropenone in acetonitrile was added to the iminophosphorane. This time, a product consistent with hydroxylamine **378** was obtained unlike when diphenylcyclopropenone was reacted in **Scheme 2.22 - 2.24**, above. With DACP, this iminophosphorane intermediate gave no reaction. The lack of consistent results at this stage

and the lack of remaining time meant that this interesting set of reactions was not explored further.



Scheme 2.25: The reactivity of (*E*)-1-azido-4-(*p*-tolyl)but-3-en-2-one with cyclopropenones and the synthesis of a natural product.

The ^{1}H NMR spectrum recorded for compound **378** showed a singlet peak for the CH of the 3-membered carbocycle at 7.80 ppm and triplet for the amine (NH) with coupling constant 4.5 Hz at 6.4 Hz. The signals for the CH=CH appeared as a doublet with coupling constant J = 16.1 Hz at 7.56 ppm and a doublet with coupling constant J = 16.1 Hz at 6.61 ppm, respectively. The proton spectrum also showed a methylene signal as doublet (J = 4.5 Hz) at 4.41 ppm. The methyl group appeared at 2.31 ppm and the aromatic protons showed between 7.56 - 6.94 ppm. The ^{13}C NMR spectrum recorded for this compound showed a peak for the

methyl carbon at 21.6 ppm and a signal at 198.5 ppm for the C=O group. There were also observed six carbon peaks for the quaternary carbons excluding the C=O and eleven CH signals in the ^{13}C NMR spectrum, consistent with the structure assigned. The structure of compound **378** was also assigned by MS and consistent HRMS which confirmed the additional oxygen. IR spectroscopy further helped to assign the structure of compound. The formation of the compounds with structures **366, 370, 374 & 378** can be explained **(Figure 2.19)** by the following suggested mechanism in which H_2O must add to the initial product at some point. We are still seeking X-ray confirmation of the structure of the N-O species **366, 370, 374 & 378**. It is possible that in compounds **366**, **370**, **374**, the OMe as the aryl group stabilises intermediate **379** whereas in compound **378**, the intermediate is stabilised by the adjacent enone.

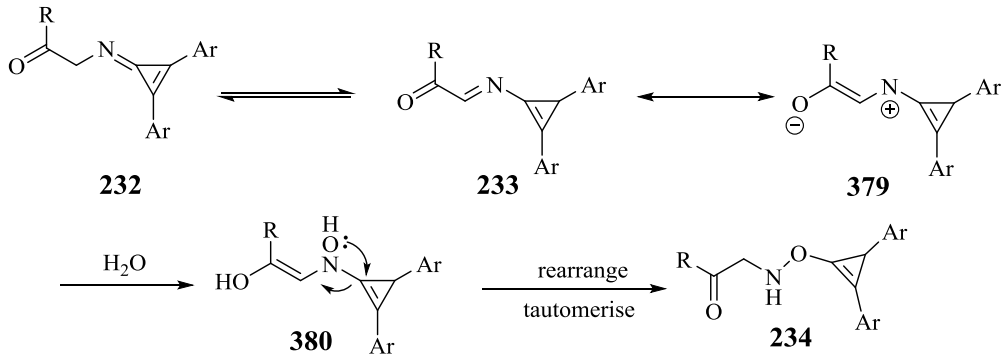
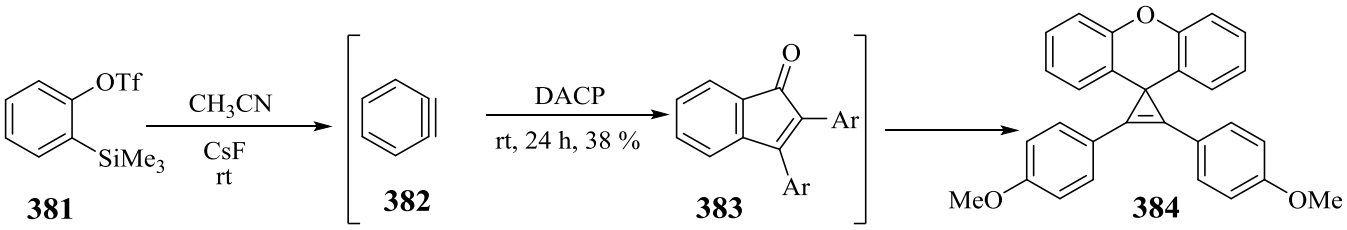


Figure 2.19: Mechanism for *N-O* formation.

3-*O*-[(*E*)-(2-Oxo-4-(*p*-tolyl)but-3-en-1-yl] kaempferol **236** was synthesised by the reaction of bromo-containing compound **235** with kaempferol. The spectral data for compound **235** matched those described in the literature[127] but the yield of the reaction has been improved from 19 % to 34 % and the unreacted kaempferol was recovered as starting material by flash chromatography. This compound 3-O-[(*E*)-(2-oxo-4-(p-tolyl)but-3-en-1-yl]kaempferol was required for a biological screening programme carried out at the University and forms part of a proposed new project area, which could not be explored in this project due to time

limitations: it was carried out in this thesis because we had ready access to the coupling partner **235**.

The final reaction explored was to check the behaviour of cyclopropenone with benzyne. There are number of methods reported in the literature to generate benzyne under harsh conditions.[128] But after generation of benzyne in 1983 by Kobayshi by the reaction of trimethylsilylphenyl triflates with fluoride source in acetonitrile under mild conditions.[129,130] The unstable benzyne was generated in situ **(see Scheme 2.26)** by the the reaction of trimethylsilylphenyl triflate **381** with cesium fluoride in acetonitrile at room temperature and tried to trap it by reaction with DACP to give the intially hoped cyclopentadienone **383.** In the event product **384** was isolated, a reaction that was reported in a full study in the literature[5j] at the time when we were starting our investigation.



Scheme 2.26: Cycloaddition reaction of benzyne with DACP.

The ^{1}H and ^{13}C NMR data of compound **384** matched that reported in the litrature,[5j] and the fact that others had now explored this key reaction led us to stop this aspect of our work.

2.15. Conclusion:

In the first part of this thesis, highly fuctionalised cycloadducts were obtained after treatment of cyclic imines with cyclopropenones *via* a formal [3+2]-cycloaddition reaction as a key step allowing the synthesis of pyridines, pyrrolo-isoquinolines and pyrrolo-β-carbolines. Some of the 6-membered ring imines explored were piprazine based *i.e.* had an extra heteroatom in the ring and were found to be unreactive. The naphthyl-substituted 4-membered cyclic imines underwent a ring expansion to give the benzoisoquinolines but 4-phenyl and 4-biphenyl-1-azetines were found not to undergo the same ring expansion. The pyrrolo-isoquinolines that were formed (from a dihydroisoquinoline) were noted to have an extra hydroxy on the bridgehead carbon.

When a 4-vinyl-1-azetine was treated with diphenylcyclopropenone the cycloaddition product rearranged to a 7-azabicyclo[4.2.1]nonane, as a result of an aza-Cope [3,3]-sigmatropic rearrangement, an observation that confirmed previous studies in the group with an analogous system. A fluorinated 1-azetine was also synthesised in order to compare reactivity to the non-fluorinated systems. Previous work was reported for the synthesis of a series of 1,2,4-oxadiazoles using 1,3-dipolar cycloadditions between non-fluorinated 1-azetines and nitrile oxides. When 2-ethylthio-3,3-difluoro-4-phenyl-1-azetine was reacted with *p*-methoxyphenyl hydroxymoyl chloride, it was found to give the F-containing cycloadduct product which could be heated in toluene to obtain the 5-ethylthio-3-(*p*-methoxyphenyl)-1,2,4-oxadiazole. This fluorinated 1-azetine was found not to react with cyclopropenones.

A novel methodology had been developed previously in the Hemming group for the synthesis of pyridines by the reaction of 4-aryl-1-azetines with diphenylcyclopropenone. This work in this thesis has extented the scope of the reaction to include other diarylcyclopropenones.

A range of azides were also synthesised, converted to iminophosphoranes as intermediates which were reacted with diphenylcyclopropenone and dianisylcyclopropenone and formed a

series of proposed cyclopropene products, some with an unexpected, tentative, *N-O* linked side-chain.

A catalytic methodology has been developed for the synthesis of primary alkyl bromide compounds from the corresponding alcohol substrates in the presence of diphenylcyclopropenone. A series of 1,2,4-oxadiazoles have been synthesised from amidoximes as starting materials which were formed with the involvement of cyclopropenone as a catalyst to couple carboxylic acids to oximes in the presence of oxalyl chloride.

2.16. Future work:

The figure below shows the diverse range of cyclopropenones that are available. The number of potential cyclic imines is also huge and so much time could be spent exploring these reactions, as summarised in **Figure 2.20**.

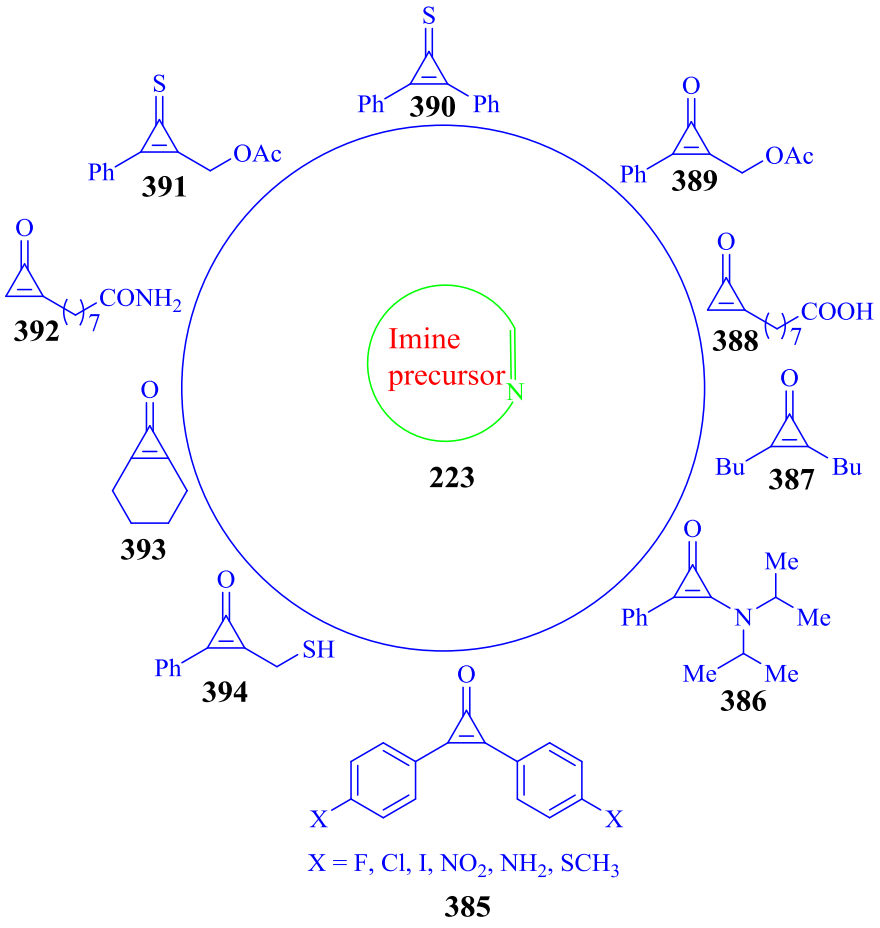
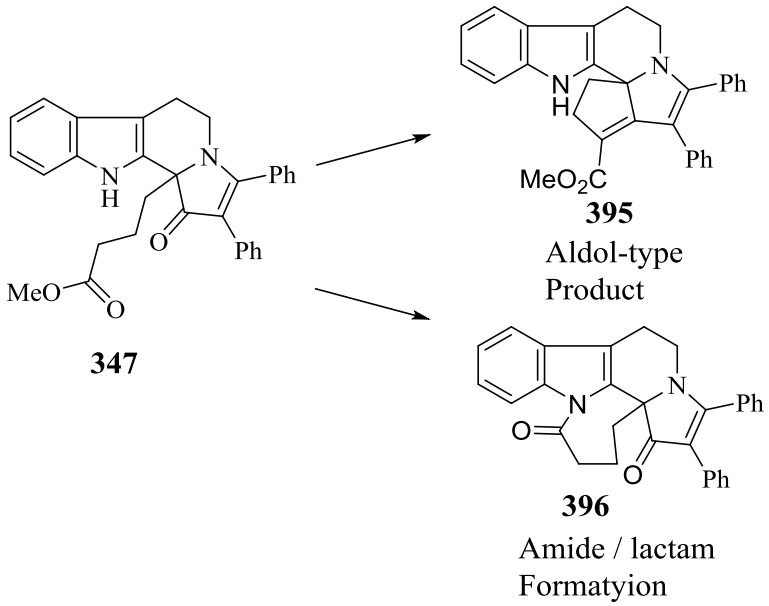


Figure 2.20: Graphical presentation for the roles of cyclopropenones.

Finally, it might be of interest to explore how compounds such as the indolizinoindole **347** can be used, as outlined below:



347

395

396

CHAPTER 3

Experimental

3.1. General Experimental

All reactions were carried out in dry glassware under an atmosphere of dry nitrogen unless mentioned otherwise.

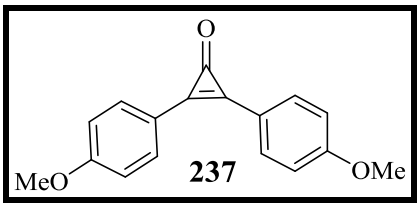
Infrared spectra were measured by Nicolet 380 FT-IR instrument as a thin film for oils and neat for solids and absorption peaks (max) are quoted in wave numbers (cm^{-1}).

Deuterated chloroform ($CDCl_3$) was used as solvent unless otherwise stated to record the nuclear magnetic resonance (NMR) spectra. ^1H NMR spectra were recorded on Bruker DPX-400 (400 MHz), Bruker DPX-500 (500 MHz). Signal splitting patterns are described as singlet (s), doublet (d), doublet of doublets (dd), doublet of triptets (dt), triplet (t), multiplet (m), quartet (q).

Low resolution mass spectra were measured on a Bruker Daltonics micrOTOF mass spectrometer operating at a positive ion mode under an electrospray ionisation method. High resolution mass spectra were measured on Kratos Concept IS spectrometer.

Reagents and solvents used during experimentation were purchased from Sigma Aldrich and Acros organics.

3.2. 2,3-Bis(*p*-methoxyphenyl)cycloprop-2-en-1-one



237

To a stirred slurry of $AlCl_3$ (2.30 g, 17.10 mmol) in dry dichloromethane (25 mL), was added tetrachlorocyclopropene (2.00 mL, 16.31 mmol) at - 78 °C under an inert N_2 atmosphere. The reaction mixture was left for 10 min with stirring at the same temperature. After this time, anisole (3.51 mL, 32.61 mmol) was added as a solution in DCM (8 mL) slowly over 15 min *via* syringe, and then the reaction mixture was kept overnight at rt with stirring. The reaction mixture was poured into water (15 mL). After this, the aqueous phase was washed with dichloromethane (10 mL x 2), and then the combined organic extracts were washed with brine (15 mL x 2). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.42 (ethyl acetate/petroleum ether = 1:2); white solid 2.20 g, 51 % yield; mp 122 - 123; lit.,[131] mp 120 - 121 ºC.

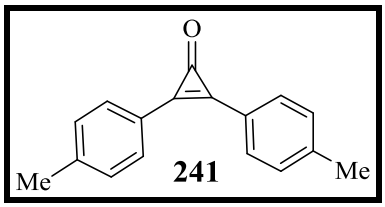
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.94 (4H, d, *J* = 8.6 Hz, Ar), 7.08 (4H, d, *J* = 8.6 Hz, Ar), 3.93 (6H, s, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.9 (C), 155.4 (C=O), 147.4 (C), 133.5 (CH), 117.1 (C), 114.7 (CH), 56.6 (OCH_3).

IR υ_{max} (cm^{-1}) 3029, 2929, 1842, 1607, 1597, 1424, 1301, 1254, 1032, 830, 710.

As reported previously.[23]

3.3. 2,3-Bis(*p*-tolyl)cycloprop-2-en-1-one



241

A solution of *N′,N′*-dicyclohexylcarbodiimide (2.71 g; 13.07 mmol) and 4-(dimethylamino)pyridine (0.40 g; 3.27 mmol) in dry tetrahydrofuran (30 mL) was stirred at rt under an inert N_2 atmosphere and treated dropwise with a solution of 4-tolylacetic acid (1.95 g; 13.01 mmol) in dry tetrahydrofuran (10 mL). The resulting mixture was stirred at rt for 16 h. After this time, the reaction mixture was filtered through Celite® The crude product was purified by flash chromatography (ethyl acetate/ petroleum ether; 1:4), affording the diaryl ketone as a yellow oil (1.08 g, 32 %, R_f = 0.35). The ketone (0.62 g; 2.60 mmol) was then dissolved in acetic acid (5 mL), and a solution of bromine (0.27 mL, 5.20 mmol) in acetic acid (2.5 mL) was added dropwise. After 0.5 h, the reaction was poured into water (20 mL) and the product was collected by filtration. The crude product (dibromoketone) was air dried for several hours, then dissolved in dry dichloromethane (5 mL). After that, triethylamine (0.55 mL, 3.91 mmol) in dry dichloromethane (5 mL) was added dropwise and then the reaction mixture was left for 1 h at room temperature with stirring. The reaction mixture was quenched with 1 M HCl (5 mL), followed by brine (10 mL). The organic layers were dried ($MgSO_4$), and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound

R_f 0.49 (ethyl acetate/ petroleum ether; 2:1); orange solid 0.087 g, 13 % yield.

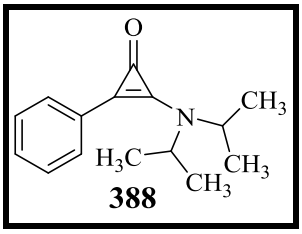
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.89 (4H, d, *J* = 8.1 Hz, Ar), 7.40 (4H, d, *J* = 8.1 Hz, Ar), 2.49 (6H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.9 (C=O), 147.1 (C), 143.5 (C), 131.6 (CH), 130.1 (CH), 121.9 (C), 21.3 (CH_3).

IR υ_{max} (cm^{-1}) 3021, 2913, 1831, 1600, 1342, 811, 1039, 489.

As reported previously.[109]

3.4. 2-(*N′,N′*-diisopropylamino)-3-phenylcycloprop-2-en-1-one



388

To a stirred slurry of $AlCl_3$ (0.79 g; 6.75 mmol) in dry dichloromethane (12.5 mL), was added tetrachlorocyclopropene (0.75 mL; 6.95 mmol) at 0 °C under an inert N_2 atmosphere. The reaction mixture was left for 10 min with stirring at the same temperature. Benzene (0.48 mL, 6.20 mmol) in dichloromethane (15 mL) was added, and then the reaction mixture was kept at rt overnight. The reaction mixture was poured into water (8 mL). After that, the aqueous phase was washed with dichloromethane (15 mL x 2), and the combined organic extracts were washed with brine (8 mL x 2). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo*. This crude oil was dissolved in acetone (3 mL) and crushed ice (8 g) was added. After this, the mixture was stirred at rt for 3 h and then acetone was removed by evaporation under reduced pressure. The remaining solution was filtered and filtrate solid was further washed with cold diethyl ether to give the crude white solid (1-hydroxy-2-phenylcyclopropenone). The crude product (0.089 g; 0.61 mmol) was cooled to 0 °C under an inert argon atmosphere and 1 drop of DMF was added followed by 0.5 mL of thionyl chloride were added. The reaction mixture was stirred at 0 °C for 10 min, allowed to warm to rt and then stirred for 10 min more at the same temperature. The reaction mixture was concentrated under reduced pressure and further put under high vacuum for 1 h to remove any excess thionyl chloride. The crude product was dissolved in DCM (3 mL) was cooled to 0 °C and diisopropylamine (0.25 mL, 1.75 mmol) was added and the reaction mixture was left to warm to rt for 3 h with stirring. The reaction mixture was quenched with saturated aqueous

ammonium chloride (5 mL) and the aqueous phase was washed with dichloromethane (10 mL x 2), and then the combined organic extracts were washed brine (5 mL x 2). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.42 (ethyl acetate/petroleum ether = 1:2); yellow solid 0.042 g, 30 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.60 (2H, d, *J* = 7.4 Hz, Ph), 7.45 - 7.34 (3H, m, Ph), 4.25 - 4.17 (IH, m, CH), 3.69 - 3.61 (1H, m, CH), 1.39 (12H, dd, *J* = 6.5 and 6.5 Hz).

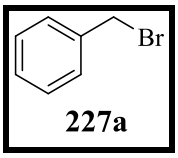
IR υ_{max} (cm^{-1}) 3031, 2976, 1855, 1603, 1579, 1440, 1143, 786.

MS $(ESI)^+$: m/z [M + H] 230.1.

HRMS: [M] for $C_{15}H_{19}NO$ calculated 229.1466, found 229.1467.

^{1}H & IR data consistent with the previous reported data.[109] Together with an unidentified product which appeared (IR; C=O at 1860 cm^{-1}) to be a cyclopropenone but lacked 14 mass units (- CH_2 by HRMS).

3.5. Benzyl bromide



227a

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and benzyl alcohol (0.22 g; 0.21 mL, 206 µL, 2.0 mmol) in dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL, 220 µL, 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography (only hexane), affording the title compound.

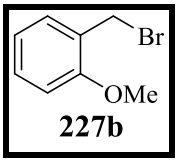
R_f 0.31 (100 % hexane); colourless oil 0.24g, 70 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 - 7.25 (2H, m, Ph), 7.23 - 7.14 (3H, m, Ph), 4.36 (2H, s, $C\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 137.8 (C), 129.1 (CH), 128.8 (CH), 128.4 (CH), 33.7 (CH_2).

Previously reported.[132]

3.6. 2-Methoxybenzyl bromide



227b

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and 4-methoxybenzyl alcohol (0.28 g; 0.27 mL, 266 µL, 2.0 mmol) in dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL; 220 µL; 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate/ hexane; 50:3), affording the title compound.

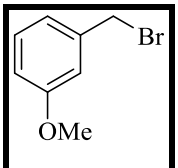
R_f 0.67 (ethyl acetate/hexane = 50:3); white solid 0.230 g, 57 % yield; mp 52-53 ºC; lit.,[133] mp 47-50 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 - 7.31 (2H, m, Ar), 6.98 - 6.91 (2H, m, Ar), 4.62 (2H, s, CH_2), 3.93 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.4 (C), 130.9 (CH), 130.2 (CH), 126.0 (C), 120.7 (CH), 110.9 (CH), 55.6 (CH_3), 29.1 (CH_2).

Previously reported.[133]

3.7. 3-Methoxybenzyl bromide



227c

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and 4-methoxylbenzyl alcohol (0.28 g; 0.27 mL, 266 µL, 2.0 mmol) in

dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL; 220 µL; 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.67 (ethyl acetate/hexane = 50:3); colorless liquid 0.26 g, 65 % yield.

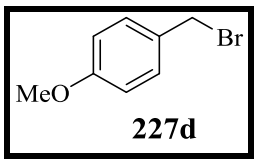
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 – 7.14 (1H, t, *J* = 7.9 Hz, Ar), 6.86 (1H, d, *J* = 7.7 Hz, Ar), 6.82 (1H, s, Ar), 6.72 (1H, dd, *J* = 8.2 and 2.1 Hz, Ar), 4.34 (2H, s, C<u>H</u>$_2$), 3.68 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.8 (C), 139.2 (C), 129.8 (CH), 121.3 (CH), 114.2 (CH), 114.2 (CH), 55.3 (CH_3), 33.6 (CH_2).

IR υ_{max} (cm^{-1}) 3001, 2939, 1599, 1585, 1487, 1453, 1263, 1154, 1038, 778, 730.

Previously reported.[134]

3.8. 4-Methoxybenzyl bromide



227d

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and 4-methoxybenzyl alcohol (0.28 g; 0.27 mL, 266 µL, 2.0 mmol) in dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL; 220 µL; 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.67 (ethyl acetate/hexane = 50:3); colorless liquid 0.28 g, 70 % yield.

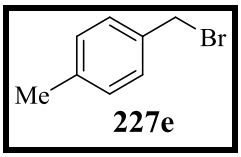
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 – 7.36 (2H, m, Ar), 6.93 - 6.91 (2H, m, Ar), 4.55 (CH_2), 3.83 (CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.7 (C), 130.5 (CH), 130.0 (C), 114.2 (CH), 55.3 (CH_3), 34.1 (CH_2).

IR υ_{max} (cm^{-1}) 3031, 2923, 1607, 1583, 1510, 1461, 1439, 1302, 1246, 1227, 1202, 1173, 1029, 828, 591.

Previously reported.[135]

3.9. 4-Methylbenzyl bromide



227e

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and 4-methylbenzyl alcohol (0.24 g; 2.0 mmol) in dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL; 220 µL; 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography (only hexane), affording the title compound.

R_f 0.24 (100 % hexane); white solid 0.230 g, 62 % yield; mp 36 - 37 ºC; lit.,[136] mp 34 ºC.

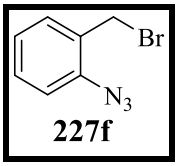
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.16 (2H, dd, *J* = 7.7 and 1.7 Hz, Ar), 7.03 (2H, d, *J* = 7.7 Hz, Ar), 4.36 (2H, s, C$\underline{H}_2$), 2.23 (3H, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.4 (C), 134.9 (C), 129.5 (CH), 129.0 (CH), 33.8 (CH_2), 21.3 (CH_3).

IR υ_{max} (cm^{-1}) 3016, 1614, 1513, 1225, 1094, 866, 810, 740, 588.

Previously reported.[137]

3.10. 2-Azidobenzyl bromide



227f

To a stirred solution of diphenylcyclopropenone (0.06 g; 0.30 mmol), lithium bromide (0.521 g; 6.0 mmol) and 2-azidobenzyl alcohol (0.30 g; 2.0 mmol) in dichloromethane (10 mL), was added oxalyl chloride (0.33 g; 0.22 mL; 220 µL; 2.60 mmol) dropwise through an addition funnel over 15 h under an inert atmosphere at rt. After this time, the reaction solution was filtered and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.28 (100 % hexane); brown solid 0.24 g, 57 % yield; mp 78 - 79 ºC; lit.,[138] mp 71 - 72 ºC.

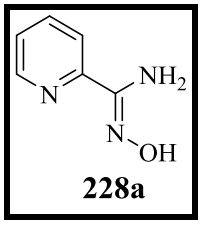
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 (2H, m, Ar), 7.20 – 7.13 (1H, m, Ar), 7.15 (1H, d, *J* = 7.5 Hz, Ar), 4.50 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 138.6 (C), 131.3 (CH), 130.1 (CH), 128.8 (C), 125.0 (CH), 118.5 (CH), 28.4 (CH_2).

IR υ_{max} (cm^{-1}); 3024, 2929, 2118, 1579, 1484, 1285, 1160, 566, 529, 510, 477.

The compound was previously reported.[138]

3.11. *N*'-Hydroxypyridine-2-carboxamidine



228a

To a stirred solution of hydroxylamine hydrochloride (0.73 g; 10.5 mmol) in water (25 mL), was added sodium carbonate (1.12 g; 10.57 mmol) in small portions. To this, 2-cyanopyridine (1.0 g; 9.61 mmol) in ethanol (25 mL) was added and the reaction mixture was left to reflux

for 24 h. After this, the mixture was extracted with dichloromethane (25 mL x 2) and then solvents were removed *in vacuo* to give the title compound.

White solid 1.2 g, 91 % yield; mp 122 - 123 ºC; lit.,[139] mp 117 - 118 ºC.

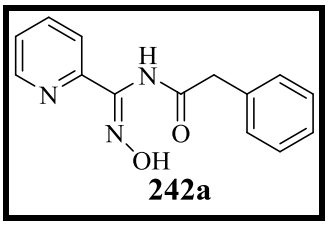
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.83 (1H, br. s, O<u>H</u>), 8.61 - 8.58 (1H, m, Ar), 7.94 (1H, d, *J* = 8.0 Hz, Ar), 7.29 (1H, td, *J* = 7.7 and 1.5 Hz, Ar), 7.35 - 7.32 (1H, m, Ar), 5.76 (2H, s, N<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.1 (C), 149.0 (C), 148.4 (CH), 136.5 (CH), 124.4 (CH), 120.0 (CH).

IR υ_{max} (cm^{-1}) 3463, 3342, 1639, 1589, 1481, 1377, 1289, 1100, 888, 740.

Previously reported.[112e]

3.12. *(Z)-N*-((Hydroxyimino)(pyridin-2-yl)methyl)-2-phenylacetamide



242a

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of phenylacetic acid (0.136 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, *N*'-hydroxypyridine-2-carboxamidine **228a** (0.15 g; 1.14 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.19 (ethyl acetate/hexane = 1:1); white solid 0.2 g, 68 % yield; mp 117 - 118 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 - 8.54 (1H, m, Ar), 8.15 (1H, dd, *J* = 7.8 and 2.5 Hz, Ar), 7.76 - 7.70 (1H, m, Ar), 7.38 - 7.28 (6H, m, Ar), 6.43 (1H, br. s, O<u>H</u>), 5.30 (1H, br. s, N<u>H</u>), 3.86 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.8 (C=O), 153.9 (C), 148.4 (CH), 147.5 (C), 136.8 (CH), 133.7 (C), 129.2 (CH), 128.7 (CH), 127.2 (CH), 125.5 (CH), 121.3 (CH), 40.4 (CH_2).

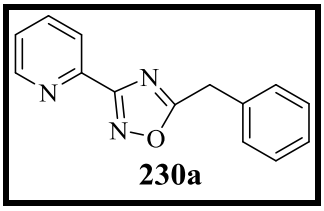
IR υ_{max} (cm^{-1}) 3473, 3316, 1692, 1573, 1532, 1443, 1357, 1178, 1017, 771, 691.

MS $(ESI)^+$: m/z [M+H] 256.1.

HRMS: [M] for $C_{14}H_{13}N_3O_2$ calculated 255.1000, found 255.1008.

New compound.

3.13. 5-Benzyl-3-(pyridin-2-yl)-1,2,4-oxadiazole



230a

(Z)-N-((Hydroxyimino)(pyridin-2-yl)methyl)-2-phenylacetamide **242a** (0.15 g; 0.59 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.5 (ethyl acetate/dichloromethane = 1:5); white solid 0.1 g, 72 % yield; mp 61 - 62 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.81 - 8.79 (1H, m, Ar), 8.12 (1H, d, *J* = 7.9 Hz, Ar), 7.86 - 7.82 (1H, m, Ar), 7.44 - 7.31 (6H, m, Ar), 4.35 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.7 (C), 168.3 (C), 150.4 (CH), 146.3 (C), 137.0 (CH), 133.3 (CH), 129.0 (CH), 128.9 (C), 127.6 (CH), 125.5 (CH), 123.1 (CH), 33.1 (CH_2).

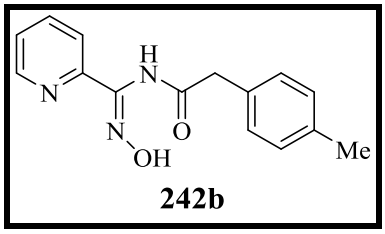
IR υ_{max} (cm^{-1}) 3029, 2931, 1586, 1562, 1494, 1452, 1439, 1411, 1372, 1346, 1179, 1127, 1074, 1020, 912, 804, 748, 734, 720, 643, 618, 595, 524.

MS $(ESI)^+$: m/z [M + H] 238.1.

HRMS: [M] for $C_{14}H_{11}N_3O$ calculated 237.0902, found 237.0906.

New compound.

3.14. *(Z)*-*N*-((Hydroxyimino)(pyridin-2-yl)methyl)-2-(*p*-tolyl)acetamide



242b

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of *p*-tolylacetic acid (0.15 g; 0.99 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, *N*'-hydroxypyridine-2-carboxamidine **228a** (0.15 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.1(ethyl acetate/hexane = 1:1); white solid 0.21 g, 72 % yield; mp 137 - 138 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.57 – 8.55 (1H, m, Ar), 8.16 (1H, d, *J* = 8.0 Hz, Ar), 7.37 (1H, td, *J* = 8.0 and 1.5 Hz, Ar), 7.38 - 7.35 (1H, m, Ar), 7.27 (2H, d, *J* = 8.0 Hz, Ar), 7.17 (2H, d, *J* = 8.0 Hz, Ar), 6.42 (1H, br. s, O<u>H</u>), 5.30 (1H, br. s, N<u>H</u>), 3.82 (2H, s, C<u>H</u>$_2$), 2.35 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.0 (C), 153.9 (C), 148.4 (CH), 147.6 (C), 136.8 (CH), 130.7 (C), 129.4 (CH), 129.1 (CH), 125.5 (CH), 121.4 (CH), 40.0 (CH_2), 21.1 (CH_3).

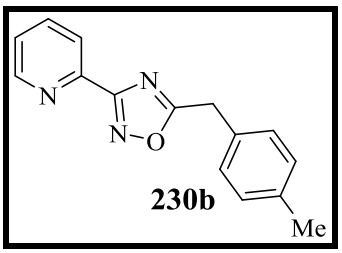
IR υ_{max} (cm^{-1}) 3469, 3301, 1740, 1632, 1566,1517, 1474, 1401, 1332, 1142, 900, 797, 760.

MS $(ESI)^+$: m/z [M + H] 270.1.

HRMS: [M] for $C_{15}H_{15}N_3O_2$ calculated 269.1164, found 269.1171.

New compound.

3.15. 5-(4-Methylbenzyl)-3-(pyridin-2-yl)-1,2,4-oxadiazole



230b

(Z)-*N*-((Hydroxyimino)(pyridin-2-yl)methyl)-2-(*p*-tolyl)acetamide **242b** (0.15 g; 0.56 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.3(ethyl acetate/hexane = 1:1); yellow oil 0.092 g, 66 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.79 – 8.77 (1H, m, Ar), 8.09 (1H, d, *J* = 7.9 Hz, Ar), 7.82 – 7.78 (1H, m, Ar), 7.40 - 7.38 (1H, m, Ar), 7.26 (2H, d, *J* = 7.9 Hz, Ar), 7.14 (2H, d, *J* = 7.8 Hz, Ar), 4.28 (2H, s, C$\underline{H}_2$), 2.32 (3H, s, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.0 (C), 168.2 (C), 150.3 (CH), 146.3 (C), 137.3 (C), 136.9 (CH), 130.2 (C), 129.6 (CH), 128.8 (CH), 125.4 (CH), 123.1 (CH), 32.7 (CH_2), 21.0 (CH_3).

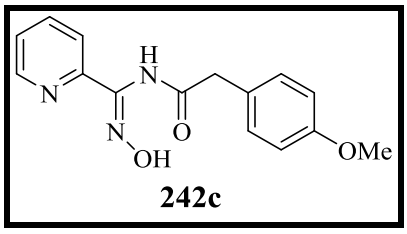
IR υ_{max} (cm^{-1}) 2996, 2931, 1579, 1563, 1514, 1421, 1362, 1148, 801, 778, 743, 721.

MS $(ESI)^+$: m/z [M + H] 252.2.

HRMS: [M] for $C_{15}H_{13}N_3O$ calculated 251.1059, found 251.1066.

New compound.

3.16. (*Z*)-*N*-((Hydroxyimino)(pyridin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide



242c

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert

atmosphere at rt. After 5 minutes, a mixture 4-methoxyphenylacetic acid (0.17 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, *N'*-hydroxypyridine-2-carboxamidine **228a** (0.15 g; 1.1 mmol) was added and the reaction mixture was left overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.38 (ethyl acetate/dichloromethane = 1:5); white solid 0.24 g, 77 % yield; mp 136 - 137 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 - 8.54 (1H, m, Ar), 8.15 (1H, d, *J* = 7.9, Hz, Ar), 7.77 - 7.71 (1H, m, Ar), 7.39 - 7.36 (1H, m, Ar), 7.29 - 7.27 (2H, m, Ar), 6.91 - 6.88 (2H, m, Ar), 6.41 (1H, br. s, O<u>H</u>), 5.31 (1H, br. s, N<u>H</u>), 3.82 (3H, s, C<u>H</u>$_3$), 3.80 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.1 (C=O), 158.7 (C), 153.9 (C), 148.4 (CH), 147.5 (C), 136.7 (CH), 130.3 (CH), 125.7 (C), 125.5 (CH), 121.3 (CH), 114.1 (CH), 55.2 (OCH_3), 39.5 (CH_2).

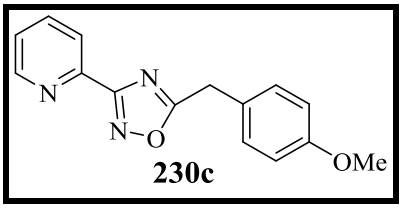
IR υ_{max} (cm^{-1}) 3470, 3313, 1743, 1632, 1613, 1584, 1565, 1513, 1329, 1317, 1243, 1208, 1135, 1039, 899, 797, 769, 520.

MS $(ESI)^+$: m/z [M + H] 286.1.

HRMS: [M] for $C_{15}H_{15}N_3O_3$ calculated 285.1113, found 285.1112.

New compound.

3.17. 5-(4-Methoxybenzyl)-3-(pyridin-2-yl)-1,2,4-oxadiazole



230c

(*Z*)-*N*-((Hydroxyimino)(pyridin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide **242c** (0.15 g; 0.53 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18

h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.55 (ethyl acetate/hexane; 1:1); yellow oil 0.092 g, 66 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.71- 8.69 (1H, m, Ar), 8.01 (1H, d, *J* = 7.8 Hz, Ar), 7.74 – 7.72 (1H, m, Ar), 7.33 - 7.30 (1H, m, Ar), 7.22 (2H, d, *J* = 8.4 Hz, Ar), 6.78 (2H, d, *J* = 8.4 Hz, Ar), 4.18 (2H, s, C$\underline{H}_2$), 3.69 (3H, s, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.1 (C), 168.2 (C), 159.0 (C), 150.3 (CH), 146.3 (C), 136.9 (CH), 130.1 (CH), 125.4 (CH), 125.2 (C), 123.1 (CH), 114.3 (CH), 55.2 (CH_3), 32.2 (CH_2).

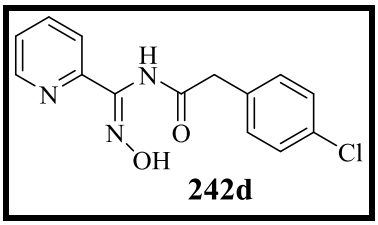
IR υ_{max} (cm^{-1}) 2932, 2837, 1610, 1579, 1564, 1511, 1421, 1363, 1245, 1177, 1148, 1030, 802, 788, 744, 721, 712.

MS $(ESI)^+$: m/z [M + H] 268.1.

HRMS: [M] for $C_{15}H_{13}N_3O_2$ calculated 267.1008, found 267.1003.

New compound.

3.18. (*Z*)-2-(4-Chlorophenyl)-*N*-((hydroxyimino)(pyridin-2-yl)methyl)acetamide



242d

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of 4-methoxyphenylacetic acid (0.17 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, *N*'-hydroxypyridine-2-carboxamidine **228a** (0.15 g; 1.1 mmol) was added and the reaction mixture was left at room

temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.31 (ethyl acetate/dichloromethane = 1:5); white solid 0.17 g, 54 % yield; mp 143 - 144 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.58 – 8.56 (1H, m, Ar), 8.15 (1H, d, *J* = 7.9 Hz, Ar), 7.78 – 7.74 (1H, m, Ar), 7.39 (1H, dd, *J* = 6.8 and 5.2 Hz, Ar), 7.34 – 7.28 (3H, m, Ar), 7.29 (1H, d, *J* = 8.3 Hz, Ar), 6.47 (1H, br. s, O<u>H</u>), 5.31 (1H, br. s, N<u>H</u>), 3.84 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.4 (C=O), 153.8 (C), 148.4 (CH), 147.4 (C), 136.8 (CH), 132.2 (C), 132.1 (C), 130.6 (CH), 128.8 (CH), 125.6 (CH), 121.3 (CH), 39.6 (CH_2).

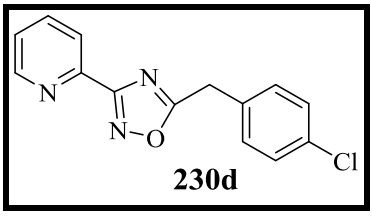
IR υ_{max} (cm^{-1}) 3468, 3300, 1739, 1631, 1565, 1493, 1475, 1402, 1334, 1210, 1145, 1084, 1014, 900, 808, 741, 688, 664.

MS $(ESI)^+$: m/z [M + H] 290.1.

HRMS: [M] for $C_{14}H_{12}{}^{35}ClN_3O_2$ calculated 289.0618, found 289.0624.

New compound.

3.19. 5-(4-Chlorobenzyl)-3-(pyridin-2-yl)-1,2,4-oxadiazole



230d

(*Z*)-2-(4-Chlorophenyl)-*N*-((hydroxyimino)(pyridin-2-yl)methyl)acetamide **242d** (0.15 g; 0.52 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.46 (ethyl acetate/dichloromethane = 1:5); yellow solid 0.16 g, 54 % yield; mp 71 - 72 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.76 – 8.74 (1H, m, Ar), 8.07 (1H, d, *J* = 7.8 Hz, Ar),

7.82 - 7.78 (1H, m, Ar), 7.39 (1H, dd, *J* = 7.2 and 5.1 Hz, Ar), 7.30 - 7.17 (4H, m, Ar), 4.27 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.2 (C), 168.3 (C), 150.4 (CH), 146.1 (C), 137.0 (CH), 133.6 (C), 131.7 (C), 130.3 (CH), 129.1 (CH), 125.5 (CH), 123.1 (CH), 32.4 (CH_2).

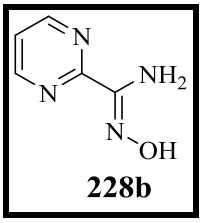
IR υ_{max} (cm^{-1}) 2929, 2880, 1589, 1576, 1562, 1488, 1444, 1375, 1346, 1141, 1091, 1014, 994, 907, 849, 801, 769, 742, 721, 715, 640, 617, 515, 507, 427, 404.

MS $(ESI)^+$: m/z [M + H] 272.0.

HRMS: [M] for $C_{14}H_{10}{}^{35}ClN_3O$ calculated 271.0512, found 271.0513.

New compound.

3.20. (*Z*)-*N'*-Hydroxypyrimidine-2-carboximidamide



228b

To a stirred solution of hydroxylamine hydrochloride (0.73 g; 10.5 mmol) in water (25 mL), was added sodium carbonate (1.12 g; 10.57 mmol) in small portions. To this, 2-cyanopyrimidine (1.0 g; 9.51 mmol) in ethanol (25 mL) was added and the reaction mixture was left at reflux for 24 h. After this, the mixture was extracted with dichloromethane (25 mL x 2) and then solvents were removed *in vacuo* to give the title compound.

White solid 1.2 g, 91 % yield; mp 143 - 144 ºC, not reported.

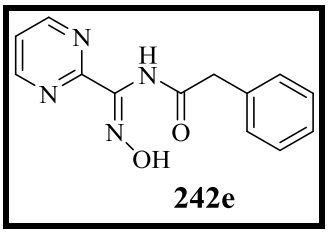
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.19 (1H, s, br, O<u>H</u>), 8.84 (2H, d, *J* = 4.8 Hz, Ar), 7.51 (1H, t, *J* = 4.8 Hz, Ar), 5.84 (2H, s, N<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.7 (C), 157.7 (CH), 149.4 (C), 121.6 (CH).

IR υ_{max} (cm^{-1}) 3416, 3324, 1650, 1561, 1455, 1375, 1002, 938, 808, 790, 663, 529.

Previously reported.[112e]

3.21. (*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-phenylacetamide



242e

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of phenylacetic acid (0.136 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxypyrimidine-2-carboximidamide **228b** (0.15 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.1 (ethyl acetate/dichloromethane = 1:1); white solid 0.18 g, 64 % yield; mp 182 - 183 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (2H, d, *J* = 4.8 Hz, Ar), 7.41 - 7.28 (6H, m, Ar), 7.01 (1H, br. s, O<u>H</u>), 7.69 (1H, br. s, N<u>H</u>), 3.85 (2H, s, C<u>H_2</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.2 (C=O), 158.1 (CH), 157.9 (C), 154.5 (C), 135.0 (C), 129.9 (CH), 128.8 (CH), 127.3 (CH), 123.0 (CH), 39.6 (CH_2).

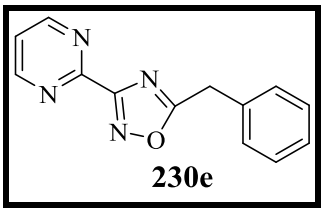
IR υ_{max} (cm^{-1}) 3411, 3303, 1731, 1621, 1590, 1384, 1305, 1240, 1126, 943, 890, 819, 768, 694, 602.

MS $(ESI)^+$: m/z [M + H] 257.1.

HRMS: [M] for $C_{13}H_{12}N_4O_2$ calculated 256.0960, found 256.0963.

New compound.

3.22. 5-Benzyl-3-(pyrimidin-2-yl)-1,2,4-oxadiazole



230e

(*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-phenylacetamide **242e** (0.17 g; 0.68 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.3 (ethyl acetate/dichloromethane = 1:1); white solid 0.14 g, 86 % yield; mp 113 - 114 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.86 (2H, d, *J* = 4.8 Hz, Ar), 7.34 (1H, t, *J* = 4.8 Hz, Ar), 7.30 - 7.23 (4H, m, Ar), 7.20 (1H, d, *J* = 7.1 Hz, Ar), 4.28 (2H, s, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.2 (C), 158.1 (CH), 159.9 (C), 154.5 (C), 135.0 (C), 129.9 (CH), 128.8 (CH), 127.3 (CH), 123.0 (CH), 39.6 (CH_2).

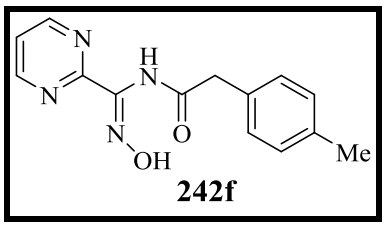
IR υ_{max} (cm^{-1}) 2931, 1575, 1558, 1455, 1417, 1371, 1211, 1191, 903, 825, 725, 704, 692.

MS $(ESI)^+$: m/z [M + H] 239.1.

HRMS: [M] for $C_{13}H_{10}N_4O$ calculated 238.0855, found 238.0859.

New compound.

3.23. (*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-(*p*-tolyl)acetamide



242f

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of *p*-tolylacetic acid (0.15 g; 0.99 mmol) and

triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxypyrimidine-2-carboximidamide **228b** (0.15 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.1 (ethyl acetate/hexane = 1:1); white solid 0.23 g, 78 % yield; mp 183 - 184 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.83 (2H, d, *J* = 4.8 Hz, Ar), 7.39 (1H, t, *J* = 4.8 Hz, Ar), 7.24 (2H, d, *J* = 7.8 Hz, Ar), 7.14 (2H, d, *J* = 7.8 Hz, Ar), 6.15 (1H, s, O<u>H</u>), 5.59 (1H, s, N<u>H</u>), 3.85 (2H, s, C<u>H</u>$_2$), 2.34 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.5 (C=O), 157.3 (CH), 157.0 (C), 152.7 (C), 136.7 (C), 130.6 (C), 129.3 (CH), 129.1 (CH), 122.1 (CH), 39.9 (CH_2), 21.1 (CH_3).

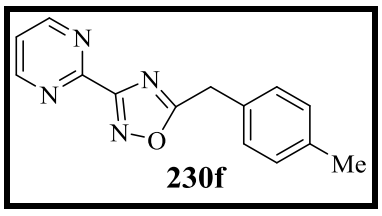
IR υ_{max} (cm^{-1}) 3424, 3318, 1741, 1625, 1556, 1377, 1332, 1187, 1127, 899, 827, 806, 769, 670, 644, 589.

MS $(ESI)^+$: m/z [M + H] 271.1.

HRMS: [M] for $C_{14}H_{14}N_4O_2$ calculated 270.1117, found 270.1125.

New compound.

3.24. 5-(4-Methylbenzyl)-3-(pyrimidin-2-yl)-1,2,4-oxadiazole



230f

(*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-(*p*-tolyl)acetamide **242f** (0.15 g; 0.56 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.26 (ethyl acetate/dichloromethane = 1:1); yellow oil 0.1 g, 71 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (2H, d, *J* = 4.9 Hz, Ar), 7.39 (1H, t, *J* = 4.9 Hz, Ar), 7.23 (2H, d, *J* = 7.8 Hz, Ar), 7.10 (2H, d, *J* = 7.8 Hz, Ar), 4.29 (2H, s, C<u>H</u>$_2$), 2.27 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.6 (C), 167.7 (C), 157.9 (CH), 156.0 (C), 137.4 (C), 129.9 (C), 129.6 (CH), 128.8 (CH), 122.1 (CH), 32.7 (CH_2), 21.0 (CH_3).

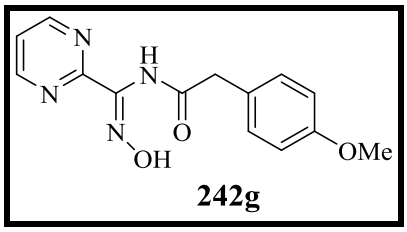
IR υ_{max} (cm^{-1}) 2966, 2933, 1612, 1537, 1423, 1342, 1249, 1182, 1022, 840, 779, 750.

MS $(ESI)^+$: m/z [M + H] 253.1.

HRMS: [M] for $C_{14}H_{14}N_4O$ calculated 252.1011, found 252.1016.

New compound.

3.25. (*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide



242g

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of 4-methoxyphenylacetic acid (0.15 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxypyrimidine-2-carboximidamide **228b** (0.15 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.08 (ethyl acetate/hexane = 1:1); white solid 0.19 g, 61 % yield; mp 181 - 182 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.85 (2H, d, *J* = 4.8 Hz, Ar), 7.41 (1H, t, *J* = 4.8 Hz, Ar), 7.29 (2H, d, *J* = 8.4 Hz, Ar), 6.89 (2H, d, *J* = 8.4 Hz, Ar), 6.15 (1H, br. s, O<u>H</u>), 5.32 (1H, br. s, N<u>H</u>), 3.84 (2H, s, C<u>H</u>$_2$), 3.82 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.6 (C=O), 158.7 (C), 157.3 (CH), 157.0 (C), 152.7 (C), 130.3 (CH), 125.7 (C), 122.1 (CH), 114.0 (CH), 55.2 (CH_3), 39.5 (CH_2).

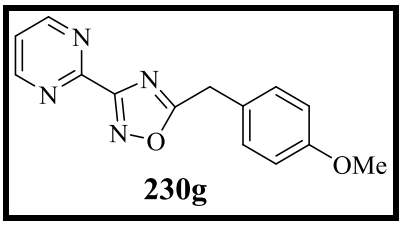
IR υ_{max} (cm^{-1}) 3424, 3318, 1784, 1615, 1589, 1440, 1337, 1310, 779, 698.

MS $(ESI)^+$: m/z [M + H] 287.1.

HRMS: [M] for $C_{14}H_{14}N_4O_3$ calculated 286.1066, found 286.1073.

New compound.

3.26. 5-(4-Methoxybenzyl)-3-(pyrimidin-2-yl)-1,2,4-oxadiazole



230g

(*Z*)-*N*-((Hydroxyimino)(pyrimidin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide **242g** (0.14 g; 0.49 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound. **R_f** 0.32 (ethyl acetate/dichloromethane = 1:1); light yellow solid 0.09 g, 68 % yield; mp 111-112 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (2H, d, *J* = 4.9 Hz, Ar), 7.40 (1H, t, *J* = 4.9 Hz, Ar), 7.32 - 7.28 (2H, d, *J* = 8.4 Hz, Ar), 6.82 (2H, d, *J* = 8.4 Hz, Ar), 4.27 (2H, s, C<u>H</u>$_2$), 3.77 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 179.8 (C), 167.7 (C), 159.0 (C), 157.9 (CH), 156.0 (C), 130.3 (CH), 125.0 (C), 122.1 (CH), 114.3 (CH), 55.2 (CH_3), 32.1 (CH_2).

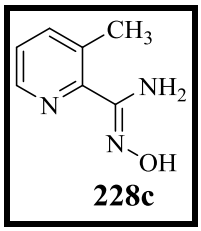
IR υ_{max} (cm^{-1}) 2998, 2933, 1613, 1577, 1560, 1560, 1443, 1372, 1302, 1240, 1175, 1034, 900, 826.

MS $(ESI)^+$: m/z [M + H] 269.1.

HRMS: [M] for $C_{14}H_{12}N_4O_2$ calculated 268.0960, found 268.0964.

New compound.

3.27. (*Z*)-*N'*-Hydroxy-3-methylpicolinimidamide



228c

To a stirred solution of hydroxylamine hydrochloride (0.73 g; 10.5 mmol) in water (25 mL), was added sodium carbonate (1.12 g; 10.57 mmol) in small portions. To this, 3-methylpicolinonitrile (1.12 g; 9.48 mmol) in ethanol (25 mL) was added and the reaction mixture was left to reflux for 24 h. After this, the mixture was extracted with dichloromethane (25 mL x 2) and then solvents were removed *in vacuo* to give the title compound.

White solid 1.12 g, 78 % yield; mp 95 - 96 ºC, m.p. not reported previously.

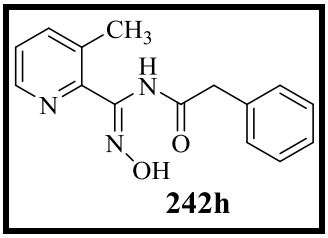
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.26 (1H, br. s, O<u>H</u>), 8.45 - 8.43 (1H, m, Ar), 7.56 (1H, d, *J* = 7.5 Hz, Ar), 7.22 (1H, dd, *J* = 7.5 and 4.8 Hz), 5.72 (2H, s, N<u>H</u>$_2$), 2.58 (C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 152.7 (C), 147.5 (C), 145.8 (CH), 139.8 (CH), 133.0 (C), 123.6 (CH), 21.5 (CH_3).

IR υ_{max} (cm^{-1}) 3457, 3345, 1638, 1561, 1451, 1405, 1369, 1111, 920, 859, 782, 687, 651, 509.

Previously reported.[112e]

3.28. (*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-phenylacetamide



242h

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of phenylacetic acid (0.136 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxy-3-methylpicolinimidamide **228c** (0.17 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.48 (ethyl acetate/dichloromethane = 1:1); white solid 0.167 g, 56 % yield; mp 115 - 116 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 - 8.34 (1H, m, Ar), 7.50 (1H, d, *J* = 7.7 Hz, Ar), 7.28 - 7.25 (3H, m, Ar), 7.26 - 7.16 (3H, m, Ar), 5.71 (1H, br. s, O<u>H</u>), 5.21 (1H, br. s, N<u>H</u>), 3.79 (C<u>H</u>$_2$), 2.59 (C<u>H</u>$_3$).

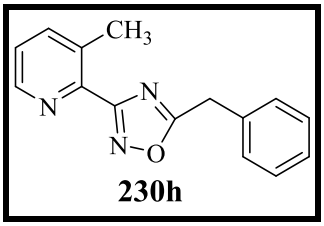
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.1 (C=O), 155.7 (C), 146.1 (C), 145.8 (CH), 140.2 (CH), 134.5 (C), 133.8 (C), 129.3 (CH), 128.6 (CH), 127.2 (CH), 124.6 (CH), 40.3 (CH_2), 21.7 (CH_3).

IR υ_{max} (cm^{-1}) 3337, 3303, 1727, 1614, 1571, 1452, 1337, 1213, 1143, 1107, 929, 882, 803, 711.

MS $(ESI)^+$: m/z [M + H] 270.1.

HRMS: [M] for $C_{15}H_{15}N_3O_2$ calculated 269.1164, found 269.1166.

3.29. 5-Benzyl-3-(3-methylpyridin-2-yl)-1,2,4-oxadiazole



230h

(*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-phenylacetamide **242h** (0.13 g; 0.48 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.54 (ethyl acetate/dichloromethane; 1:1); yellow oil 0.087 g, 72 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.68 - 8.64 (1H, m, Ar), 7.67 (1H, d, *J* = 7.6 Hz, Ar), 7.42 - 7.38 (3H, m, Ar), 7.35 - 7.29 (3H, m, Ar), 4.38 (2H, s, C$\underline{H}_2$), 2.65 (3H, s, C$\underline{H}_3$).

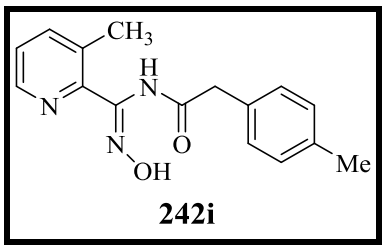
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.7 (C), 168.6 (C), 147.5 (CH), 144.9 (C), 139.4 (CH), 134.5 (C), 133.4 (C), 129.0 (CH), 128.9 (CH), 127.6 (CH), 124.7 (CH), 33.0 (CH_2), 20.6 (CH_3).

MS $(ESI)^+$: m/z [M + H] 252.1.

HRMS: [M] for $C_{15}H_{13}N_3O$ calculated 251.1059, found 251.1058.

New compound.

3.30. (*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-(*p*-tolyl)acetamide



242i

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of *p*-tolylacetic acid (0.15 g; 0.99 mmol) and

triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxy-3-methylpicolinimidamide **228c** (0.17 g; 1.1 mmol) was added and the reaction mixture was left at overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.48 (ethyl acetate/dichloromethane = 1:1); white solid 0.19 g 61 % yield; mp 125 - 126 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 - 8.44 (1H, m, Ar), 7.60 (1H, d, *J* = 7.5 Hz, Ar), 7.29 - 7.25 (3H, m, Ar), 7.18 (2H, d, *J* = 7.8 Hz, Ar), 5.75 (1H, s, O<u>H</u>), 5.31 (1H, s, N<u>H</u>), 3.85 (2H, s, C<u>H</u>$_2$), 2.69 (3H, s, C<u>H</u>$_3$), 2.36 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.3 (C=O), 155.7 (C), 146.1 (C), 145.8 (CH), 140.1 (CH), 136.8 (C), 134.4 (C), 130.8 (C), 129.3 (CH), 129.1 (CH), 124.5 (CH), 39.9 (CH_2), 21.7 (CH_3), 21.1 (CH_3).

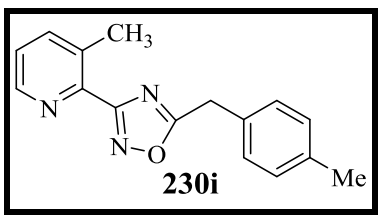
IR υ_{max} (cm^{-1}) 3378, 3304, 1732, 1695, 1620, 1516, 1336, 1220, 1205, 1144, 1106, 889, 803, 768.

MS $(ESI)^+$: m/z [M + H] 284.1.

HRMS: [M] for $C_{16}H_{17}N_3O_2$ calculated 283.1321, found 283.1322.

New compound.

3.31. 5-(4-Methylbenzyl)-3-(3-methylpyridin-2-yl)-1,2,4-oxadiazole



230i

(*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-(*p*-tolyl)acetamide **242i** (0.12 g; 0.42 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h

with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/dichloromethane = 1:1); yellow oil 0.077 g, 68 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.66 - 8.64 (1H, m, Ar), 7.65 (1H, d, *J* = 7.7 Hz, Ar), 7.33 - 7.28 (3H, m, Ar), 7.16 (2H, d, *J* = 7.7 Hz, Ar), 4.32 (2H, s, C$\underline{H}_2$), 2.63 (3H, s, C$\underline{H}_3$), 2.33 (3H, s, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.9 (C), 168.5 (C), 147.5 (CH), 144.9 (C), 139.3 (CH), 137.3 (C), 134.5 (C), 130.3 (C), 129.6 (CH), 128.9 (CH), 124.7 (CH), 32.6 (CH_2), 21.0 (CH_3), 20.6 (CH_3).

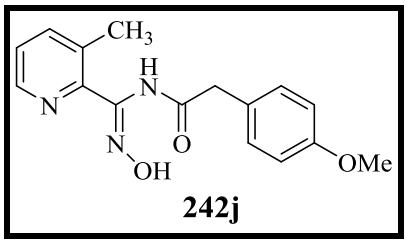
IR υ_{max} (cm^{-1}) 3031, 2927, 1564, 1513, 1358, 1140, 1107, 1038, 972, 886, 803, 786, 774, 727, 702, 677.

MS $(ESI)^+$: m/z [M + H] 266.1.

HRMS: [M] for $C_{16}H_{15}N_3O$ calculated 265.1215, found 265.1205.

New compound.

3.32. (*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide



242j

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of 4-methoxyphenylacetic acid (0.15 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, (*Z*)-*N'*-hydroxy-3-methylpicolinimidamide **228c** (0.17 g; 1.1 mmol) was added and the reaction mixture was left

at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.37 (ethyl acetate/dichloromethane = 1:1); white solid 0.2 g, 61 % yield; mp 127 - 128 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 - 8.34 (1H, m, Ar), 7.50 (1H, d, *J* = 7.6 Hz, Ar), 7.20 - 7.13 (3H, m, Ar), 6.80 (2H, d, *J* = 8.1 Hz, Ar), 5.67 (1H, br. s, O<u>H</u>), 5.43 (1H, br. s, N<u>H</u>), 3.72 (2H, s, C<u>H</u>$_2$), 3.71 (3H, s, C<u>H</u>$_3$), 2.58 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.5 (C=O), 158.7 (C), 155.6 (C), 146.1 (C), 145.8 (CH), 140.2 (CH), 134.4 (C), 130.3 (CH), 125.9 (C), 124.6 (CH), 114.0 (CH), 55.2 (CH_3), 39.4 (CH_2), 21.7 (CH_3).

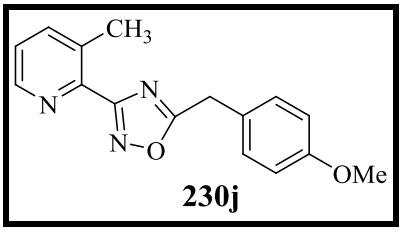
IR υ_{max} (cm^{-1}) 3446, 3330, 1726, 1614, 1558, 1513, 1465, 1407, 1379, 1331, 1245, 1151, 1110, 1032, 884, 804, 725, 579.

MS $(ESI)^+$: m/z [M + H] 300.1.

HRMS: [M] for $C_{16}H_{17}N_3O_3$ requires 299.1270, found 299.1262.

New compound.

3.33. 5-(4-Methoxybenzyl)-3-(3-methylpyridin-2-yl)-1,2,4-oxadiazole



230j

(*Z*)-*N*-((Hydroxyimino)(3-methylpyridin-2-yl)methyl)-2-(4-methoxyphenyl)acetamide **242j** (0.16 g; 0.53 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.47 (ethyl acetate/dichloromethane = 1:1); yellow oil 0.13 g, 86 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (2H, d, *J* = 4.8 Hz, Ar), 7.40 - 7.38 (1H, dd, *J* = 4.8 and 4.8 Hz, Ar), 7.26 (2H, d, *J* = 8.4 Hz, Ar), 6.82 (2H, d, *J* = 8.4 Hz, Ar), 4.26 (2H, s, C<u>H</u>$_2$), 3.73 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.0 (C), 168.5 (C), 159.0 (C), 147.5 (CH), 144.9 (C), 139.4 (CH), 134.5 (C), 130.1 (CH), 125.4 (C), 124.7 (CH), 114.3 (CH), 55.2 (OCH_3), 32.1 (CH_2), 20.6 (CH_3).

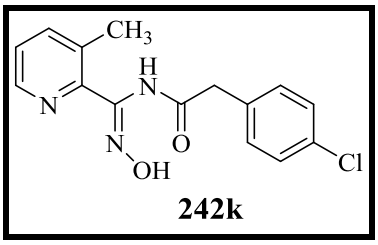
IR υ_{max} (cm^{-1}) 2981, 2937, 1726, 1614, 1558, 1513, 1465, 1407, 1379, 1331, 1245, 1151, 1110, 1032, 884, 804, 725.

MS $(ESI)^+$: m/z [M + H] 282.1.

HRMS: [M] for $C_{16}H_{15}N_3O_2$ calculated 281.1164, found 281.1163.

New compound.

3.34. (*Z*)-2-(4-Chlorophenyl)-N-((hydroxyimino)(3-methylpyridin-2-yl)methyl)acetamide



242k

To a stirred solution of diphenylcyclopropenone (0.23 g; 1.1 mmol) in dichloromethane (15 mL), was added oxalyl chloride (0.13 g; 0.084 mL; 1.0 mmol) dropwise under an inert atmosphere at rt. After 5 minutes, a mixture of 4-methoxyphenylacetic acid (0.17 g; 1.0 mmol) and triethylamine (0.22 g; 0.31 mL; 2.2 mmol) in dichloromethane (15 mL) was added in one portion to the reaction mixture. After 15 minutes, *N*'-hydroxypyridine-2-carboxamidine **228c** (0.17 g; 1.1 mmol) was added and the reaction mixture was left at room temperature overnight. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.39 (ethyl acetate/dichloromethane = 1:5); white solid 0.19 g, 57 % yield; mp 137 - 138 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (1H, d, *J* = 4.9 Hz, Ar), 7.61 (1H, d, *J* = 7.7 Hz, Ar), 7.36 - 7.31 (3H, m, Ar), 7.30 - 7.27 (2H, m, Ar), 5.75 (1H, br. s, O<u>H</u>), 5.39 (1H, br. s, N<u>H</u>), 3.87 (2H, s, C<u>H</u>$_2$), 2.69 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.8 (C=O), 155.7 (C), 145.9 (C), 145.8 (CH), 140.2 (CH), 134.4 (C), 133.1 (C), 132.2 (C), 130.7 (CH), 128.8 (CH), 124.6 (CH), 39.5 (CH_2), 21.8 (CH_3).

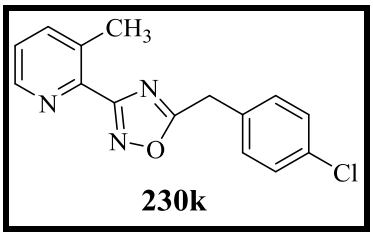
IR υ_{max} (cm^{-1}) 3381, 3304, 1730, 1621, 1607, 1568, 1492, 1446, 1406, 1381, 1335, 1211, 1155 **MS** $(ESI)^+$: m/z [M+H] 230.1., 1108, 1088, 1012, 884, 804, 764, 732, 684, 666, 642.

MS $(ESI)^+$: m/z [M + H] 304.1.

HRMS: $C_{15}H_{14}{}^{35}ClN_3O_2$ calculated 303.0775, found 303.0772.

New compound.

3.35. 5-(4-Chlorobenzyl)-3-(3-methylpyridin-2-yl)-1,2,4-oxadiazole



230k

(*Z*)-2-(4-Chlorophenyl)-*N*-((hydroxyimino)(3-methylpyridin-2-yl)methyl)acetamide **242k** (0.15 g; 0.53 mmol) was added to xylene (10 mL) and the reaction mixture was heated at reflux for 18 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.47 (ethyl acetate/dichloromethane = 1:1); yellow oil 0.11 g, 70 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.68 -8.64 (1H, d, *J* = 4.4 Hz, Ar), 7.67 (1H, d, *J* = 7.7 Hz, Ar), 7.36 - 7.28 (5H, m, Ar), 4.34 (2H, s, C<u>H</u>$_2$), 2.64 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 177.2 (C), 168.6 (C), 147.6 (CH), 144.7 (C), 139.4 (CH), 134.6 (C), 133.7 (C), 131.8 (C), 130.4 (CH), 129.1 (CH), 124.8 (CH), 32.3 (CH_2), 20.7 (CH_3).

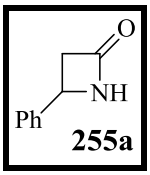
IR υ_{max} (cm^{-1}) 2931, 1556, 1491, 1454, 1416, 1350, 1091, 1015, 895, 801, 784, 772, 722, 701.

MS $(ESI)^+$: m/z [M + H] 286.1.

HRMS: [M] for $C_{15}H_{12}{}^{35}ClN_3O$ calculated 285.0669, found 285.0666.

New compound.

3.36. 4-Phenylazetidin-2-one



255a

To a stirred solution of styrene (3.70; 31.90 mmol) in dry diethyl ether (15 mL), *N*-chlorosulfonyl isocyanate (3.20 mL; 37.10 mmol) was added dropwise at rt under an inert N_2 atmosphere over 10 min. The reaction mixture was kept at rt for 2 h with stirring, and then solvent was removed in *vacuo* to give an oily residue. After that diethyl ether (20 mL) was added and this solution was added dropwise to a vigorously stirred solution of water (30 mL), sodium carbonate (9.00 g; 107.10 mmol), sodium sulfite (6.01 g, 47.60 mmol) and ice (40 g) over 10 min. The reaction mixture was kept at rt for 1 h with stirring and filtered under vacuum. After separation, the aqueous phase was washed with dichloromethane (10 mL x 5), and then the combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.65 (ethyl acetate/petroleum ether = 3:1); white solid 0.75 g, 57 % yield; mp 111 - 112 ºC; lit.,[8] mp 102 - 103 ºC.

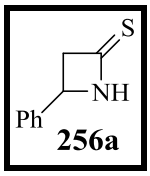
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 - 7.30 (5H, m, Ph), 6.15 (1H, br. s, NH), 4.75 (1H, dd, *J* = 5.3 Hz and 2.3 Hz, CH), 3.47 (1H, ddd, *J* = 14.9, 5.3 and 2.3 Hz, CH_2), 2.92 (1H, dd, *J* = 14.9 and 2.3 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.0 (C=O), 140.2 (C), 128.9 (CH), 128.3 (CH), 125.7 (CH), 50.4 (CH), 48.1 (CH_2).

IR υ_{max} (cm^{-1}) 3208, 1706, 1677, 1453, 1367, 1170, 961, 695.

As reported previously.[8]

2.37. 4-Phenylazetidin-2-thione



256a

To a stirred solution of 4-phenylazetidin-2-one **255a** (1.07 g; 7.31 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.54 g; 3.80 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.65 (ethyl acetate/petroleum ether = 1:3); white solid 0.91 g, 66 % yield; mp 113-114 ºC; lit.,[8] mp 117-118 ºC.

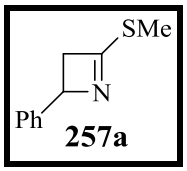
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.19 (1H, br. s, NH), 7.44 – 7.36 (5H, m, Ph), 5.20 (1H, dd, *J* = 4.6 Hz and 2.1 Hz, CH), 3.53 (1H, ddd, *J* = 15.5, 4.6, and 2.1 Hz, CH_2), 3.08 (1H, dd, *J* = 15.5 and 2.1 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 204.5 (C=S), 138.1 (C), 129.1 (CH), 128.9 (CH), 125.8 (CH), 58.9 (CH), 51.3 (CH_2).

IR υ_{max} (cm^{-1}) 3136, 2926, 1486, 1489, 1235, 979, 754, 684.

As reported previously.[8]

3.38. 2-Methylthio-4-phenyl-1-azetine



257a

Trimethyloxonium tetrafluoroborate (0.16 g; 1.06 mmol) was added in one portion to 4-phenylazetidin-2-thione **256a** (0.10 g; 0.61 mmol) in anhydrous dichloromethane (3.5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.67 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.055 g, 51 % yield.

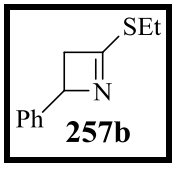
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 - 7.17 (5H, m, Ph), 4.93 (1H, dd, *J* = 4.3 and 2.1 Hz, C<u>H</u>), 4.28 (1H, dd, *J* = 14.6 and 4.3 Hz, C<u>H</u>$_2$), 2.90 (1H, dd, *J* = 14.6 and 2.1 Hz, C<u>H</u>$_2$), 2.39 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 183.9 (C), 140.8 (C), 128.5 (CH), 127.5 (CH), 126.1 (CH), 64.9 (CH), 43.1 (CH_2), 11.5 (CH_3).

IR υ_{max} (cm^{-1}) 3031, 2943, 1516, 1437, 1264, 1029, 859, 755, 688.

As reported previously.[8]

3.39. 2-Ethylthio-4-phenyl-1-azetine



257b

Triethyloxonium tetrafluoroborate (0.20 g; 1.06 mmol) was added in one portion to 4-phenylazetidin-2-thione **256a** (0.10 g; 0.61 mmol) in anhydrous dichloromethane (3.5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried ($MgSO_4$). The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.66 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.074 g, 63 % yield.

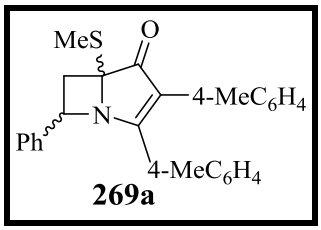
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.20 (5H, m, Ph), 5.05 (1H, dd, *J* = 4.3 and 2.1 Hz, C<u>H</u>), 3.59 (1H, dd, *J* = 14.7 and 4.3 Hz, C<u>H</u>$_2$), 3.08 (2H, q, *J* = 7.5 Hz, C<u>H</u>$_2$), 2.99 (1H, dd, *J* = 14.7 and 2.1 Hz, C<u>H</u>$_2$), 1.43 (3H, t, *J* = 7.5, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm, 183.7 (C), 140.9 (C), 128.5 (CH), 127.4 (CH), 126.1 (CH), 65.2 (CH), 43.7 (CH_2), 23.5 (CH_2), 11.5 (CH_3).

IR υ_{max} (cm^{-1}) 3021, 2961, 1522, 1419, 1224, 1067, 887, 757, 697.

As reported previously.[8]

3.40. 5-Methylthio-7-phenyl-2,3-bis(*p*-tolyl)-1-azabicyclo[3.2.0]hept-2-en-4-one



269a

To a stirred solution of 2-methylthio-4-phenyl-1-azetine **257a** (0.04 g; 0.21 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(*p*-tolyl)cycloprop-2-ene-1-one **241** (0.05 g; 0.21 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 72 h

and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a mixture of diastereoisomers (1:1).

R_f 0.58 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.045 g, 65 % yield; mp 138-139 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (2 x diastereo, 2H, d, *J* = 7.3, Ar), 7.37 – 6.82 (2 x diastereo, 22H, m, Ar), 6.66 (2 x diastereo, 2H, d, *J* = 8.0 Hz, Ar), 5.45 (1 x diastereo, 1H, t, *J* = 8.3 Hz, PhC<u>H</u>), 4.15 (1 x diastereo, 1H, dd, *J* = 9.6 and 5.6 Hz, PhC<u>H</u>), 3.06 (1 x diastereo, 1H, dd, *J* = 12.6 and 9.6 Hz, C<u>H</u>$_2$), 2.93 – 2.83 (2 x diastereo, 2H, m, C<u>H</u>$_2$), 2.38 (1 x diastereo, 1H, dd, *J* = 12.6 and 5.6 Hz, C<u>H</u>$_2$), 2.31 (3H, s, C<u>H</u>$_3$), 2.22 (3H, s, C<u>H</u>$_3$), 2.17 (3H, s, C<u>H</u>$_3$), 2.11 (3H, s, C<u>H</u>$_3$), 2.02, (3H, s, C<u>H</u>$_3$), 1.97 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.7, 202.5 (C=O), 177.2 (C), 174.9 (C), 142.5 (C), 141.1 (C), 141.5 (C), 137.1 (C), 136.7 (C), 135.3 (C), 130.1 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 129.1 (C), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (C), 128.1 (C), 127.8 (CH), 127.7 (CH), 127.2 (C), 126.9 (CH), 125.8 (C), 123.4 (C), 76.6 (C), 76.5 (C), 66.4 (CH), 65.9 (CH), 34.5 (CH_2), 31.2 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 11.7 (CH_3), 11.5 (CH_3).

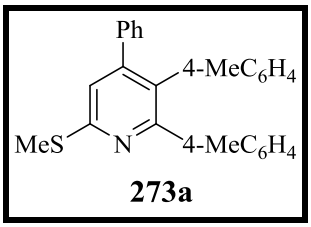
IR υ_{max} (cm^{-1}) 2986, 2906, 1675, 1579, 1496, 1372, 1182, 1018, 821, 758, 733, 696, 517.

MS $(ESI)^+$: m/z [M+H] 412.2.

HRMS: [M] for $C_{27}H_{25}NOS$ calculated 411.1657, found 411.1664.

New compound.

3.41. 6-Methylthio-4-phenyl-2,3-bis(*p*-tolyl)pyridine



273a

5-Methylthio-7-phenyl-2,3-bis(p-tolyl)-1-azabicyclo[3.2.0]hept-2-en-4-one **269a** (0.03 g; 0.08 mmol) was added to toluene (10 mL) and the reaction mixture was heated at reflux for 16 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound. **R_f** 0.48 (ethyl acetate/petroleum ether = 1:5); brown solid 0.019 g, 58 % yield; mp 180-181 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.20 - 7.11 (5H, m, Ar), 7.09 (1H, s, pyrid H), 6.97 – 6.95 (2H, m, Ar), 6.91 (2H, d, *J* = 7.8 Hz, Ar), 6.77 (2H, d, *J* = 7.8 Hz, Ar), 6.65 (2H, d, *J* = 7.8 Hz, Ar), 2.57 (3H, s, SC$\underline{H}_3$), 2.21 (3H, s, PhC$\underline{H}_3$), 1.15 (3H, s, PhC$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.5 (C), 157.4 (C), 150.2 (C), 139.5 (C), 137.6 (C), 137.1 (C), 135.9 (C), 134.6 (C), 131.2 (CH), 129.9 (CH), 129.2 (CH), 129.0 (C), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.2 (CH), 120.8 (CH), 21.2 (CH_3), 21.1 (CH_3), 13.3 (CH_3).

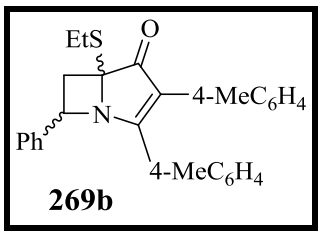
IR υ_{max} (cm^{-1}) 2955, 1555, 1510, 1491, 1354, 1159, 830, 815, 726, 701, 611.

MS $(ESI)^+$: m/z [M + H] 382.2.

HRMS: [M] for $C_{26}H_{23}NS$ calculated 381.1551, found 381.1581.

New compound

3.42. 5-Ethylthio-7-phenyl-2,3-bis(*p*-tolyl)-1-azabicyclo[3.2.0]hept-2-en-4-one



269b

To a stirred solution of 2-ethylthio-4-phenyl-1-azetine **257b** (0.04 g; 0.21 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(*p*-tolyl)cyclopropenone **241** (0.05 g; 0.21 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 72 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a mixture of diastereoisomers (2:1).

R_f 0.29 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.070 g, 67 % yield; mp 143 - 144 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (2 x diastereo, 2H, d, *J* = 7.4, Ar), 7.34 – 6.81 (2 x diastereo, 22H, m, Ar), 6.65 (2 x diastereo, 2H, d, *J* = 8.1 Hz, Ar), 5.45 (1 x diastereo, 1H, t, *J* = 8.3 Hz, PhC<u>H</u>), 4.15 (1 x diastereo, 1H, dd, *J* = 9.7 and 5.5 Hz, PhC<u>H</u>), 3.06 (1 x diastereo, 1H, dd, *J* = 12.7 and 9.7 Hz, CHC<u>H</u>$_2$), 2.92 – 2.81 (2 x diastereo, 2H, m, CHC<u>H</u>$_2$), 2.35 – 2.44 (1 x diastereo, 1H, m, CHC<u>H</u>$_2$), 2.45 – 2.76 (2 x diastereo, 4H, m, CH_3C<u>H</u>$_2$), 2.27 (3H, s, C<u>H</u>$_3$), 2.17 (3H, s, C<u>H</u>$_3$), 2.14 (3H, s, C<u>H</u>$_3$), 2.08, (3H, s, C<u>H</u>$_3$), 1.12 – 1.17 (6H, m, 2 x C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 203.0, 202.4 (C=O), 176.7 (C), 174.6 (C), 142.4 (C), 141.6 (C), 141.0 (C), 137.0 (C), 136.6 (C), 135.4 (C), 130.1 (CH), 129.5 (CH), 129.4 (CH), 129.3 (C), 129.3 (CH), 128.2 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (C), 128.2 (C), 127.8 (CH), 127.7 (CH), 127.1 (C), 125.7 (C), 123.3 (C), 76.8 (C), 76.7 (C), 66.6 (CH), 65.9 (CH), 35.3 (CH_2), 31.9 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 21.6 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 21.3 (CH_3), 14.6 (CH_3), 14.5 (CH_3).

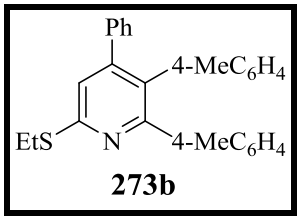
IR υ_{max} (cm^{-1}) 2988, 2945, 1677, 1608, 1495, 1374, 1242, 1013, 821, 757, 743, 696.

MS $(ESI)^+$: m/z [M + H] 426.2.

HRMS: [M + H] for $C_{28}H_{28}NOS$ calculated 426.1813, found 426.1886.

New compound.

3.43. 6-Ethylthio-4-phenyl-2,3-bis(*p*-tolyl)pyridine



273b

5-Ethylthio-7-phenyl-2,3-bis(*p*-tolyl)-1-azabicyclo[3.2.0]hept-2-en-4-one **269b** (0.03 g; 0.08 mmol) was added to toluene (10 mL) and the reaction mixture was heated at reflux for 16 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in*

vacuo. The crude product was purified by flash chromatography affording the title compound. **R_f** 0.49 (ethyl acetate/petroleum ether = 1:5); brown solid 0.022 g, 67 % yield; mp 189 - 190 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.15 – 7.08 (5H, m, Ar), 7.07 (1H, s, pyrid H), 6.97 - 6.94 (2H, m, Ar), 6.90 (2H, d, *J* = 8.0 Hz, Ar), 6.77 (2H, d, *J* = 8.0 Hz, Ar), 6.65 (2H, d, *J* = 8.0, Hz, Ar), 3.19 (2H, q, *J* = 7.3 Hz, CH_2), 2.22 (3H, s, $PhCH_3$), 2.16 (3H, s, $PhCH_3$), 1.36 (3H, t, *J* = 7.3 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.4 (C), 157.0 (C), 149.7 (C), 139.2 (C), 137.5 (C), 136.6 (C), 135.5 (C), 134.3 (C), 130.9 (CH), 129.6 (CH), 128.8 (CH), 128.4 (C), 127.9 (CH), 127.7 (CH), 127.4 (CH), 126.7 (CH), 121.0 (CH), 20.9 (CH_3), 20.8 (CH_3), 24.1 (CH_2), 14.6 (CH_3).

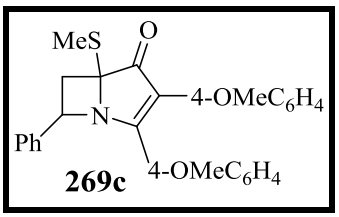
IR υ_{max} (cm^{-1}) 2966, 1554, 1510, 906, 812, 765, 727, 710, 611.

MS $(ESI)^+$: m/z [M + H] 396.2.

HRMS: [M] for $C_{27}H_{25}NS$ calculated 395.1708, found 395.1726.

New compound.

3.44. 5-Methylthio-7-phenyl-2,3-bis(*p*-methoxyphenyl)-1-azabicyclo[3.2.0]hept-2-en-4-one



269c

To a stirred solution of 2-methylthio-4-phenyl-1-azetine **257a** (0.03 g; 0.19 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(*p*-methoxyphenyl)cycloprop-2-en-1-one **237** (0.05 g; 0.19 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 72 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a single diastereoisomer. The crude

material was observed as a mixture of diastereoisomers (4:1) but unfortunately we could not obtain the second diastereoisomer in pure form.

R_f 0.41 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.035 g, 42 % yield; mp 113-114 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54 (2H, d, *J* = 7.4, Ar), 7.35 – 7.25 (7H, m, Ar), 6.81 (2H, d, *J* = 8.6 Hz, Ar), 6.61 (2H, d, *J* = 8.6 Hz, Ar), 4.16 (1H, dd, *J* = 9.6 and 5.6 Hz, PhC<u>H</u>), 3.75 (3H, s, OC<u>H</u>$_3$), 3.69 (3H, s, OC<u>H</u>$_3$), 3.69 (1H, dd, *J* = 12.6 and 9.6 Hz, C<u>H</u>$_2$), 2.38 (1H, dd, *J* = 12.6 Hz and 5.6 Hz, C<u>H</u>$_2$), 1.97 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.2 (C=O), 176.6 (C), 162.4 (C), 158.8 (C), 141.5 (C), 132.0 (CH), 130.1 (CH), 128.6 (CH), 127.9 (CH), 127.1 (CH), 123.7 (C), 122.3 (C), 122.2 (C), 114.0 (CH), 113.9 (CH), 76.4 (C), 66.6 (CH), 55.3 (OCH_3), 55.2 (OCH_3), 34.7 (CH_2), 11.5 (CH_3).

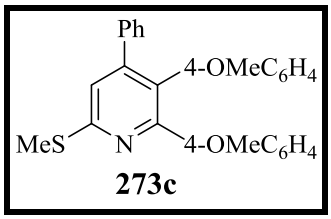
IR υ_{max} (cm^{-1}) 1673, 1601, 1496, 1370, 1241, 1171, 1024, 832, 761, 697.

MS $(ESI)^+$: m/z [M + H] 444.1.

HRMS: [M] for $C_{27}H_{25}NO_3S$ calculated 443.1555, found 443.1563.

New compound.

3.45. 6-Methylthio-4-phenyl-2,3-bis(*p*-methoxyphenyl)pyridine



273c

2,3-Bis(4-methoxyphenyl)-5-methylthio-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one **269c** (0.03 g; 0.06 mmol) was added to toluene (10 mL) and the reaction mixture was heated at reflux for 16 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.45 (ethyl acetate/petroleum ether = 1:5); brown solid 0.014 g, 61 % yield; mp 167 - 168 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 – 7.20 (5H, m, Ar), 7.17 (1H, s, pyrid-H), 7.08 – 7.04 (2H, m, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 6.63 (2H, d, *J* = 8.7 Hz, Ar), 3.79 (3H, s, CH_3), 3.74 (3H, s, CH_3), 2.67 (3H, s, SCH_3).

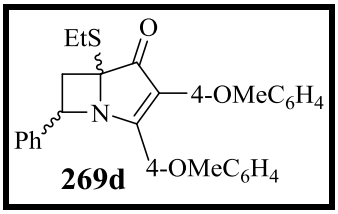
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.9 (C), 158.1 (C), 157.4 (C), 157.1 (C), 150.2 (C), 139.6 (C), 133.2 (C), 132.5 (CH), 131.4 (CH), 130.1 (C), 129.5 (C), 129.2 (CH), 127.8 (CH), 127.2 (CH), 120.6 (CH), 113.3 (CH), 112.9 (CH), 55.2 (CH_3), 55.1 (CH_3), 13.4 (CH_3).

IR υ_{max} (cm^{-1}) 2958, 2933, 1607, 1556, 1510, 1246, 1177, 1033, 836, 700.

MS $(ESI)^+$: m/z [M + H] 414.1.

HRMS [M] for $C_{26}H_{23}NO_2S$ calculated 413.1449, found 413.1453.

3.46. 5-Ethylthio-7-phenyl-2,3-bis(*p*-methoxyphenyl)-1-azabicyclo[3.2.0]hept-2-en-4-one



269d

To a stirred solution of 2-ethylthio-4-phenyl-1-azetine **257b** (0.05 g; 0.26 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.07 g; 0.26 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 72 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a mixture of diastereoisomers.

R_f 0.26 (ethyl acetate/petroleum ether; 1:5); orange yellow solid 0.047 g, 39 % yield; mp 136 - 137 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 (2 x diastereo, 2H, d, *J* = 7.5 Hz, Ar), 7.45 - 6.90 (2 x diastereo, 14H, m, Ar), 6.84 (2 x diastereo, 4H, d, *J* = 7.5 Hz, Ar), 6.48 (2 x diastereo, 4H, d, *J* = 7.5 Hz, Ar), 6.48 (2 x diastereo, 2H, *J* = 7.5 Hz, Ar), 5.46 -5.44 (1 x diastereo, 1H, m, *J* =

8.0 Hz, PhC<u>H</u>), 4.15 (1 x diastereo, 1H, dd, *J* = 9.2 and 5.4 Hz, PhC<u>H</u>), 3.84 (3H, s, OCH_3), 3.79 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $OC\underline{H}_3$), 3.72 (3H, s, $OC\underline{H}_3$), 3.17 (1 x diastereo, 1H, dd, *J* = 12.7 and 9.2 Hz, $CHC\underline{H}_2$), 3.02 – 2.85 (2 x diastereo, 2H, m, $CHC\underline{H}_2$), 2.74 – 2.53 (2 x diastereo, 4H, m, $C\underline{H}_2$), 2.48 (1 x diastereo, 1H, dd, *J* = 12.7 and 5.4 Hz, $C\underline{H}_2$), 2.53 – 2.74 (2 x diastereo, 6H, s, 2 x $C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.8, 202.3 (C=O), 176.1 (C), 173.8 (C), 162.3 (C), 161.4 (C), 158.8 (C), 158.6 (C), 141.6 (C), 135.4 (C), 131.9 (CH), 131.2 (CH), 130.0 (CH), 129.7 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.2 (C), 128.1 (C), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 124.8 (C), 124.5 (C), 123.8 (C), 123.7 (C), 122.3 (C), 122.2 (C), 114.0 (CH), 113.9 (CH), 113.8 (CH), 113.1 (CH), 76.8 (C), 76.7 (C), 66.7 (CH), 65.8 (CH), 55.3 (CH_3), 55.2 (CH_3), 55.1 (CH_3), 55.0 (CH_3), 35.5 (CH_2), 31.1 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 14.6 (CH_3), 14.5 (CH_3).

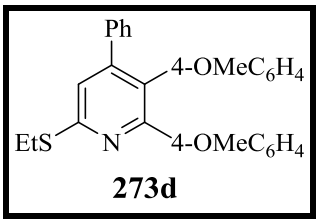
IR υ_{max} (cm^{-1}) 2932, 1673, 1602, 1515, 1496, 1372, 1244, 1171, 833, 755, 697.

MS $(ESI)^+$: m/z [M + H] 458.2.

HRMS [M] for $C_{28}H_{27}NO_3S$ calculated 457.1712, found 457.1716.

New compound.

3.47. 6-Ethylthio-4-phenyl-2,3-bis(*p*-methoxyphenyl)pyridine



273d

5-Ethylthio-2,3-bis(4-methoxyphenyl)-7-phenyl-1-azabicyclo[3.2.0]hept-2-en-4-one **269d** (0.035 g; 0.06 mmol) was added to toluene (10 mL) and the reaction mixture was heated at reflux for 16 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.45 (ethyl acetate/petroleum ether; 1:5); brown solid 0.022 g, 55 % yield; mp 173 - 174 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.17 – 7.09 (5H, m, Ar), 7.06 (1H, s, pyrid-H), 6.97 – 6.92 (2H, m, Ar), 6.68 (2H, d, *J* = 8.6, Ar), 6.64 (2H, d, *J* = 8.6, Ar), 6.53 (2H, d, *J* = 8.6, Ar), 3.70 (3H, s, C<u>H</u>$_3$), 3.65 (3H, s, C<u>H</u>$_3$), 3.19 (2H, q, *J* = 7.3 Hz, C<u>H</u>$_2$), 1.37 (3H, t, *J* = 7.3 Hz, CH_2C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.9 (C), 158.1 (C), 157.2 (C), 156.9 (C), 150.2 (C), 139.6 (C), 133.3 (C), 132.5 (CH), 131.4 (CH), 130.2 (C), 129.5 (C), 129.2 (CH), 127.8 (CH), 127.2 (CH), 121.2 (CH), 113.3 (CH), 112.9 (CH), 55.2 (CH_3), 55.1 (CH_3), 24.5 (CH_2), 14.9 (CH_3).

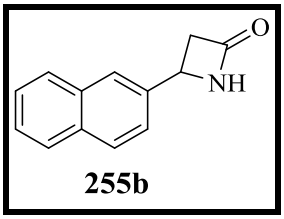
IR υ_{max} (cm^{-1}) 1607, 1556, 1510, 1245, 1176, 1034, 836, 821, 700.

MS $(ESI)^+$: m/z [M + H] 428.2.

HRMS [M] for $C_{27}H_{25}NO_2S$ calculated 427.1606, found 427.1609.

New compound.

3.48. 4-(2′-Naphthyl)-1-azetidin-2-one



255b

To a stirred solution of 2-vinylnaphthalene (1.00 g; 6.48 mmol) in dry diethyl ether (15 mL), *N*-chlorosulfonyl isocyanate (0.68 mL; 7.78 mmol) was added dropwise at rt under an inert N_2 atmosphere over 10 min. The reaction mixture was kept at rt for 2 h with stirring, and then solvent was removed *in vacuo* to give an oily residue. After that diethyl ether (20 mL) was added and this solution was added dropwise to a vigorously stirred solution of water (30 mL), sodium carbonate (2.30 g, 21.39 mmol), sodium sulfite (1.21 g, 9.72 mmol) and ice (15 g) over 10 min. The reaction mixture was kept at rt for 1 h with stirring and filtered under

vacuum. After separation, the water phase was washed with dichloromethane (10 mL x 5), and then the combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

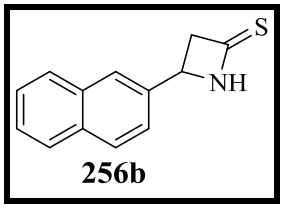
R_f 0.22 (ethyl acetate/petroleum ether = 3:1); white solid 0.66 g, 48 % yield; mp 160 - 161 ºC lit.,[106] 153 - 155 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 – 7.84 (5H, m, Ar), 7.55 – 7.49 (2H, m, Ar), 6.29 (1H, br. s, NH), 4.90 (1H, dd, *J* = 5.2 Hz and 2.4 Hz, CH), 3.54 (1H, ddd, *J* = 14.9, 5.2 and 2.4 Hz, CH_2), 2.97 (1H, dd, *J* = 14.9 and 1.9 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.9 (C=O), 137.4 (C), 133.1 (C), 128.9 (C), 127.8 (CH), 127.7 (CH), 126.6 (CH), 126.3 (CH), 124.8 (CH), 123.1 (CH), 50.0 (CH), 48.0 (CH_2); **IR** υ_{max} (cm^{-1}) 3234, 3053, 1760, 1563, 1506, 1354, 1268, 1180, 968, 885, 853, 740.

As reported previously.[106, 140]

3.49. 4-(2′-Naphthyl)-1-azetidin-2-thione



256b

To a stirred solution of 4-(2′-naphthyl)-1-azetidin-2-one **255b** (1.08 g; 5.49 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.12 g; 2.74 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.48 (ethyl acetate/petroleum ether = 1:3); white solid 0.72 g, 67 % yield; mp 161-162 ºC lit., not reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.55 (1H, br. s, NH), 7.90 (1H, d, *J* = 8.6 Hz, Ar), 7.85 (2H, dd, *J* = 9.3 and 5.1 Hz, Ar), 7.81 (1H, s, Ar), 7.56 – 7.52 (2H, m, Ar), 7.48 (1H, dd, *J* =

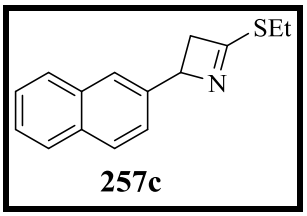
8.5 Hz and 1.6 Hz, C<u>H</u>), 4.35 (1H, dd, *J* = 4.6 and 1.6 Hz, C<u>H</u>), 3.61 (1H, ddd, *J* = 15.6, 4.6, and 2.0 Hz, C<u>H</u>$_2$), 3.10 (1H, dd, *J* = 15.6 and 1.2 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 204.4 (C=S), 135.3 (C), 133.3 (C), 133.1 (C), 129.1 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 126.6 (CH), 125.2 (CH), 122.9 (CH), 59.1 (CH), 51.2 (CH_2).

IR υ_{max} (cm^{-1}) 3114, 2950, 1598, 1480, 1401, 1336, 1248, 1167, 973, 895, 865, 819, 766, 705.

As reported previously.[82, 106]

3.50. 4-Ethylthio-2-(2′-naphthyl)-1-azetine



257c

Triethyloxonium tetrafluoroborate (0.24 g; 1.27 mmol) was added in one portion to 4-(2′-naphthyl)-1-azetidine-2-thione **256b** (0.16 g; 0.75 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 h under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.29 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.11 g, 59 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87 – 7.82 (4H, m, Ar), 7.51 – 7.44 (3H, m, Ar), 5.22 (1H, dd, *J* = 4.4 and 2.1 Hz, C<u>H</u>), 3.66 (1H, dd, *J* = 14.6 and 4.2 Hz, C<u>H</u>$_2$), 3.13 (2H, q, *J* = 7.4 Hz, SC<u>H</u>$_2$CH$_3$) 3.06 (1H, dd, *J* = 14.6 and 2.1 Hz, C<u>H</u>$_2$), 1.46 (3H, t, *J* = 7.4, C<u>H</u>$_3$).

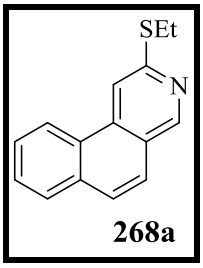
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 183.8 (C), 138.5 (C), 133.3 (C), 132.8 (C), 128.3 (CH), 127.9 (CH), 127.6 (CH), 126.1 (CH), 125.8 (CH), 124.8 (CH), 123.9 (CH), 65.2 (CH), 43.6 (CH_2), 23.5 (CH_2), 14.7 (CH_3).

IR υ_{max} (cm^{-1}) 3030, 1567, 1429, 1403, 1309, 1227, 1073, 963, 710.

HRMS: Mass spectrometry data could not be obtained due to the degradation of the title compound at rt.

New compound.

3.51. 2-Ethylthiobenzo[*f*]isoquinoline



268a

Triethyloxonium tetrafluoroborate (0.24 g; 1.27 mmol) was added in one portion to 4-(2′-naphthyl)-1-azetidin-2-thione **256b** (0.16 g; 0.75 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 h under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo* and the crude product was kept at rt in deuterated chloroform for 7-days and after that it was purified by flash chromatography affording the title compound.

R_f 0.48 (ethyl acetate/petroleum ether; 1:3); light yellow oil 0.13 g, 73 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.30 (1H, d, *J* = 7.6 Hz, Ar), 7.96 – 7.90 (2H, m, Ar), 7.75 - 7.68 (3H, m, Ar), 7.64 (1H, d, *J* = 8.7, Ar), 7.37 (1H, d, *J* = 8.4, Ar), 3.52 (2H, q, *J* = 7.3 Hz, $SC\underline{H}_2CH_3$) 1.59 (3H, t, *J* = 7.3, $C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.1 (C), 146.2 (C), 135.3 (CH), 133.9 (C), 130.9 (C), 128.0 (CH), 127.7 (CH), 126.7 (CH), 126.0 (CH), 125.2 (CH), 124.3 (CH), 123.2 (C), 121.2 (CH), 24.5 (CH_2), 14.6 (CH_3).

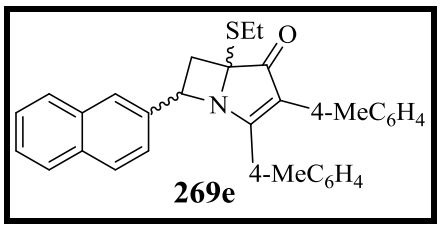
IR υ_{max} (cm^{-1}) 3051, 2922, 2022, 1586, 1556, 1493, 1123, 1074, 836, 747.

MS $(ESI)^+$: m/z [M + H] 240.1.

HRMS: [M] for $C_{15}H_{13}NS$ calculated 239.0769, found 239.0779.

New compound.

3.52. 5-Ethylthio-7-methyl-2,3-bis(*p*-tolyl)-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one



269e

To a stirred solution of 4-ethylthio-2-(2-naphthyl)-1-azetine **257c** (0.09 g; 0.13 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(*p*-tolyl)cyclopropenone **241** (0.09 g; 0.13 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 72 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a mixture of diastereoisomers (1:1).

R_f 0.4 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.077 g, 42 % yield; mp 180 - 181 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 – 7.88 (2 x diastereo, 5H, m, Ar), 7.61 – 7.44 (4 x diastereo, 5H, m, Ar), 7.38 – 7.24 (2 x diastereo, 10H, m, Ar), 7.19 (2 x diastereo, 2H, d, *J* = 7.7, Ar), 7.08 (2 x diastereo, 2H, d, *J* = 7.7, Ar), 7.04 – 6.91 (2 x diastereo, 2H, m, Ar), 6.80 (2 x diastereo, 2H, d, *J*= 7.7 Hz, Ar), 6.76 (2 x diastereo, 2H, d, *J* = 7.7 Hz, Ar), 5.74 (1 x

diastereo, 1H, t, *J* = 8.1 Hz, PhC<u>H</u>), 4.42 (1 x diastereo, 1H, dd, *J* = 9.3 and 5.4 Hz, PhC<u>H</u>), 3.23 (1 x diastereo, 1H, dd, *J* = 12.2 and 9.9 Hz, CHC<u>H</u>$_2$), 3.15 (1 x diastereo, 1H, dd, *J* = 13.1 and 8.1 Hz, CHC<u>H</u>$_2$), 3.01 (1 x diastereo, 1H, dd, *J* = 13.1 and 8.5 Hz, CHC<u>H</u>$_2$), 2.81 – 2.59 (2 x diastereo, 4H, m, $CH_3C\underline{H}_2$), 2.54 (1 x diastereo, 1H, dd, *J* = 13.1 and 5.4 Hz, CHC<u>H</u>$_2$), 2.39 (3H, s, C<u>H</u>$_3$), 2.30 (3H, s, C<u>H</u>$_3$), 2.28 (3H, s, C<u>H</u>$_3$), 1.98 (3H, s, C<u>H</u>$_3$), 1.30 – 1.24 ((6H, m, 2 x C<u>H</u>$_3$).

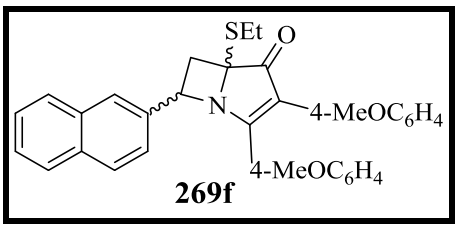
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.9, 202.4 (C=O), 176.6 (C), 174.8 (C), 142.4 (C), 140.9 (C), 138.9 (C), 137.0 (C), 136.6 (C), 133.1 (C), 133.0 (C), 132.8 (C), 132.4 (C), 132.3 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.9 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.2 (C), 128.1 (CH), 128.0 (CH), 127.8 (CH), 128.7 (CH), 127.3 (CH), 127.2 (CH), 127.1 (C), 126.3 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 125.5 (C), 124.9 (CH), 123.3 (C), 76.9 (C), 76.8 (C), 66.7 (CH), 66.1 (CH), 35.3 (CH_2), 31.5 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 14.6 (CH_3), 14.5 (CH_3); **IR** υ_{max} (cm^{-1}) 3011, 1673, 1574, 1496, 1370, 1258, 1015, 790, 737.

MS $(ESI)^+$: m/z [M + H] 276.2.

HRMS: [M] for $C_{32}H_{29}NOS$ calculated 475.1970, found 475.1981.

New compound.

3.53. 5-Ethylthio-2,3-bis(*p*-methoxyphenyl)-7-naphthyl-1-azabicyclo[3.2.0]hept-2-en-4-one



269f

To a stirred solution of 4-ethylthio-2-(2-naphthyl)-1-azetine **257c** (0.09 g; 0.13 mmol) in anhydrous acetonitrile (5 mL), was added 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.09 g; 0.13 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred

at rt for 72 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a mixture of diastereoisomers (1.5:1).

R_f 0.39 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.065 g, 33 % yield; mp 174 - 175 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 – 7.78 (2 x diastereo, 5H, m, Ar), 7.52 – 7.43 (4 x diastereo, 5H, m, Ar), 7.33 – 7.21 (2 x diastereo, 8H, m, Ar), 7.94 – 6.89 (2 x diastereo, 2H, m, Ar), 6.83 (2 x diastereo, 2H, d, *J* = 8.6, Ar), 6.77 (2 x diastereo, 2H, d, *J* = 8.6, Ar), 6.72 (2 x diastereo, 2H, d, *J* = 8.6 Hz, Ar), 6.57 (2 x diastereo, 2H, d, *J* = 8.6 Hz, Ar), 6.11 (2 x diastereo, 2H, d, *J* = 8.6 Hz, Ar), 5.63 (1 x diastereo, 1H, t, *J* = 8.1 Hz, PhC<u>H</u>), 4.30 (1 x diastereo, 1H, dd, *J* = 9.5 and 5.4 Hz, PhC<u>H</u>), 3.76 (3H, s, OC<u>H</u>$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.62 (3H, s, OC<u>H</u>$_3$), 3.40 (3H, s, OC<u>H</u>3), 3.14 (1 x diastereo, 1H, dd, *J* = 12.4 and 9.6 Hz, CHC<u>H</u>$_2$), 3.05 (1 x diastereo, 1H, dd, *J* = 13.1 and 7.9 Hz, CHC<u>H</u>$_2$), 2.92 (1 x diastereo, 1H, dd, *J* = 13.1 and 8.5 Hz, CHC<u>H</u>$_2$), 2.64 – 2.49 (2 x diastereo, 4H, m, CH_3C<u>H</u>$_2$), 2.45 (1 x diastereo, 1H, dd, *J* = 12.4 and 5.4 Hz, CHC<u>H</u>$_2$), 1.30 – 1.24 (6H, m, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.8, 202.2 (C=O), 176.0 (C), 174.1 (C), 162.3 (C), 161.2 (C), 158.8 (C), 158.5 (C), 139.0 (C), 133.2 (C), 132.6 (C), 132.3 (C), 131.9 (C), 131.0 (CH), 130.0 (CH), 129.6 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 127.2 (C), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.7 (CH), 125.0 (CH), 124.6 (C), 124.5 (C), 123.8 (C), 123.7 (C), 122.3 (C), 122.2 (C), 114.1 (CH), 114.0 (CH), 113.8 (C), 112.8 (CH), 71.1 (C), 77.0 (C), 66.8 (CH), 66.1 (CH), 55.3 (OCH_3), 55.2 (OCH_3), 55.1 (OCH_3), 55.0 (OCH_3), 35.5 (CH_2), 31.7 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 14.6 (CH_3), 14.5 (CH_3).

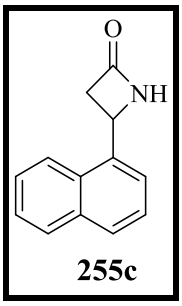
IR υ_{max} (cm^{-1}) 3037, 2941, 1605, 1443, 1249, 1177, 1031, 834.

MS $(ESI)^+$: m/z [M+H] 508.2.

HRMS: [M] for $C_{32}H_{29}NO_3S$ calculated 507.1868, found 507.1876.

New compound.

3.54. 4-(1'-Naphthyl)-1-azetidin-2-one



255c

To a stirred solution of 1-vinylnaphthalene (1.00 g; 6.48 mmol) in dry diethyl ether (15 mL), *N*-chlorosulfonyl isocyanate (0.68 mL; 7.78 mmol) was added dropwise at rt under an inert N_2 atmosphere over 10 min. The reaction mixture was kept at rt for 2 h with stirring, and then solvent was removed *in vacuo* to give an oily residue whivh was dissolved in rther (20 mL). The ethereal solution was added dropwise to a vigorously stirred solution of water (30 mL), sodium carbonate (2.30 g, 21.39 mmol), sodium sulfite (1.21 g, 9.72 mmol) and ice (15 g) over 10 min. The reaction mixture was kept for 1 h with stirring at rt and filtered under vacuum. After separation, the water phase was washed with dichloromethane (10 mL x 5), and then the combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.22 (ethyl acetate/petroleum ether = 3:1); white solid 0.57 g, 53 % yield; mp 155-156 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.95 - 7.93 (2H, m, Ar), 7.87 - 7.84 (2H, m, Ar), 7.60 - 7.49 (3H, m, Ar), 6.53 (1H, br. s, N<u>H</u>), 5.44 (1H, dd, *J* = 4.9 and 2.5 Hz, C<u>H</u>), 3.70 (1H, ddd, *J* = 14.6, 5.4 and 2.7 Hz, C<u>H</u>$_2$), 2.92 (1H, dd, 14.6 and 2.5 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.8 (C=O), 135.7 (C), 133.6 (C), 130.0 (C), 129.0 (CH), 128.3 (CH), 126.5 (CH), 126.1 (CH), 125.4 (CH), 122.3 (CH), 121.6 (CH), 48.1 (CH), 47.0 (CH_2).

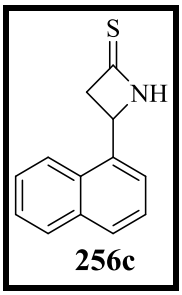
IR υ_{max} (cm^{-1}) 3183, 2931, 1751, 1665, 1594, 1505, 1354, 1284, 1190, 971, 798.

MS $(ESI)^+$: m/z [M + H] 198.1.

HRMS: [M] for $C_{13}H_{11}NO$ calculated 197.0841, found 197.0854.

Previously unreported.

3.55. 4-(1′-Naphthyl)-1-azetidine-2-thione



256c

To a stirred solution of 4-(1′-naphthyl)-1-azetidin-2-one **255c** (1.08 g; 5.49 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.12 g; 2.74 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.48 (ethyl acetate/petroleum ether = 1:3); white solid 0.72 g, 67 % yield; mp 156 - 157 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.52 (1H, br. s, NH), 7.96 - 7.77 (3H, m, Ar), 7.62 - 7.51 (4H, m, Ar), 5.94 (1H, dd, *J* = 4.7 and 2.1 Hz, CH), 3.61 (1H, ddd, *J* = 15.3, 4.7, and 2.4 Hz, CH_2), 3.10 (1H, dd, *J* = 15.3 and 2.1 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 204.1 (C=S), 133.8 (C), 133.6 (C), 129.5 (C), 129.1 (CH), 128.8 (CH), 126.8 (CH), 126.3 (CH), 125.4 (CH), 122.1 (CH), 122.0 (CH), 56.5 (CH), 50.3 (CH_2).

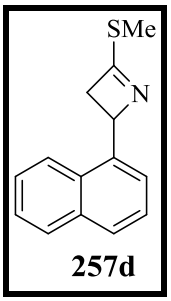
IR υ_{max} (cm^{-1}) 3028, 2913, 1573, 1487, 1417, 1338, 1246, 1164, 972, 893, 821, 765, 706.

MS $(ESI)^+$: m/z [M + H] 214.1.

HRMS: [M] for $C_{13}H_{11}NS$ calculated 213.0610, found 213.0615

Previously unreported.

3.56. 4-Methylthio-2-(1′-naphthyl)-1-azetine



257d

Trimethyloxonium tetrafluoroborate (0.14 g; 1.01 mmol) was added in one portion to 4-(1′-naphthyl)-1-azetidin-2-thione **256c** (0.13 g; 0.56 mmol) in anhydrous dichloromethane (10 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried ($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.29 (ethyl acetate/petroleum ether; 1:3); yellow oil 0.053 g, 40 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 – 7.69 (3H, m, Ar), 7.53 (1H, d, *J* = 6.9 Hz, Ar), 7.46 – 7.38 (3H, m, Ar), 5.56 (1H, dd, *J* = 4.2 and 2.0 Hz, C<u>H</u>), 3.68 (1H, dd, *J* = 14.4 and 4.2 Hz, C<u>H</u>$_2$), 2.89 (1H, dd, *J* = 14.4 and 2.0 Hz, C<u>H</u>$_2$), 2.44 (3H, s, C<u>H</u>$_3$).

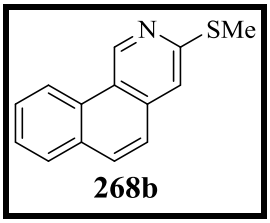
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 183.6 (C), 137.0 (C), 133.5 (C), 130.1 (C), 128.9 (CH), 127.5 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 123.1 (CH), 122.6 (CH), 62.0 (CH), 43.2 (CH_2), 11.6 (CH_3).

IR υ_{max} (cm^{-1}) 3016, 2929, 1727, 1431, 1329, 1241, 1173, 97, 890, 609.

HRMS: Mass spectrometry data could not be obtained due to the degradation of the title compound at rt.

New compound.

3.57. 2-Methylthiobenzo[*f*]isoquinoline



268b

Trimethyloxonium tetrafluoroborate (0.14 g; 1.01 mmol) was added in one portion to 4-(1′-naphthyl)-1-azetidin-2-thione **256c** (0.13 g; 0.56 mmol) in anhydrous dichloromethane (10 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried ($MgSO_4$). The solvents were removed *in vacuo* and the crude product was kept at rt in deuterated chloroform for 7-days and after that it was purified by flash chromatography affording the title compound.

R_f 0.66 (ethyl acetate/petroleum ether = 1:3); light yellow solid 0.11 g, 87 % yield; mp 93 - 94 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.62 (1H, d, *J* = 8.8 Hz, Ar), 8.46 (1H, d, *J* = 8.2 Hz, Ar) 7.89 - 7.81 (3H, m, Ar), 7.61 - 7.50 (2H, m, Ar), 7.34 (1H, d, *J* = 8.8 Hz, Ar), 2.66 (3H, s, $C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.5 (C), 148.2 (C), 131.1 (C), 130.9 (CH), 130.2 (CH), 129.8 (C), 128.7 (CH), 127.5 (CH), 127.0 (CH), 126.5 (CH), 122.2 (CH), 122.1 (C), 120.2 (CH), 13.1 (CH_3).

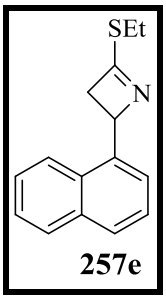
IR υ_{max} (cm^{-1}) 3047, 2923, 1574, 1562, 1445, 1166, 1141, 1077, 869, 838, 747.

MS $(ESI)^+$: m/z [M + H] 226.1.

HRMS: [M] for $C_{14}H_{11}NS$ calculated 225.0612, found 225.0620.

Novel compound.

3.58. 2-Ethylthio-4-(1ˈ-naphthyl)-1-azetine



257e

Triethyloxonium tetrafluoroborate (0.24 g; 1.28 mmol) was added in one portion to 4-(1-naphthyl)-1-azetidine-2-thione **256c** (0.16 g; 0.54 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50% aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.35 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.091 g, 51 % yield.

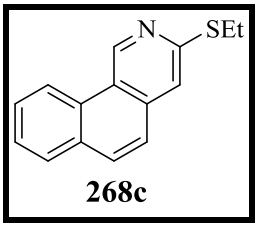
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.93 - 7.79 (3H, m, Ar), 7.43 (1H, d, *J* = 7.0 Hz, Ar), 7.56 - 7.49 (3H, m, Ar), 5.69 (1H, d, *J* = 1.8 Hz, CH), 3.66 (1H, dd, *J* = 14.3 and 4.2 Hz, CHC$\underline{H}_2$), 3.21 - 3.11 (2H, m, C$\underline{H}_2$CH$_3$) 2.99 (1H, dd, *J* = 14.3 and 4.2 Hz, CHC$\underline{H}_2$), 1.48 (3H, t, *J* = 7.4, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 183.4 (C), 137.1 (C), 133.5 (C), 130.1 (C), 128.9 (CH), 127.5 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 123.1 (CH), 122.6 (CH), 62.3 (CH), 43.7 (CH_2), 23.6 (CH_2), 14.8 (CH_3).

HRMS: Mass spectrometry data could not be obtained due to the degradation of the title compound at rt.

New compound.

3.59. 2-Ethylthiobenzo[*f*]isoquinoline



268c

Triethyloxonium tetrafluoroborate (0.24 g; 1.28 mmol) was added in one portion to 4-(1′-naphthyl)-1-azetidine-2-thione **256c** (0.16 g; 0.54 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo* and the crude product was kept at rt in deuterated chloroform for 7-days and after that it was purified by flash chromatography affording the title compound.

R_f 0.61 (ethylacetate/hexane = 1:3); light yellow solid 0.11 g, 78 % yield; mp 94 - 95 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.61 (1H, d, *J* = 8.7 Hz, Ar), 8.45 (1H, d, *J* = 8.2 Hz, Ar) 7.88 - 7.80 (3H, m, Ar), 7.60 - 7.50 (2H, m, Ar), 7.31 (1H, d, *J* = 8.7 Hz, Ar), 3.29 (2H, q, *J* = 7.3 Hz, C$\underline{H}_2$), 1.39 (3H, t, *J* = 7.3, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.1 (C), 148.3 (C), 131.1 (C), 130.8 (CH), 130.3 (CH), 129.8 (C), 128.6 (CH), 127.6 (CH), 127.0 (CH), 126.5 (CH), 122.3 (CH), 122.2 (C), 120.3 (CH), 24.4 (CH_2), 14.7 (CH_3).

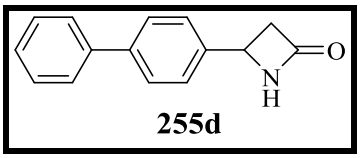
IR υ_{max} (cm^{-1}) 3049, 2920, 1581, 1573, 1562, 1445, 1144, 1129, 1078, 838, 774, 749.

MS $(ESI)^+$: m/z [M + H] 240.1.

HRMS: [M] for $C_{15}H_{13}NS$ calculated 239.0769, found 239.0776.

New compound.

3.60. 4-Biphenyl-1-azetidin-2-one



255d

To a stirred solution of 4-vinylbiphenyl (1.00 g; 5.55 mmol) in dry diethyl ether (15 mL), *N*-chlorosulfonyl isocyanate (0.58 mL; 6.66 mmol) was added dropwise at rt under an inert N_2 atmosphere over 10 min. The reaction mixture was kept at rt for 2 h with stirring, and then solvent was removed *in vacuo* to give an oily residue. After that, diethyl ether (20 mL) was added and the solution was added dropwise to a vigorously stirred solution of water (30 mL), sodium carbonate (2.31 g, 21.39 mmol), sodium sulfite (1.20 g, 9.72 mmol) and ice (15 g) over 10 min. The reaction mixture was kept at rt for 1 h with stirring and filtered under vacuum. The water phase was washed with dichloromethane (10 mL x 5), and then the combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f (ethyl acetate/petroleum ether = 3:1); white solid 0.50 g, 47 % yield; mp 178 - 179 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 (2H, d, *J* = 8.3 Hz, Ar), 7.61 (2H, d, *J* = 8.0 Hz, Ar), 7.49 - 7.45 (4H, m, Ar), 7.39 (1H, t, *J* = 7.3 Hz, Ar), 6.18 (1H, br. s, N<u>H</u>), 4.80 (1H, dd, *J* = 5.3 Hz and 2.4 Hz, C<u>H</u>), 3.51 (1H, ddd, *J* = 14.9, 5.3 and 2.4 Hz, C<u>H</u>$_2$), 2.96 (1H, dd, *J* = 14.9 and 2.4 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.8 (C=O), 141.3 (C), 140.4 (C), 139.1 (C), 128.8 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.1 (CH), 50.1 (CH), 48.1 (CH_2).

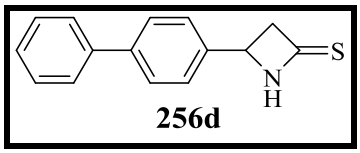
IR υ_{max} (cm^{-1}) 3189, 3021, 2913, 4, 1348, 1272, 1187, 1171, 1005, 970, 833, 759, 730, 699.

MS $(ESI)^+$: m/z [M + H] 224.1.

HRMS: [M] for $C_{15}H_{13}NO$ calculated 223.0997, found 223.0998.

New compound.

3.61. 4-Biphenyl-1-azetidin-2-thione



256d

To a stirred solution of 4-biphenyl-1-azetidin-2-one **255d** (0.27 g; 1.21 mmol) in dry tetrahydrofuran (5 mL), was added Lawesson's reagent (0.24 g; 0.60 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.52 (ethyl acetate/petroleum ether = 1:3); white solid 0.16 g, 54 % yield; mp 180 - 181 ºC;

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.08 (1H, br. s, N<u>H</u>), 7.55 (2H, d, *J* = 8.1 Hz, Ar), 7.52 (2H, d, *J* = 7.4 Hz, Ar), 7.40 - 7.35 (4H, m, Ar), 7.30 (1H, t, *J* = 7.3 Hz, Ar), 5.15 (1H, dd, *J* = 4.6 and 2.1 Hz, C<u>H</u>), 2.47 (1H, ddd, *J* = 14.6, 4.6, and 2.1 Hz, C<u>H</u>$_2$), 2.99 (1H, dd, *J* = 14.6 and 2.1 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 204.4 (C=S), 141.9 (C), 140.2 (C), 137.0 (C), 128.9 (CH), 127.8 (CH), 127.7 (CH), 127.1 (CH), 126.3 (CH), 58.7 (CH), 51.4 (CH_2).

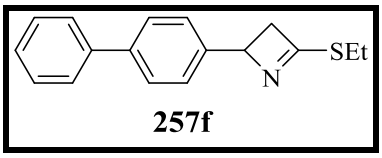
IR υ_{max} (cm^{-1}) 3157, 3030, 1681, 1479, 1402, 1359, 1235, 1196, 1166, 1133, 1005, 963, 837, 764, 727, 690.

MS $(ESI)^+$: m/z [M + H] 240.1.

HRMS: [M] for $C_{15}H_{13}NS$ calculated 239.0769, found 239.0773.

New compound.

3.62. 2-Ethylthio-4-biphenyl-1-azetine



257f

Triethyloxonium tetrafluoroborate (0.09 g; 0.45 mmol) was added in one portion to 4-biphenyl-1-azetidin-2-thione **256d** (0.06 g; 0.26 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried ($MgSO_4$). The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.29 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.04 g, 52 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (4H, d, *J* = 8.0 Hz, Ar), 7.37 (2H, d, *J* = 7.4 Hz, Ar), 7.33 (2H, d, *J* = 8.0 Hz, Ar), 7.26 (1H, t, *J* = 7.3 Hz, Ar), 4.99 (1H, dd, *J* = 4.2 and 1.9 Hz, C<u>H</u>), 3.52 (1H, dd, *J* = 14.6 and 4.2 Hz, C<u>H</u>$_2$), 3.01 (2H, q, *J* = 7.4 CH_3C<u>H</u>$_2$), 2.93 (1H, dd, *J* = 14.6 and 1.9 Hz, C<u>H</u>$_2$), 1.34 (3H, t, *J* = 7.4, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 183.7 (C), 140.9 (C), 140.3 (C), 139.9 (C), 128.7 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 64.9 (CH), 43.6 (CH_2), 23.4 (CH_2), 14.7 (CH_3).

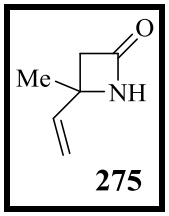
MS $(ESI)^+$: m/z [M + H] 268.1.

HRMS: [M] for $C_{17}H_{17}NS$ calculated 267.1082, found 267.1084.

IR υ_{max} (cm^{-1}) 3029, 1657, 1543, 1449, 1367, 1237, 1144, 1168, 1041, 964, 836, 762, 690.

New compound.

3.63. 4-Methyl-4-vinyl-1-azetidin-2-one



275

To a stirred solution of isoprene (2.33 g; 3.43 mL; 34.41 mmol) in dry diethyl ether (15 mL), *N*-chlorosulfonyl isocyanate (4.88 g; 3.01 mL; 34.01 mmol) in dry diethyl ether (10 mL) was added dropwise at - 78 ºC under an inert N_2 atmosphere over 1 h. After this, the reaction mixture was allowed to warm to - 10 ºC, and then the reaction flask was transferred to an ice-salt bath. This solution was added dropwise to a vigorously stirred solution of water (50 mL), sodium carbonate (9.00 g; 107.10 mmol) sodium sulfite (6.01 g; 47.60 mmol) and ice (30 g) over 10 min. The reaction mixture was kept for 1 h at -10 ºC with stirring. After this, the reaction mixture was allowed to warm to ambient temperature and then extracted with diethyl ether (20 mL x 6). The combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo* to obtain the title compound.

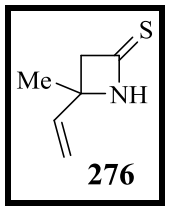
Yellow oil 2.2 g, 58 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.75 (1H, s, N<u>H</u>), 6.03 (1H, dd, *J* = 17.2 and 10.6 Hz, C<u>H</u>), 5.24 (1H, d, *J* = 17.2 Hz, CH=C<u>H</u>$_2$), 5.11 (1H, d, *J* = 10.6 Hz, CH=C<u>H</u>$_2$), 2.81 (2H, s, C<u>H</u>$_2$), 1.51 (C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.5 (C=O), 114.1 (CH), 113.8 (CH_2), 54.5 (C), 50.8 (CH_2), 24.8 (CH_3).

Previously reported.[82]

3.64. 4-Methyl-4-vinyl-1-azetidin-2-thione



276

To a stirred solution of 4-methyl-4'-vinyl-azetidin-2-one **275** (0.55 g; 4.97 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (1.01 g; 2.48 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.35 g, 56 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.38 (1H, s, NH), 5.97 (1H, dd, *J* = 17.2 and 10.6 Hz, CH), 5.24 (1H, d, *J* = 17.2 Hz, CH=CH_2), 5.11 (1H, d, *J* = 10.6 Hz, CH=CH_2), 2.89 (2H, s, CH_2), 1.51 (CH_3).

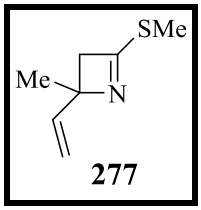
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 202.2 (C=S), 139.9 (CH), 115.1 (CH_2), 63.6 (C), 54.6 (CH_2), 23.7 (CH_3).

IR υ_{max} (cm^{-1}) 3235, 2970, 1720, 1643, 1412, 1372, 1304, 12074, 1226, 1188, 1153, 923.

MS $(ES)^+$: m/z [M + H] 134.1.

Previously reported.[82]

3.65. 2-Methylthio-4-methyl-4-vinyl-1-azetidine



277

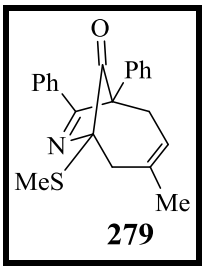
Trimethyloxonium tetrafluoroborate (0.059 g; 0.41 mmol) was added in one portion to 4-methyl-4-vinyl-azetidine-2-thione **276** (0.31 g; 0.24 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at -78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried

($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound. The product was used in next step without NMR analysis.

R_f 0.25 (ethyl acetate/petroleum ether = 1:2); yellow oil 0.03 g, 87 % yield.

Previously reported.[28a]

3.66. 4-Methyl-6-methylthio-1,8-diphenyl-7-azabicyclo[4.2.1]non-3-en-9-one



279

To a stirred solution of 2-methylthio-4-methyl-4-vinyl-1-azetidine **277** (0.04 g; 0.27 mmol) in anhydrous acetonitrile (5 mL), was added diphenylcyclopropenone (0.05 g; 0.27 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 24 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

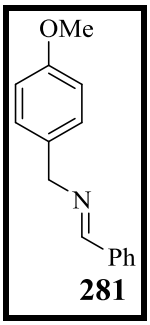
R_f 0.48 (ethyl acetate/ hexane; 1:3); white solid 0.05 g, 52 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.57 (2H, d, *J* = 7.5 Hz, Ar), 7.28 - 7.22 (4H, m, Ar), 7.20 - 7.14 (2H, m, Ar), 7.06 (2H, d, *J* = 6.7 Hz, Ar), 5.32 (1H, dd, *J* = 6.5 and 1.3 Hz, $H_3CC=C\underline{H}$), 3.04 (1H, dd, *J* = 16.6 Hz and 1.3 Hz, $C\underline{H}_2$), 2.90 (1H, dd, *J* = 16.6 and 6.5 Hz, $C\underline{H}_2$), 2.71 (1H, d, *J* = 17.0 Hz, $C\underline{H}_2$), 2.56 (1H, d, *J* = 17.0 Hz, $C\underline{H}_2$), 2.03 ($C\underline{H}_3$), 1.65 ($C\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 214.4 (C=O), 174.4 (C), 136.5 (C), 132.3 (C), 131.9 (C), 131.1 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 127.1 (CH), 118.6 (CH), 82.4 (C), 64.1 (C), 42.7 (CH_2), 34.9 (CH_2), 27.7 (CH_3), 12.5 (CH_3).

Novel compound.

3.67. (*E*)-*N*-(*p*-methoxybenzyl)-1-phenylmethanimine



281

To the stirred solution of anhydrous magnesium sulfate (2.00 g; 16.60 mmol) and benzaldehyde (1.06 g; 1.01 mL; 10.01 mmol) in dry dichloromethane (10 mL) was added 4-methoxybenzylamine (1.37 g; 1.31 mL; 10.01 mmol) dropwise at rt under an inert N_2 atmosphere. The reaction mixture was kept for 12 h with stirring at rt and then filtered under vacuum. The filtrate was washed with dichloromethane (20 mL x 2) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.55 (ethyl acetate/petroleum ether = 1:1); yellow oil 1.90 g, 89 % yield.

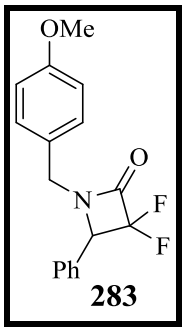
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (1H, s, C<u>H</u>), 7.82 - 7.79 (2H, m, Ar), 7.45 - 4.41 (3H, m, Ar), 7.29 (2H, d, *J* = 8.1 Hz, Ar), 6.92 (2H, d, *J* = 8.1 Hz, Ar), 4.80 (2H, s, C<u>H</u>$_2$), 3.83 (2H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.6 (CH), 158.7 (C), 136.2 (C), 131.3 (C), 130.7 (CH), 129.2 (CH), 128.6 (CH), 128.2 (CH), 113.9 (CH), 64.5 (CH_2), 55.3 (OCH_3).

IR (neat) υ_{max} 2833, 1641, 1609, 1579, 1509, 1450, 1300, 1242, 1172, 1031, 814, 760, 744, 692.

Previously reported.[141]

3.68. 3,3-Difluoro-1-(*p*-methoxybenzyl)-4-phenyl-1-azetidin-2-one



283

To a stirred solution of (*E*)-*N*-(*p*-methoxybenzyl)-1-phenylmethanimine **281** (1.50 g; 6.67 mmol) and ethyl bromodifluoroacetate (2.70 g; 1.71 mL; 13.22 mmol) in dry tetrahydrofuran (10 mL) was added laboratory prepared activated zinc dust (1.37 g; 1.31 mL; 10.01 mmol) gradually under inert N_2 atmosphere. The reaction mixture was heated at reflux for 1 h with stirring. After this, the mixture was allowed to cool to rt and then quenched with saturated aqueous ammonium chloride (20 mL). The water phase was washed with dichloromethane (20 mL x 2) and the combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

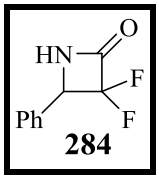
R_f 0.36 (ethyl acetate/petroleum ether = 1:1); yellow oil 1.3 g, 67 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46 - 7.41 (2H, m, Ar), 7.28 - 4.25 (3H, m, Ar), 7.05 (2H, d, *J* = 7.7 Hz, Ar), 6.85 (2H, d, *J* = 7.7 Hz, Ar), 4.91 (1H, d, *J* = 14.7 Hz, NC$\underline{H}_2$), 4.70 (1H, d, *J* = 7.3 Hz, PhC$\underline{H}$), 4.70 (1H, d, *J* = 14.7 Hz, NC$\underline{H}_2$), 3.77 (3H, s, OC$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.6 (C=O), 130.1 (C), 130.0 (CH), 129.8 (C), 129.5 (C), 129.0 (CH), 128.0 (CH), 125.3 (CH), 120.2 (CF_2, dd, *J* = 293 and 287 Hz), 114.4 (CH), 67.8 (CH, dd, *J* = 26.4 and 23.9 Hz), 55.3 (CH_3), 43.7 (CH_2).

Previously reported.[114]

3.69. 3,3-Difluoro-4-phenyl-azetidin-2-one



284

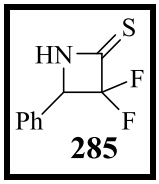
To a stirred solution of 3,3-difluoro-1-(*p*-methoxybenzyl)-4-phenyl-1-azetidin-2-one **283** (1.22 g; 4.03 mmol) in acetonitrile/water (9:1; 25 mL) at 0 ºC was added ceric ammonium nitrate (6.62 g; 12.11 mmol) slowly in small portions. After 20 min, the reaction mixture was left at rt for 6 h with stirring and the reaction mixture was poured into water (50 mL). The aqueous phase was washed with ethyl acetate (20 mL x 2) and the combined organic extracts were washed with 5 % $NaHCO_3$ (10 mL), 10 % Na_2SO_3 (10 mL), 5 % $NaHCO_3$ (10 mL) and brine (10 mL). The organic layers were dried ($MgSO_4$) and then solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound. **R_f** 0.28 (ethyl acetate/petroleum ether = 1:5); yellow solid 0.6 g, 79 % yield; mp 96-97 ºC lit., not reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 - 7.44 (3H, m, Ph), 7.39 - 7.35 (2H, m, Ph), 6.82 (1H, br, s, N<u>H</u>), 5.08 (1H, dd, *J* = 7.5 and 2.5 Hz, PhC<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 161.4 (C=O, t, *J* = 29.9 Hz), 131.8 (C), 129.6 (CH), 128.9 (CH), 127.1 (CH), 120.2 (CF_2, dd, *J* = 293 and 287 Hz), 67.8 (CH, dd, *J* = 26.5 and 24.4 Hz).

Consistent with values reported in the literature.[114]

3.70. 3,3-Difluoro-4-phenyl-1-azetidin-2-thione



285

To a stirred solution of 3,3-difluoro-4-phenyl-1-azetidin-2-one **284** (0.20 g; 1.09 mmol) in dry tetrahydrofuran (5 mL), was added Lawesson's reagent (0.22 g; 0.55 mmol) at rt under an

inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.38 (ethyl acetate/petroleum ether = 1:3); white solid 0.13 g, 59 % yield; mp 98 - 99 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (1H, br. s, NH), 7.40 - 7.37 (3H, m, Ph), 7.28 - 7.26 (2H, m, Ph), 5.44 (1H, dd, *J* = 6.9 and 2.5 Hz, PhCH).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 194.7 (C=S, t, *J* = 30.3 Hz), 130.9 (C), 130.0 (CH), 129.1 (CH), 127.3 (CH), 113.9 (CF_2, dd, *J* = 293 and 287 Hz), 73.8 (CH, dd, *J* = 27.8 and 26.0 Hz).

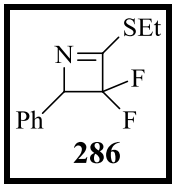
IR υ_{max} (cm^{-1}) 3289, 1496, 1453, 1289, 1197, 1115, 707, 691, 647, 564, 499.

MS $(ES)^+$: m/z [M + H] 200.0.

HRMS: could not find due to decomposition of compound during MS.

Previously unreported.

2.71. 2-Ethylthio-3,3-difluoro-4-phenyl-1-azetine



286

Triethyloxonium tetrafluoroborate (0.11 g; 0.60 mmol) was added in one portion to 3,3-difluoro-4-phenyl-azetidine-2-thione **285** (0.07 g; 0.35 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at -78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried

($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.66 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.04 g, 44 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 - 7.33 (3H, m, Ph), 7.28 - 7.24 (2H, m, Ph), 4.55 - 4.39 (1H, m, PhC<u>H</u>), 2.96 - 2.88 (2H, dd, *J* = 7.4 and 1.8 Hz, C<u>H</u>$_2$), 1.16 (3H, t, *J* = 7.4 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.8 (C), 136.1 (C), 128.6 (CH), 128.5 (CH), 128.1 (CH), 116.7 (CF_2, dd, *J* = 298 and 17.3 Hz), 58.0 (CH, t, *J* = 23.5 Hz), 23.1 (CH_2), 13.9 (CH_3).

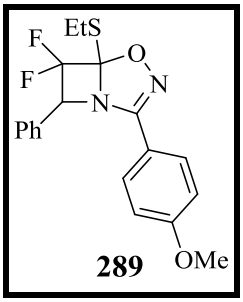
IR υ_{max} (cm^{-1}) 2989, 1514, 1449, 1274, 1171, 1098, 1033, 923, 698, 631.

MS $(ES)^+$: m/z [M + H] 228.1.

HRMS: Could not find by MS.

Previously unreported.

2.72. 5-Ethylthio-6,6-difluoro-2-(*p*-methoxyphenyl)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene



289

To a stirred solution of 2-ethylthio-3,3-difluoro-4-phenyl-1-azetine **286** (0.10 g; 0.44 mmol) and 4-methoxybenzohydroximoylchloride (0.08 g; 0.44 mmol) in dry diethyl ether (20 mL) was added triethylamine (0.06 g; 0.09 mL) in dry diethyl ether (25 mL) dropwise at rt under an inert N_2 atmosphere over 7 h. The reaction mixture was stirred at rt overnight. After that, the precipitates were filtered and the solvent was removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.56 (ethyl acetate/petroleum ether = 3:1); yellow oil 0.10 g, 60 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.47 (2H, d, *J* = 6.6 Hz, Ar), 7.43 (2H, d, *J* = 8.9 Hz, Ar), 7.40 - 7.32 (3H, m, Ar), 6.71 (2H, d, *J* = 8.9 Hz, Ar), 5.03 (1H, dd, *J* = 16.3 and 3.5 Hz, PhC<u>H</u>), 3.67 (3H, s, C<u>H</u>$_3$), 2.87 - 2.72 (2H, m, C<u>H</u>$_2$), 1.29 (3H, t, *J* = 7.5 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.3 (C), 160.8 (C), 131.8 (C), 131.7 (C), 129.5 (CH), 129.3 (CH), 128.9 (CH), 127.6 (CH), 117.3 (C, dd, *J* = 29.4 and 23.8 Hz), 115.4 (C, dd, *J* = 295.1 and 6.3 Hz), 114.6 (CH), 79.4 (CH, dd, *J* = 27.1 and 24.7 Hz), 55.4 (CH_3), 21.9 (CH_2), 14.9 (CH_3).

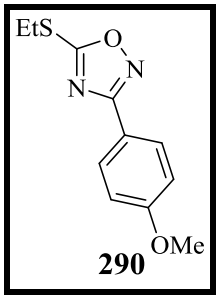
IR υ_{max} (cm^{-1}) 2983, 2950, 1606, 1511, 1256, 1222, 1172, 1087, 1027, 834, 703.

MS $(ESI)^+$: m/z [M + H] 377.1.

HRMS: [M] for $C_{19}H_{18}F_2N_2O_2S$ calculated 376.1057, found 376.1055.

New compound.

2.73. 5-Ethylthio-3-(*p*-methoxyphenyl)-1,2,4-oxadiazole



290

5-Ethylthio-6,6-difluoro-2-(*p*-methoxyphenyl)-7-phenyl-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-ene **289** (0.085 g; 0.23 mmol) was added to toluene (10 mL) and the reaction mixture was heated at reflux for 22 h with stirring. After this, the mixture was allowed to cool to rt and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.45 (ethyl acetate/petroleum ether = 1:2); white solid 0.045 g, 83 % yield; mp 71 - 72 ºC lit., not reported.

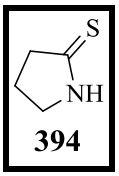
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91 (2H, d, *J* = 8.8 Hz, Ar), 6.88 (2H, d, *J* = 8.8 Hz, Ar), 3.77 (CH_3), 3.23 (2H, q, *J* = 7.3 Hz, CH_2), 1.43 (3H, t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 178.2 (C), 168.8 (C), 162.5 (C), 129.6 (CH), 119.6 (C), 114.8 (CH), 55.9 (CH_3), 27.8 (CH_2), 15.4 (CH_3).

IR υ_{max} (cm^{-1}) 2966, 2935, 1612, 1509,1424, 1342, 1305, 1250, 1182, 1022, 879, 839, 779, 749, 710, 635, 628.

Consistent with the previously reported data.[106]

3.74. Pyrrolidine-2-thione



394

To a stirred solution of 2-pyrrolidinone (0.90 mL; 16.40 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (2.43 g; 5.98 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

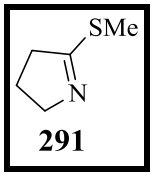
R_f 0.23 (ethyl acetate/petroleum ether = 2:3); white solid 0.91 g, 76 % yield; mp 112 - 113 ºC lit.,[113] 112 - 115 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.74 (1H, s, N<u>H</u>), 3.63 (2H, t, *J* = 7.3 Hz, NC<u>H</u>$_2$), 2.92 (2H, t, *J* = 7.9 Hz, SCC<u>H</u>$_2$), 2.18-2.11 (2H, m, CH_2C<u>H</u>$_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 206.07 (C), 49.9 (CH_2), 43.2 (CH_2), 22.9 (CH_2).

As reported previously.[28b]

3.75. 2-Methylthio-1-pyrrolidine

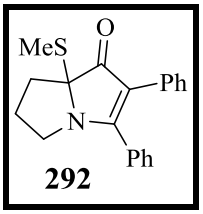


291

Dimethyl sulfate (0.41 g; 4.33 mmol) was added in one portion to pyrrolidin-2-one **394** (0.40 g; 3.94 mmol) and the reaction mixture was stirred at rt for 16 h under an inert N_2 atmosphere. After this time, ether (10 mL) was added and the resulting mixture was washed with 10 % aqueous potassium carbonate (20 mL) and then extracted with dichloromethane (25 mL x 3). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo* to leave 2 mL of liquid product as dark orange oil which was used crude in the next step.

As reported previously.[28b]

3.76. 5-Methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



292

To a stirred solution of 2-methylthio-1-pyrrolidine **291** (0.43 g; 3.75 mmol) in anhydrous acetonitrile (10 mL), was added diphenylcyclopropenone (0.77 g; 3.75 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 12 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography to afford the title compound.

R_f 0.31 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.54 g, 65 % yield; mp 114 - 115 ºC lit., not reported.

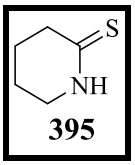
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.47 - 7.43 (3H, m, Ph), 7.39 - 7.35 (2H, m, Ph), 7.26 - 7.18 (4H, m, Ph), 7.17 - 7.12 (1H, m, Ph), 3.56 - 3.52 (1H, m, NC$\underline{H}_2$), 3.36 - 3.30 (1H, m, NC$\underline{H}_2$), 2.28 - 2.20 (2H, m, SCC$\underline{H}_2$), 2.05 (3H, s, C$\underline{H}_3$), 1.89 - 1.79 (2H, m, $CH_2C\underline{H}_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.9 (C=O), 175.3 (C), 131.3(C), 131.2 (C), 131.0 (CH), 129.6 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 126.2 (CH), 116.6 (C), 80.3 (C), 48.6 (CH_2), 32.3 (CH_2), 26.6 (CH_2), 11.7 (CH_3).

IR υ_{max} (cm^{-1}) 2955, 2888, 1657, 1651, 1599, 1547, 1538, 1402, 1302, 1279, 1047, 782, 794.

As reported previously.[28b]

3.77. Piperidone-2-thione



395

To a stirred solution of 2-piperidone (1.00 g; 10.01 mmol) in dry tetrahydrofuran (15 mL), was added Lawesson's reagent (2.03 g; 5.02 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.22 (ethyl acetate/petroleum ether = 2:3); white solid 0.91 g, 66 % yield; mp 92-93 ºC; lit.,[112f]: 92-93 ºC.

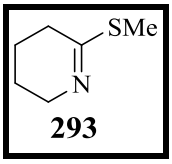
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 (1H, s, N<u>H</u>), 3.31 (2H, td, *J* = 5.8 Hz and 2.7 Hz, NC<u>H</u>$_2$), 2.84 (2H, t, *J* = 6.2 Hz, SCC<u>H</u>$_2$), 1.66 - 1.79 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 203.1 (C=S), 44.9 (CH_2), 39.1 (CH_2), 20.8 (CH_2) 20.2 (CH_2).

IR υ_{max} (cm^{-1}) 3308, 2949, 1673, 1530, 1497, 1453, 1426, 1333, 1213, 1126, 1040, 973, 909, 730, 695.

As reported previously.[113]

3.78. 2-Methylthio-1-piperidine



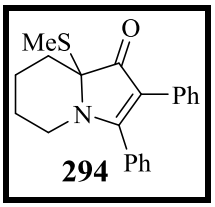
293

Dimethyl sulfate (0.34 g; 3.61 mmol) was added in one portion to piperidone-2-thione **395** (0.40 g; 3.84 mmol) and the reaction mixture was stirred at rt for 16 h under an inert N_2 atmosphere. After this time, ether (10 mL) was added and the resulting mixture was washed

with 10 % aqueous potassium carbonate (20 mL) and then extracted with DCM (25 mL x 3). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo* to leave 2 mL of liquid product as dark orange oil which was used crude in the next step.

As reprted previously.[28b]

3.79. 5-Methylthio-2,3-diphenyl-1-azabicyclo[4.3.0]non-2-ene-4-one



294

To a stirred solution of 2-methylthio-1-piperidine **293** (0.35 g; 2.70 mmol) in anhydrous acetonitrile (10 mL), was added diphenylcyclopropenone (0.56 g; 0.77 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred ar rt for 12 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

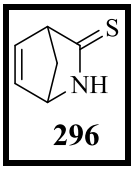
R_f 0.31 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.54 g, 65 % yield; mp 117-118 ºC lit., not reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 - 7.39 (3H, m, Ph), 7.22 - 7.19 (2H, m, Ph), 7.07 - 7.02 (4H, m, Ph), 6.99 - 6.95 (1H, m, Ph), 3.57 (1H, ddd, *J* = 13.4, 12 and 4.7 Hz, NC$\underline{H}_2$), 3.43 (1H, td, *J* = 13.4 and 3.2 Hz, NC$\underline{H}_2$), 2.18 - 2.14 (1H, m, SCC$\underline{H}_2$), 1.92 (3H, s, C$\underline{H}_3$), 1.89 – 1.80 (1H, m, SCC$\underline{H}_2$), 1.79 – 1.60 (2H, - 1.60 (2H, m, C$\underline{H}_2$) 1.33 - 1.20 - (2H, m, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.7 (C=O), 170.5 (C), 131.6 (C), 130.4 (C), 130.3 (CH), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.8 (CH), 125.2 (CH), 109.9 (C), 72.1 (C), 41.4 (CH_2), 32.6 (CH_2), 27.4 (CH_2), 20.4 (CH_2), 10.5 (CH_3).

As reported previously.[28b]

3.80. 2-Azabicyclo[2.2.1]hept-5-en-3-thione



296

To a stirred solution of 2-azabicyclo[2.2.1]hept-5-en-2-one (0.50 g; 4.58 mmol) in dry tetrahydrofuran (10 mL), was added Lawesson's reagent (0.93 g; 2.29 mmol) at rt under an inert N_2 atmosphere. The mixture was stirred at rt for 0.5 h and then at reflux for 4 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/petroleum ether = 1:2); white solid 0.33 g, 58 % yield; mp 102 - 103 ºC.

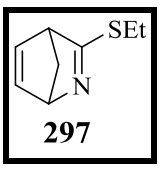
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.17 (1H, s, NH), 6.81 (1H, td, *J* = 5.1 and 1.2 Hz, CH=CH), 6.72 (1H, dd, *J* = 5.1 and 1.6 Hz, CH=CH), 4.77 - 4.73 (1H, m, NCH), 3.95 - 4.73 (1H, m, SCCH), 2.39 (1H, dt, *J* = 7.7 and 1.6 Hz CH_2), 2.24 (1H, dd, *J* = 7.7 and 1.2 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 211.8 (C=S), 139.3 (CH), 137.7 (CH), 65.6 (CH), 65.0 (CH), 63.7 (CH_2).

IR υ_{max} (cm^{-1}) 3319, 3029, 2928, 1661, 1528, 1494, 1337, 1218, 1124, 1044, 968.

New compound.

3.81. 3-Ethylthio-2-azabicyclo[2.2.1]hept-2,5-diene



297

Triethyloxonium tetrafluoroborate (0.51 g; 2.71 mmol) was added in one portion to 1-azabicyclo[2.2.1]hept-4-en-2-thione **296** (0.20 g; 1.60 mmol) in anhydrous dichloromethane (10 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 1 hour. After this time, the reaction mixture was allowed to cool to rt and then 50 %

aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$) and then solvents removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.49 (ethyl acetate/petroleum ether = 1:2); yellow oil 0.15 g, 61 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.81 (1H, dd, *J* = 5.1 and 1.6 Hz, C<u>H</u>=CH), 6.67(1H, td, *J* = 5.1 and 1.2 Hz, CH=C<u>H</u>), 5.20 - 5.15 (1H, m, NC<u>H</u>), 3.80 - 3.76 (1H, m, SCC<u>H</u>), 3.07 - 2.93 (2H, m, $CH_3C\underline{H}_2$), 2.12 (1H, dt, *J* = 7.3 and 1.6 Hz, C<u>H_2</u>), 1.93 – 1.88 (1H, m, C<u>H_2</u>), 1.32 (3H, t, *J* = 7.3 Hz, CH_3).

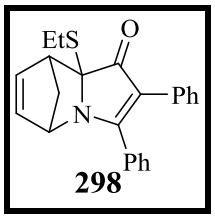
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 185.3 (C–S), 141.7 (CH), 137.6 (CH), 74.2 (CH), 68.6 (CH), 58.7 (CH_2), 25.1 (CH_2), 14.1 (CH_3).

IR υ_{max} (cm^{-1}) 3021, 2931, 1680, 1578, 1372, 1240, 1029, 768, 688.

MS : Could not obtain due to the decomposition of the tiltle compound at rt.

New compound.

3.82. 8a-(Ethylthio)-2,3-diphenyl-8,8a-dihydro-5,8-methanoindolizin-1-one



298

To a stirred solution of 3-ethylthio-2-azabicyclo[2.2.1]hept-2,5-diene **297** (0.08 g; 0.52 mmol) in anhydrous acetonitrile (5 mL), was added diphenylcyclopropenone (0.11 g; 0.52 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 24 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.27 (ethyl acetate/petroleum ether = 1:5); orange yellow solid 0.12 g, 61 % yield; mp 109-110 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (2H, d, *J* = 7.2 Hz, Ar), 7.46 – 7.44 (2H, m, Ar), 7.38 - 7.34 (3H, m, Ar), 7.31 - 7.15 (3H, m, Ar), 6.69 (1H, dd, *J* = 5.3 and 2.9 Hz, C<u>H</u>=CH), 6.50 (1H, dd, *J* = 5.3 and 2.9 Hz, CH=C<u>H</u>), 4.01-3.94 (1H, m, NC<u>H</u>), 3.54 - 3.43 (1H, m, SCC<u>H</u>), 2.76 - 2.53 (2H, m, $CH_3C\underline{H_2}$), 1.82 (1H, d, *J* = 9.4 Hz, C<u>H_2</u>), 1.69 (1H, d, *J* = 9.4 Hz, C<u>H_2</u>), 1.34 (3H, t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 201.0 (C=O), 175.3 (C), 140.6 (CH), 134.2 (CH), 131.6 (C), 131.2 (CH), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.1 (C), 126.9 (CH), 126.3 (C), 79.8 (C), 66.7 (CH), 47.2 (CH), 44.1 (CH_2), 22.9 (CH_2), 14.1 (CH_3).

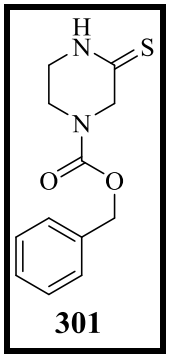
IR υ_{max} (cm^{-1}) 3027, 2931, 1736, 1681, 1579, 1431, 1373, 1238, 1043, 751, 723, 695.

MS $(ESI)^+$: m/z [M + K] 398.1.

HRMS: [M+Na] for $C_{23}H_{21}NOSNa$ calculated 382.1230, found 382.1236.

New compound.

3.83. Benzyl 3-thioxopiperazine-1-carboxylate



301

To a stirred solution of benzyl 3-oxopiperazine-1-carboxylate (0.50 g; 2.13 mmol) in dry tetrahydrofuran (10 mL), was added Lawesson's reagent (0.43 g; 1.07 mmol) at rt under an inert N_2 atmosphere. The mixture was stirred at rt for 0.5 h and then at reflux for 2.5 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.38 (ethyl acetate/petroleum ether = 1:2); white solid 0.27 g, 51 % yield; mp 131 - 132 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.01 (1H, br. s, N<u>H</u>), 7.32 - 7.24 (5H, m, Ph), 5.07 (2H, s, C<u>H</u>$_2$), 4.53 (2H, s, C<u>H</u>$_2$), 3.66 (2H, t, *J* = 5.2 Hz, C<u>H</u>$_2$), 3.35-3.38 (2H, m, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 199.8 (C=S), 154.2 (C=O), 135.8 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 67.9 (CH_2), 53.2 (CH_2), 43.7 (CH_2), 38.9 (CH_2).

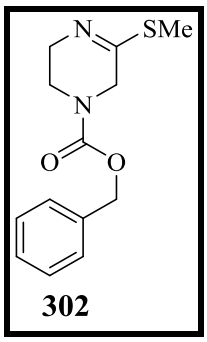
IR υ_{max} (cm^{-1}) 3334, 3168, 3085, 2968, 1698, 1569, 1453, 1405, 1339, 1322, 1286, 1232, 1197, 1110, 763.

MS $(ESI)^+$: m/z [M + H] 251.1.

HRMS: [M] for $C_{11}H_{12}N_2OS$ calculated 250.0766, found 250.0772.

New compound.

3.84. Benzyl 6-methyl-3,5-dihydro-2H-pyrazine-4-carboxylate



302

Trimethyloxonium tetrafluoroborate (0.14 g; 0.95 mmol) was added in one portion to benzyl 3-thioxopiperazine-1-carboxylate **301** (0.14 g; 0.56 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 4 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) was added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and the combined organic extracts were dried over ($MgSO_4$). The solvents were removed in *vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.35 (ethyl acetate/petroleum ether = 1:2); yellow oil 0.087 g, 60 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27 – 7.12 (5H, m, Ph), 5.08 (2H, s, PhC$\underline{H}_2$), 4.01 (2H, s, SCC$\underline{H}_2$), 3.75 - 3.66 (2H, m, C$\underline{H}_2$), 3.41 (2H, t, *J* = 5.2 Hz, C$\underline{H}_2$), 2.25 (3H, s, C$\underline{H}_3$).

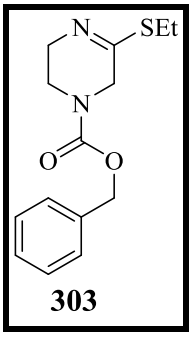
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.4 (C), 154.7 (C=O), 136.3 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 67.5 (CH_2), 53.5 (CH_2), 49.7 (CH_2), 46.6 (CH_2), 11.8 (CH_3).

IR υ_{max} (cm^{-1}) 3034, 2962, 1664, 1529, 1436, 1328, 1228, 1026.

MS $(ESI)^+$: Could not obtain due to the degradation of the title compound at rt.

New compound.

3.85. Benzyl 6-ethylsulfanyl-3,5-dihydro-2H-pyrazine-4-carboxylate



303

Triethyloxonium tetrafluoroborate (0.26 g; 1.36 mmol) was added in one portion to benzyl 3-thioxopiperazine-1-carboxylate **301** (0.20 g; 0.80 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 hour under an inert N_2 atmosphere then heated at reflux for 4 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at -78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and then the combined organic extracts were dried over ($MgSO_4$). The solvents were removed in *vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.36 (ethyl acetate/petroleum ether = 1:2); yellow oil 0.087 g, 62 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 – 7.12 (5H, m, Ar), 5.08 (2H, s, PhC$\underline{H}_2$), 3.97 (2H, s, SCC$\underline{H}_2$), 3.68 - 3.56 (2H, m, C$\underline{H}_2$), 3.42 (2H, t, *J* = 5.3 Hz, SCNC$\underline{H}_2$), 2.87 (2H, q, *J* = 7.4 Hz, CH_2), 1.20 (3H, t, *J* = 7.4, CH_3).

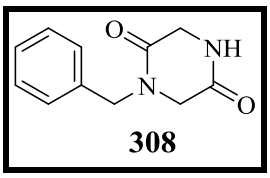
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.7 (C), 154.7 (C=O), 136.3 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 67.4 (CH_2), 49.6 (CH_2), 46.6 (CH_2), 32.9 (CH_2), 23.1 (CH_2), 14.3 (CH_3).

IR υ_{max} (cm^{-1}) 3023, 2941, 1653, 1543, 1441, 1329, 1244, 968.

MS $(ESI)^+$: Could not obtain due to the degradation of the title compound at rt.

New compound.

3.86. 1-Benzylpiperazin-2,5-dione



308

To a stirred solution of *N*-azidoacetyl-*N*-benzylglycine ethyl ester (0.50 g; 1.91 mmol) in wet tetrahydrofuran (15 mL), was added triphenylphosphine (0.75 g; 2.86 mmol) at rt. The reaction mixture was left to stir for 45 min at the same temperature. After this, solvent was removed *in vacuo* and the crude product was purified by flash chromatography affording the title compound.

R_f 0.22 (dichloromethane/methanol = 10:1); white solid 0.33 g, 82 % yield; mp 219 - 220 ºC lit.,[73] 208 - 210 ºC.

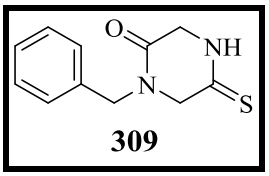
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 (1H, br. s, N$\underline{H}$), 7.37 - 7.34 (2H, m, Ph), 7.31 - 7.26 (3H, m, Ph), 4.51 (2H, s, C$\underline{H}_2$), 3.88 (2H, s, C$\underline{H}_2$), 3.78 (2H, s, C$\underline{H}_2$).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 166.0 (C=O), 164.9 (C=O), 136.7 (C), 129.0 (CH), 128.3 (CH), 127.9 (CH), 49.5 (CH_2), 48.6 (CH_2), 44.9 (CH_2).

IR υ_{max} (cm^{-1}) 3239, 1684, 1650, 1639, 1472, 1454, 1431, 1322, 1273, 1255, 1114, 1049, 937.

Previously reported.[73]

3.87. 1-Benzyl-5-thioxopiperazin-2-one



309

To a stirred solution of 1-benzylpiperazine-2,5-dione **308** (0.12 g; 0.61 mmol) in dry tetrahydrofuran (5 mL), was added Lawesson's reagent (0.12 g; 0.31 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.28 (ethyl acetate/petroleum ether = 1:3); white solid 0.05 g, 37 % yield; mp 230 - 231 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.67 (1H, br. s, N<u>H</u>), 7.37 - 7.34 (2H, m, Ph), 7.31 - 7.26 (3H, m, Ph), 4.54 (2H, s, C<u>H</u>$_2$), 4.24 (2H, s, C<u>H</u>$_2$), 3.97 (2H, s, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 193.2 (C=S), 163.6 (C=O), 136.6 (C), 129.0 (CH), 128.3 (CH), 127.9 (CH), 57.1 (CH_2), 48.1 (CH_2), 47.5 (CH_2).

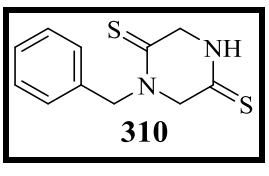
IR υ_{max} (cm^{-1}) 3327, 3110, 2998, 1643, 1597, 1495, 1320, 1249, 1144, 1042, 940, 768, 695.

MS $(ESI)^+$: m/z [M + H] 221.1.

HRMS: [M] for $C_{11}H_{12}N_2OS$ calculated 220.0670, found 220.0677.

Previously unreported.

3.88. 1-Benzylpiperazin-2,5-dithione



310

To a stirred solution of 1-benzylpiperazine-2,5-dione **308** (0.12 g; 0.61 mmol) in dry tetrahydrofuran (5 mL), was added Lawesson's reagent (0.12 g; 0.31 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 2 h. After this time, the

reaction mixture was allowed to cool to rt and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound

R_f 0.59 (ethyl acetate/ petroleum ether; 1:3); light yellow solid 0.02 g, 15 % yield; mp 245 - 246 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.88 (1H, br. s, NH), 7.39 - 7.30 (5H, m, Ph), 5.22 (2H, s, CH_2), 4.44 (2H, s, CH_2), 4.42 (2H, s, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 196.8 (C=S), 195.5 (C=S), 139.9 (C), 133.9 (CH), 133.0 (CH), 132.9 (CH), 64.8 (CH_2), 60.8 (CH_2), 59.8 (CH_2).

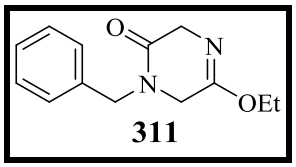
IR υ_{max} (cm^{-1}) 3214, 3089, 2899, 1598, 1532, 1313, 1188, 1144, 1074, 1025, 932, 752, 707, 591.

MS $(ESI)^+$: m/z [M + H] 237.1.

HRMS: [M] for $C_{11}H_{12}N_2S_2$ calculated 236.0442, found 236.0453.

Previously unreported.

3.89. 5-Ethoxy-3,6-dihydro-1-benzyl-2(1*H*)-pyrazinone



311

Triethyloxonium tetrafluoroborate (0.05 g; 0.26 mmol) was added in one portion 1-benzyl-piperazine-2,5-dione **308** (0.03 g; 0.15 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 h under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at - 78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and then the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.24 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.014 g, 40 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.23 (3H, m, Ph), 7.21 - 7.19 (2H, m, Ph), 4.54 (2H, s, C$\underline{H}_2$), 4.14 (2H, s, C$\underline{H}_2$), 4.01 (2H, q, *J* = 7.1 Hz, C$\underline{H}_2$), 3.72 (2H, s, C$\underline{H}_2$), 1.16 (3H, t, *J* = 7.1 Hz, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.2 (C), 157.2 (C=O), 135.4 (C), 128.8 (CH), 128.4 (CH), 127.9 (CH), 61.4 (CH_2), 50.3 (CH_2), 49.1 (CH_2), 45.6 (CH_2), 14.1 (CH_3).

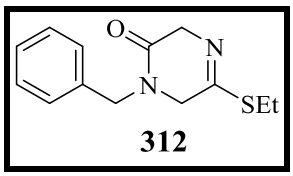
IR υ_{max} (cm^{-1}) 2999, 1703, 1645, 1389, 1227, 943, 790, 730, 699.

MS $(ESI)^+$: m/z [M + H] 233.1.

HRMS: [M] for $C_{13}H_{16}N_2O_2$ calculated 232.1212, found 232.1206.

Previously reported.[142]

3.90. 5-Ethylthio-3,6-dihydro-1-benzyl-2(1*H*)-pyrazinone



312

Triethyloxonium tetrafluoroborate (0.04 g; 0.22 mmol) was added in one portion to 1-benzyl-5-thioxopiperazin-2-one **309** (0.03 g; 0.13 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 1 h under an inert N_2 atmosphere then heated at reflux for 1 h. After this time, the reaction mixture was allowed to cool to rt and then a 50 % aqueous solution of potassium carbonate (10 mL) added dropwise at -78 ºC. The solution was then filtered through Celite® and the organic layer was separated. The water phase was washed with dichloromethane (10 mL x 2), and then the combined organic extracts were dried over ($MgSO_4$). The solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.66 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.035 g, 44 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.21 (3H, m, Ph), 7.20 - 7.17 (2H, m, Ph), 4.55 (2H, s, C$\underline{H}_2$), 4.27 (2H, s, C$\underline{H}_2$), 3.77 (2H, s, C$\underline{H}_2$), 2.87 (2H, q, *J* = 7.3 Hz, C$\underline{H}_2$), 1.19 (3H, t, *J* = 7.3 Hz, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.1 (C=O), 161.0 (C-S), 135.4 (C), 128.9 (CH), 128.2 (CH), 128.0 (CH), 54.2 (CH_2), 50.1 (CH_2), 49.0 (CH_2), 23.7 (CH_2), 14.2 (CH_3).

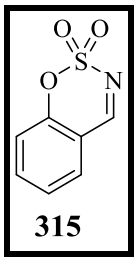
IR υ_{max} (cm^{-1}) 2979, 1650, 1494, 1453, 1263, 1111, 1068, 941, 736, 698.

MS $(ESI)^+$: m/z [M + H] 249.1.

HRMS: [M] for $C_{13}H_{16}N_2OS$ calculated 248.0983, found 248.0989.

Previously unreported.

3.91. Benzo[e][1,2,3]oxathiazine 2,2-dioxide



315

To a stirred solution of salicylaldehyde (0.78 g; 0.68 mL; 6.39 mmol) in anhydrous *N, N*-dimethylacetamide (12 mL), was added freshly prepared* sulfamoyl chloride (2.22 g; 19.2 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was allowed to stir at rt for 16 h. After this, the reaction mixture was quenched with buffer solution at pH 7 (3 g of NaH_2PO_4 in 25 mL H_2O /15 mL of 0.1 NaOH; 10 mL) and then aqueous solution was extracted with diethyl ether (20 mL x 2). The combined organic layers were washed successively with water (10 mL x 2) and brine (10 mL x 2). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.17 (ethyl acetate/hexane = 3:7); white solid 0.9 g, 75 % yield; mp 87-88 ºC lit.,[116c] 92 - 94 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 (1H, s, NC<u>H</u>), 7.78 (1H, t, *J* = 8.0 Hz, Ar), 7.73 (1H, d, *J* = 7.6 Hz, Ar), 7.45 (1H, t, *J* = 7.6 Hz, Ar), 7.28 (1H, d, *J* = 8.1 Hz, Ar).

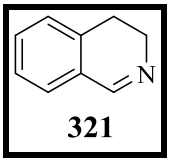
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.1 (CH), 154.1 (C), 137.8 (CH), 131.1 (CH), 126.4 (CH), 118.5 (CH), 115.3 (C).

IR υ_{max} (cm^{-1}) 3031, 2926, 1600, 1560, 1373, 1201, 1177, 905, 819, 768, 755.

* A solution of formic acid (1.28 g; 1.045 mL; 27.72 mmol) in anhydrous DCM (7 mL) was added dropwise to a solution of *N*-chlorosulfonyl isocyanate (3.93 g; 2.41 mL; 27.69 mmol) in anhydrous DCM (7 mL) and allowed to heat for reflux for 15 min to yield sulfamoyl chloride (1.6 g, 50 %).

Consistent with the previously reported data.[116]

3.92. 3,4-Dihydroisoquinoline



321

To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (3.33 g; 3.12 mL; 25.01 mmol) in anhydrous dichloromethane (50 mL), was slowly added *N*-bromosuccinimide (5.01 g; 27.51 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 0.5 h. An aqueous solution of 30 % sodium hydroxide (16.7 mL) was added to the reaction mixture. After this, the resulting reaction mixture was stirred at rt for 1 h, and then the mixture was washed with water (70 mL) and then 1 M HCl (70 mL). The acid extracts were basified with 1 M sodium hydroxide until the pH of the solution reached a value greater than 9.0. The water phase was washed with dichloromethane (150 mL x 2) and then finally washed with brine (100 mL). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

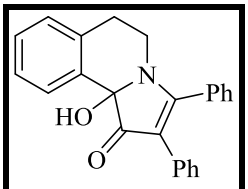
R_f 0.41 (dichloromethane/methanol = 15:1); yellow oil 2.0 g, 61 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32 (1H, s, NC<u>H</u>), 7.35 - 7.24 (3H, m, Ar), 7.14 (1H, d, *J* = 7.2 Hz, Ar), 3.76 (2H, td, *J* = 7.6 and 1.9 Hz, C<u>H</u>$_2$), 2.73 (2H, t, *J* = 7.6 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 160.3 (CH), 136.3 (C), 131.1 (CH), 128.5 (C), 127.4 (CH), 127.2 (CH), 127.1 (CH), 47.4 (CH_2), 25.0 (CH_2).

Previously reported.[117]

3.93. 10b-Hydroxy-2,3-diphenyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one



323

To a stirred solution of 3,4-dihydroisoquinoline **321** (0.03 g; 0.24 mmol) in $CDCl_3$ (5 mL), was added diphenylcyclopropenone (0.05 g; 0.24 mmol) at rt under an air atmosphere. The reaction mixture was stirred at rt for 3 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.42 (ethyl acetate/hexane = 1:1); orange yellow solid 0.05 g, 59 % yield; mp 169 - 170 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.07 (1H, d, *J* = 7.7 Hz, Ar), 7.45 - 7.38 (3H, m, Ar), 7.31 (2H, t, *J* = 7.5 Hz, Ar), 7.22 (2H, t, *J* = 7.5 Hz, Ar), 7.04 - 6.96 (4H, m, Ar), 6.91 (2H, dd, *J* = 7.7 and 1.4 Hz, Ar), 3.82 (1H, dd, *J* = 5.1 and 1.7 Hz, C<u>H</u>$_2$), 3.78 (1H, dd, *J* = 5.1 and 1.7 Hz, C<u>H</u>$_2$), 3.54 (1H, td, *J* = 13.7 and 3.8 Hz, C<u>H</u>$_2$), 2.63 - 2.47 (2H, m, C<u>H</u>$_2$ & O<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.1 (C=O), 174.2 (C), 133.9 (C), 133.3 (C), 130.7 (CH), 130.6 (C), 130.4 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 125.9 (CH), 113.3 (C), 85.7 (C), 40.7 (CH_2), 29.3 (CH_2).

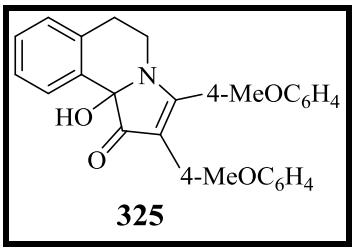
IR υ_{max} (cm^{-1}) 3256, 3019, 2921, 1657, 1601, 1542, 1427, 1350, 1121, 1074, 973, 791, 767, 720, 527.

MS $(ESI)^+$: m/z [M + H] 354.1.

HRMS: [M] for $C_{24}H_{19}NO_2$ calculated 353.1416, found 353.1420.

Previously not reported.

3.94. 10b-Hydroxy-2,3-bis(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquiolin-1-one



325

To a stirred solution of 3,4-dihydroisoquinoline **321** (0.03 g; 0.19 mmol) in $CDCl_3$ (5 mL), was added 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.05 g; 0.19 mmol) at rt under an air atmosphere. The reaction mixture was stirred at rt for 3 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.35 (ethyl acetate/petroleum ether = 1:5); yellow solid 0.04 g, 52 % yield; mp 86 - 87 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (1H, d, *J* = 8.0 Hz, Ar), 7.30 - 7.16 (4H, m, Ar), 6.99 (1H, d, *J* = 7.2 Hz, Ar), 6.89 - 6.79 (4H, m, Ar), 6.58 (2H, d, *J* = 8.7 Hz, Ar), 3.89 - 3.66 (2H, m, C<u>H</u>$_2$), 3.58 - 3.23 (1H, m, C<u>H</u>$_2$), 3.78 (OC<u>H</u>$_3$), 3.65 (OC<u>H</u>$_3$), 2.59-2.43 (2H, m, C<u>H</u>$_2$ & O<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.2 (C=O), 173.5 (C), 161.4 (C), 157.7 (C), 134.1 (C), 133.5 (C), 130.1 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 123.3 (C), 122.4 (C), 114.5 (CH), 113.4 (CH), 112.9 (C), 85.7 (C), 55.4 (OCH_3), 55.1 (OCH_3), 40.9 (CH_2), 28.1 (CH_2).

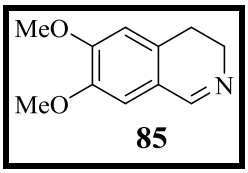
IR υ_{max} (cm^{-1}) 3341, 1668, 1604, 1518, 1456, 1289, 1243, 1173, 1110, 1024, 832, 747, 581, 531.

MS $(ESI)^+$: m/z [M + H] 414.2.

HRMS: [M] for $C_{26}H_{23}NO_4$ calculated 413.1627, found 413.1627.

Previously not reported.

3.95. 6,7-Dimethoxy-3,4-dihydroisoquinoline



85

To a stirred solution of hexamethylenetetramine (3.87 g; 27.61 mmol) and 2-(dimethoxyphenyl) ethylamine (2.51 g; 2.33 mL; 13.81 mmol) in acetic acid (15 mL) was added trifluoroacetic acid (5.58 g; 3.75 mL; 48.94 mmol) dropwise under an inert N_2 atmosphere. The reaction mixture was heated at 90 ºC for 0.5 h with stirring. After this time, the reaction mixture was allowed to cool to rt. The reaction was quenched with water (15 mL) and then solid potassium carbonate was added gradually until the pH of the solution reached a value greater than 9.0. The water phase was washed with dichloromethane (20 mL x 2) and the combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

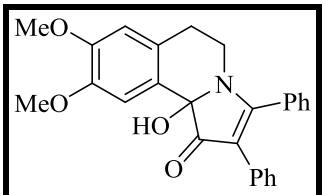
R_f 0.36 (ethyl acetate/methanol = 5:1); yellow oil 2.5 g, 94 % yield; R_f = 0.36).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.14 (1H, s, NC<u>H</u>), 6.72 (1H, s, Ar), 6.59 (1H, s, Ar), 3.83 (3H, s, C<u>H</u>$_3$), 3.81 (3H, s, C<u>H</u>$_3$), 3.64 (2H, td, *J* = 7.8 and 1.9 Hz, C<u>H</u>$_2$), 2.58 (2H, t, *J* = 7.8 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.5 (CH), 151.1 (C), 147.7 (C), 129.7 (C), 121.4 (C), 110.3 (CH), 110.2 (CH), 56.0 (CH_3), 55.9 (CH_3), 47.3 (CH_2), 24.6 (CH_2).

Previously reported.[44]

3.96. 8,9-Dimethoxy-10b-hydroxy-2,3-diphenyl-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one



329

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisiquinoline **85** (0.09 g; 0.48 mmol) in $CDCl_3$ (5 mL), was added diphenylcyclopropenone (0.10 g; 0.48 mmol) at rt under an air atmosphere. The reaction mixture was stirred at rt for 3 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.25 (ethyl acetate/hexane = 1:1); orange yellow solid 0.13 g, 65 % yield; mp 86 - 87 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.57 (1H, s, Ar), 7.48 - 7.22 (5H, m, Ar), 7.14 - 6.97 (3H, m, Ar), 6.92 (2H, d, *J* = 7.5 Hz, Ar), 6.47 (1H, s, Ar), 3.93 (3H, s, C$\underline{H}_3$), 3.79 (3H, s, C$\underline{H}_3$), 3.75 - 3.49 (3H, m, O$\underline{H}$ and C$\underline{H}_2$), 2.57 - 2.49 (1H, m, C$\underline{H}_2$), 2.39 (1H, dd, *J* = 15.3 and 2.3 Hz, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.1 (C=O), 173.8 (C), 149.4 (C), 148.5 (C), 130.7 (CH), 130.6 (C), 130.4 (C), 129.8 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 126.6 (C), 125.9 (CH), 124.9 (C), 113.2 (C), 110.3 (CH), 110.2 (CH), 85.4 (C), 56.1 (CH_3), 55.9 (CH_3), 40.7 (CH_2), 28.9 (CH_2).

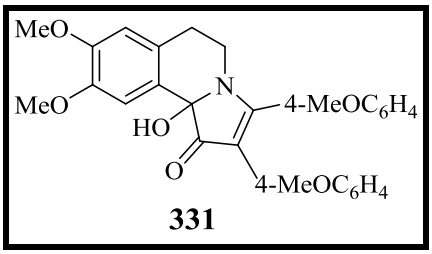
IR υ_{max} (cm^{-1}) 3361, 1842, 1615, 1513, 1444, 1338, 1258, 1224, 1106, 781, 760, 726, 684.

MS $(ESI)^+$: m/z [M + H] 414.2.

HRMS: [M] for $C_{26}H_{23}NO_4$ calculated 413.1627, found 413.1617.

New compound.

3.97. 8,9-Dimethoxy-10b-hydroxy-2,3-bis(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-a]isoquinolin-1-one



331

To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **85** (0.15 g; 0.78 mmol) in $CDCl_3$ (5 mL), was added 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.21 g; 0.78 mmol) at rt under an air atmosphere. The reaction mixture was stirred at rt for 3 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.25 (ethyl acetate/hexane = 2:1); orange yellow solid 0.16 g, 69 % yield; mp 142-143 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.51 (1H, s, Ar), 7.32 (2H, d, *J* = 8.5 Hz, Ar), 7.07 (2H, d, *J* = 7.8 Hz, Ar), 6.85 (2H, d, *J* = 7.8 Hz, Ar), 6.68 (2H, d, *J* = 8.5 Hz, Ar), 6.67 (1H, s, Ar), 3.82 (3H, s, C$\underline{H}_3$), 3.80 (3H, s, C$\underline{H}_3$), 3.72 (3H, s, C$\underline{H}_3$), 3.66 (3H, s, C$\underline{H}_3$), 3.72 - 3.29 (3H, m, O$\underline{H}$ and CH_2), 2.72-2.43 (2H, m, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 197.7 (C=O), 172.6 (C), 161.1 (CH), 157.4 (C), 149.1 (C), 147.9 (C), 130.5 (C), 129.9 (CH), 127.2 (C), 126.6 (C), 124.4 (C), 122.9 (C), 115.1 (CH), 113.6 (CH), 111.9 (CH), 111.3 (C), 111.2 (CH), 85.5 (C), 56.0 (OCH_3), 55.9 (OCH_3), 55.7 (OCH_3), 55.3 (OCH_3), 40.9 (CH_2), 28.7 (CH_2).

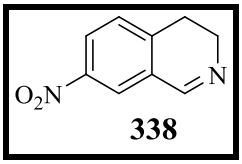
IR υ_{max} (cm^{-1}) 3318, 1644, 1604, 1517, 2492, 1337, 1248, 1172, 1113, 1014, 1001, 828, 725, 583, 561, 540, 528.

MS $(ESI)^+$: m/z [M + H] 274.2.

HRMS: [M] for $C_{28}H_{27}NO_6$ calculated 473.1838, found 473.1837.

New compound.

3.98. 7-Nitro-3,4-dihydroisoquinoline



338

To a stirred solution of potassium nitrate (0.71 g; 6.78 mmol) in sulfuric acid (4.6 mL), was added 3,4-dihydroisoquinoline in one portion at 0 ºC and the mixture was gradually warmed up to rt over 2 h. The reaction mixture was heated at 60 ºC for 4 h and then allowed to cool to rt. After this, the reaction mixture was basified with an aqueous solution of 3 M NaOH until the pH of the solution reached a value greater than 9.0. The water phase was washed with dichloromethane (20 mL x 3) and finally washed with brine (20 mL). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

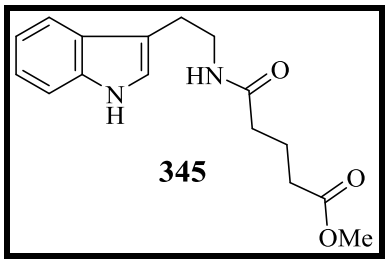
R_f 0.14 (ethyl acetate/hexane = 2:1); yellow oil 0.6 g, 76 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36 (1H, s, NC<u>H</u>), 7.16 (1H, dd, *J* = 8.3 and 2.2 Hz, Ar), 8.08 (1H, d, *J* = 2.2 Hz, Ar), 7.29 (1H, d, *J* = 8.3 Hz, Ar), 3.79 (2H, td, *J* = 7.6 and 2.1 Hz, NC<u>H</u>$_2$), 2.80 (2H, t, *J* = 7.6 Hz, NCH$_2$C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.2 (CH), 143.6 (C), 158.3 (C), 143.6 (C), 128.6 (CH), 125.7 (CH), 121.8 (CH), 46.8 (CH_2), 25.1 (CH_2).

Previously reported.[117]

3.99. Methyl 5-((2-(1H-indol-3-yl)ethyl)amino)-5-oxopentanoate



345

To a stirred solution of of tryptamine (0.400 g, 2.51 mmol) in dichloromethane (5 mL), was added glutaric anhydride (0.254 g, 2.51 mmol) in CH_2Cl_2 (1.1 mL). The reaction mixture was

kept at rt with stirring. After 20 minutes, the solvent was removed under reduced pressure. The residue was dissolved in methanol (4.0 mL) and then thionyl chloride (0.2 mL, 2.8 mmol) was added dropwise. The reaction mixture was stirred for 3h at rt. The solvents were removed *in vacuo* and the crude product was purified by flash chromatography affording the title compound.

R_f 0.52 (ethyl acetate/petroleum ether/methanol = 2:1:0.1); white solid 0.59 g, 83 % yield; mp 121 - 122 ºC; lit.,[122] : 102 - 103 ºC.

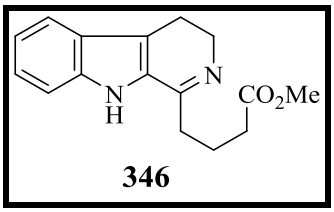
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.76 (1H, br. s, NH), 7.56 (1H, d, *J* = 7.8 Hz, Ar), 7.33 (1H, d, *J* = 8.1 Hz, Ar), 7.11 - 6.99 (3H, m, Ar), 3.64 (CH_3), 3.49 (2H, dd, *J* = 13.1 and 7.0 Hz, CH_2), 2.94 (2H, t, *J* = 7.3 Hz, C<u>H</u>$_2$), 2.29 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$), 2.19 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$), 1.86 (2H, qd, *J* = 7.4 Hz, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.8 (C=O), 173.7 (C=O), 136.7 (C), 127.4 (C), 122.0 (CH), 120.9 (CH), 118.2 (CH), 117.9 (CH), 111.8 (C), 110.8 (CH), 50.6 (CH_3), 40.1 (CH_2), 34.7 (CH_2), 32.5 (CH_2), 24.8 (CH_2), 20.8 (CH_2).

IR υ_{max} (cm^{-1}) 3357, 3311, 1712, 1626, 1536, 1415, 1309, 1180, 728, 645.

Previously reported.[122]

3.100. Methyl 4-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)butanoate



346

To a stirred solution of of methyl 5-((2-(1H-indol-3-yl)ethyl)amino)-5-oxopentanoate **345** (0.320 g, 1.11 mmol) in toluene (7 mL) and acetonitrile (3 mL), was added phosphorous oxychloride (0.3 mL, 3 mmol) dropwise under an inert N_2 atmosphere. The reaction mixture was heated at reflux for 5 h. After this time, the mixture was cooled to rt and the solvent was removed under reduced pressure. The crude product was dissolved in dichloromethane (20

mL) and the resulting mixture was washed with 1 M aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried ($MgSO_4$) and the solvents were removed *in vacuo* to give the title product.

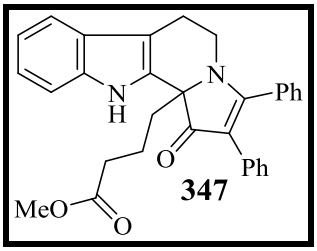
R_f 0.32 (ethyl acetate/petroleum ether/methanol = 1:1); yellow oil 0.29 g, 97 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.92 (N<u>H</u>), 7.48 (1H, d, *J* = 7.9 Hz, Ar), 7.36 (1H, d, *J* = 8.2 Hz, Ar), 7.18 (1H, dd, *J* = 7.5 and 7.5 Hz, Ar), 7.03 (1H, dd, *J* = 7.5 and 7.5 Hz, Ar), 3.78 (2H, t, *J* = 8.4 Hz, C<u>H</u>$_2$), 3.64 (3H, s, C<u>H</u>$_3$), 2.79 (2H, t, *J* = 8.4 Hz, C<u>H</u>$_2$), 2.62 (2H, t, *J* =7.9 Hz, C<u>H</u>$_2$), 2.40 (2H, t, *J* = 6.4 Hz, C<u>H</u>$_2$), 1.96 - 1.82 (1H, m, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.4 (C=O), 161.4 (C), 137.2 (C), 128.3 (C), 125.3 (C), 124.7 (CH), 120.2 (CH), 120.0 (CH), 117.1 (C), 112.4 (CH), 51.9 (CH_3), 47.8 (CH_2), 34.8 (CH_2), 32.8 (CH_2), 22.1 (CH_2), 19.3 (CH_2).

Previously reported.[122]

3.101. Methyl 4-(1-oxo-2,3-diphenyl-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)butanoate



347

To a stirred solution of methyl 4-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)butanoate **346** (0.12 g; 0.44 mmol) in acetonitrile (5 mL), was added diphenylcyclopropenone (0.09 g; 0.44 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 24 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.78 (ethyl acetate/hexane = 1:1); orange yellow solid 0.169 g, 80 % yield; mp 180 - 181 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.97 (NH), 7.55 - 7.44 (4H, m, Ar), 7.43 (1H, d, *J* = 7.8 Hz, Ar), 7.41 (1H, d, *J* = 8.1 Hz, Ar), 7.21 (1H, t, *J* = 7.5 Hz, Ar), 7.15 - 7.05 (7H, m, Ar), 4.11 (1H, dd, *J* = 13.9 and 5.6 Hz, CH_2), 3.69 (3H, s, CH_3), 3.63 - 3.55 (1H, m, CH_2), 2.76 (1H, dd, *J* = 15.4 and 4.1 Hz, CH_2), 2.63 - 2.55 (1H, m, CH_2), 2.52 - 2.32 (3H, m, CH_2), 2.24 (1H, ddd, *J* = 12.8 and 4.3 Hz, CH_2), 1.92 - 1.81 (1H, m, CH_2), 1.79 - 1.70 (1H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 197.9 (C=O), 175.4 (C=O), 173.6 (C), 136.7 (C), 131.7 (C), 131.1 (C), 130.7 (C), 130.6 (CH), 130.4 (CH), 129.1 (CH) 128.4 (CH), 127.8 (CH), 126.4 (C), 125.6 (CH), 122.3 (CH), 119.7 (CH), 118.3 (CH), 114.9 (C), 111.7 (CH), 106.9 (C), 69.9 (C), 51.6 (CH_3), 41.6 (CH_2), 36.7 (CH_2), 33.7 (CH_2), 22.3 (CH_2), 19.1 (CH_2).

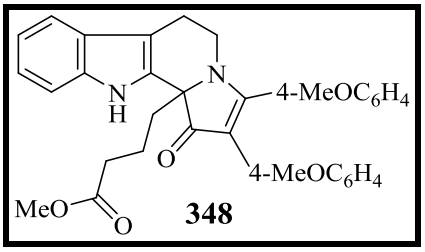
IR υ_{max} (cm^{-1}) 3246, 1731, 1644, 1538, 1422, 1351, 1315, 1254, 1083, 988, 908, 769, 696.

MS $(ESI)^+$: m/z [M + H] 477.2.

HRMS: [M] for $C_{31}H_{28}N_2O_3$ calculated 476.2100, found 476.2089.

Novel compound.

3.102. Methyl 4-(2,3-bis(4-methoxyphenyl)-1-oxo-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)butanoate



348

To a stirred solution of methyl 4-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)butanoate **346** (0.15 g; 0.55 mmol) in acetonitile (5 mL), was added 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.15 g; 0.55 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 24 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.72 (ethyl acetate/hexane = 1:1); orange yellow solid 0.22 g, 74 % yield; mp 188 - 189 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.11 (NH), 7.44 (1H, d, *J* = 7.8 Hz, Ar), 7.40 (1H, d, *J* = 8.2 Hz, Ar), 7.34 – 7.16 (3H, m, Ar), 7.11 (1H, t, *J* = 7.4 Hz, Ar), 7.08 - 7.00 (4H, m, Ar), 6.72 (2H, d, *J* = 8.8 Hz, Ar), 4.20 – 4.15 (1H, m, CH_2), 3.90 (3H, s, CH_3), 3.74 (3H, s, CH_3), 3.68 (3H, s, CH_3), 3.60 – 3.53 (1H, m, CH_2), 2.74 – 2.69 (1H, m, CH_2), 2.60 – 2.30 (4H, m, CH_2), 2.25 – 2.17 (1H, m, CH_2), 1.90 – 1.68 (2H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 197.9 (C=O), 174.8 (C=O), 173.6 (C), 161.1 (C), 157.5 (C), 136.6 (C), 131.9 (C), 130.6 (CH), 130.3 (C), 129.7 (CH), 126.4 (C), 123.8 (C), 122.6 (C), 122.1 (CH), 119.5 (CH), 118.2 (CH), 114.5 (CH), 113.4 (CH), 111.6 (CH), 106.8 (C), 69.8 (C), 55.3 (CH_3), 55.1 (CH_3), 51.6 (CH_3), 41.7 (CH_2), 36.6 (CH_2), 33.7 (CH_2), 22.2 (CH_2), 19.2 (CH_2).

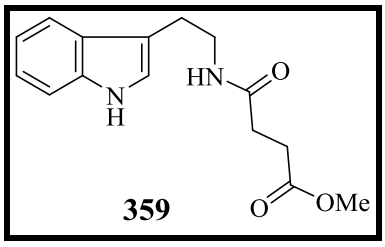
IR υ_{max} (cm^{-1}) 3270, 2929, 2839, 1742, 1635, 1606, 1577, 1519, 1462, 1437, 1344, 1295, 1243, 1171, 1023, 829, 759.

MS $(ESI)^+$: m/z [M + H] 537.2.

HRMS: [M] for $C_{33}H_{32}N_2O_5$ calculated 536.2311, found 536.2308.

Novel compound.

3.103. Methyl 4-((2-(1H-indol-3-yl)ethyl)amino)-4-oxobutanoate



359

To a stirred solution of of tryptamine (0.400 g, 2.50 mmol) in dichloromethane (10 mL), was added succinic anhydride (0.25 g, 2.50 mmol). The reaction mixture was kept at rt with stirring. After 20 minutes, the solvent was removed under reduced pressure. The residue was dissolved in methanol (4.0 mL) and then thionyl chloride (0.2 mL, 2.8 mmol) was added

dropwise. The reaction mixture was stirred at rt for 3 h. The solvents were removed *in vacuo* and the crude product was purified by flash chromatography affording the title compound.

R_f 0.56 (ethyl acetate/petroleum ether/methanol = 2:1:0.1); white solid 0.57 g, 83 % yield; mp 115-116 ºC lit.,[122] 102-103 ºC.

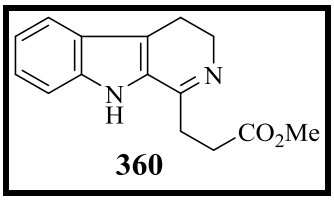
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.82 (1H, s, NH), 8.01 (1H, s, NH), 7.52 (1H, d, *J* = 7.6 Hz, Ar), 7.33 (1H, d, *J* = 7.8 Hz, Ar), 7.15 (1H, s, CH), 7.08 – 6.96 (2H, m, Ar), 3.58 (3H, s, CH_3), 3.31 (2H, t, *J* = 6.4 Hz, CH_2), 2.81 (2H, t, *J* = 7.33 Hz, CH_2), 2.61 - 2.51 (2H, m, CH_2), 2.36 (2H, t, *J* = 6.8 Hz, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.3 (C=O), 170.9 (C=O), 136.6 (C), 127.6 (C), 123.0 (CH), 121.3 (CH), 118.6 (CH), 112.2 (C), 111.8 (CH), 51.7 (CH_3), 40.0 (CH_2), 30.3 (CH2), 29.2 (CH_2), 25.6 (CH_2).

IR υ_{max} (cm^{-1}) 3331, 2928, 2839, 1721, 1651, 1536, 1432, 1368, 1213, 1171, 988, 738, 670.

Previously reported.[122]

3.104. Methyl 3-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)propanoate

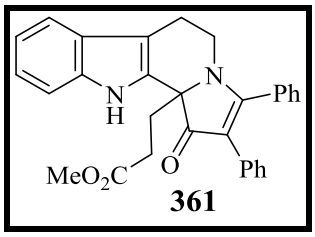


360

To a stirred solution of methyl 4-((2-(1H-indol-3-yl)ethyl)amino)-4-oxobutanoate **359** (0.15 g, 0.55 mmol) in 1,2-dichloroethane (7 mL), was added phosphorus (V) oxychloride (0.3 mL, 0.50 g, 3.23 mmol) dropwise at rt under an inert N_2 atmosphere. The resulting solution was heated to reflux for 40 min. After that the reaction mixture was allowed to cool to rt and the solvents were removed under reduced pressure. The crude product was dissolved in dichloromethane (10 mL) and the resulting mixture was washed with 1 M aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried ($MgSO_4$) and the solvents were

removed *in vacuo* to give the title product as yellow solid (0.098 g, 70 %). The residue was used for next step without further purification. Previously reported.[143]

3.105. Methyl 3-(1-oxo-2,3-diphenyl-6,11-dihydro-1H-indolizino[8,7-b]indol-11b(5H)-yl)propanoate



361

To a stirred solution of methyl 3-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)propanoate **360** (0.06 g; 0.24 mmol) in acetonitrile (5 mL), was added diphenycyclopropenone (0.05 g; 0.24 mmol) at rt under an inert N_2 atmosphere. The reaction mixture was stirred at rt for 24 h and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.77 (ethyl acetate/hexane = 1:1); orange yellow solid 0.09 g, 81 % yield; mp 182 - 183 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.27 (NH), 7.57 - 7.53 (2H, m, Ar), 7.47 (2H, d, *J* = 7.8 Hz, Ar), 7.43 (2H, d, *J* = 8.3 Hz, Ar), 7.24 – 7.10 (8H, m, Ar), 4.06 (1H, dd, *J* = 5.5 and 3.9 Hz, CH_2), 3.62 – 3.55 (1H, m, CH_2), 3.75 (3H, s, CH_3), 2.86 – 2.81 (1H, m, CH_2), 2.75 (1H, dd, *J* = 15.5 and 4.0 Hz, CH_2), 2.70 – 2.55 (3H, m, CH_2), 2.53 – 2.43 (1H, m, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 197.6 (C=O), 175.8 (C=O), 173.2 (C), 136.8 (C), 131.2 (C), 130.9 (C), 130.7 (CH), 130.6 (C), 130.5 (CH), 129.1 (CH), 128.5 (CH), 127.8 (CH), 126.3 (CH), 125.8 (CH), 122.4 (CH), 119.6 (CH), 118.2 (CH), 115.6 (C), 111.8 (C), 107.0 (C), 69.6 (C), 51.8 (CH_3), 41.6 (CH_2), 31.8 (CH_2), 28.7 (CH_2), 22.3 (CH_2).

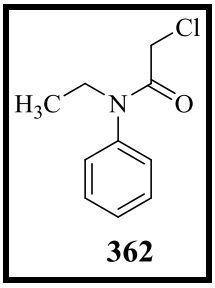
IR υ_{max} (cm^{-1}) 3269, 2928, 2839, 1744, 1639, 1601, 1536, 1469, 1428, 1351, 1171, 1060, 859, 736, 694, 511.

MS $(ESI)^+$: m/z [M + H] 463.2.

HRMS: [M] for $C_{30}H_{26}N_2O_3$ calculated 462.1943, found 462.1939.

New compound.

3.106. 2-Chloro-*N*-ethyl-*N*-phenylacetamide



362

To a stirred solution of chloroacetyl chloride (1.05 g; 0.49 mL; 9.31 mmol) in dry dichloromethane (60 mL), were added *N*-ethylaniline (0.94 g; 0.97 mL; 7.74 mmol) and tetrabutylammonium hydrogen sulfate (0.31 g; 0.90 mmol) in dry dichloromethane (60 mL) at rt under an inert N_2 atmosphere. A solution of potassium carbonate (1.61 g; 11.59 mmol) in water (30 mL) was added slowly in small portions. After this, the reaction mixture was stirred for 45 min at rt, and then the mixture was washed with 5 % aqueous HCl (40 mL x 2), 10 % aqueous NaOH (40 mL x 2) and brine (40 mL). The organic layers were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

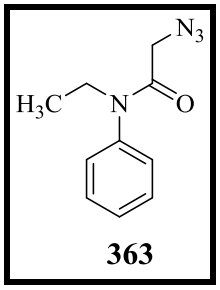
R_f 0.22 (ethyl acetate/petroleum ether = 1:4); colorless oil 1.7 g, 92 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39 - 7.30 (3H, m, Ph), 7.14 (2H, d, *J* = 7.5 Hz, Ph), 3.72 (2H, s, C$\underline{H}_2$), 3.67 (2H, q, *J* = 7.2 Hz, C$\underline{H}_2$), 1.04 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.5 (C=O), 140.8 (C), 129.9 (CH), 128.6 (CH), 128.1 (CH), 44.8 (CH_2), 42.1 (CH_2), 12.7 (CH_3).

Consistent with the previously reported data.[144]

3.107. 2-Azido-*N*-ethyl-*N*-phenylacetamide



363

To a stirred solution of 2-chloro-*N*-ethyl-*N*-phenylacetamide **362** (1.01 g; 5.07 mmol) in dry dimethylformamide (15 mL), was added sodium azide (0.82 g; 12.68 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was heated at 90 ºC for 1 h. After this, the reaction mixture was allowed to cool to rt and the organic layer was extracted with dichloromethane (50 mL x 3). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.41 (ethyl acetate/petroleum ether = 1:3); yellow oil 0.9 g, 93 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.28 (3H, m, Ph), 7.11 (2H, d, *J* = 7.5 Hz, Ph), 3.71 (2H, q, *J* = 7.2 Hz, C$\underline{H}_2$), 3.48 (2H, s, C$\underline{H}_2$), 1.06 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$).

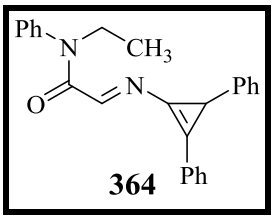
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.7 (C=O), 140.3 (C), 130.0 (CH), 128.7 (CH), 128.1 (CH), 50.8 (CH_2), 44.4 (CH_2), 12.8 (CH_3).

IR υ_{max} (cm^{-1}) 2976, 2942, 2099, 1663, 1595, 1494, 1404, 1254, 1133, 1090, 1074, 948, 889.

MS $(ESI)^+$: Mass spectrometry did not give the required MS spectrum due to the degradation of the title compound.

New compound.

3.108. (*E*)-*N*-(2-((2,3-diphenylcycloprop-1-en-1-yl)imino)-*N*-ethyl-*N*-phenylacetamide



364

To a stirred solution of ethyl 2-azido-*N*-ethyl-*N*-phenylacetamide **363** (0.25 g; 1.31 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.52 g; 0.97 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, diphenylcyclopropenone (0.26 g; 1.28 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/petroleum ether; 1:3); yellow oil 0.27 g, 57 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56 (2H, d, *J* = 7.4 Hz, Ph), 7.48-7.41 (3H, m, CH and Ph), 7.39 - 7.32 (4H, m, Ph), 7.29 - 7.23 (4H, m, Ph), 7.01 - 6.95 (3H, m, Ph), 6.74 (1H, s, C<u>H</u>), 3.59 (2H, q, *J* = 7.2 Hz, C<u>H</u>$_2$), 1.17 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.4 (C=O), 152.2 (C), 144.9 (C), 139.5 (C), 136.9 (C), 134.0 (CH), 129.8 (C), 129.2 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 121.5 (CH), 117.7 (CH), 113.7 (CH), 46.0 (CH_2), 12.9 (CH_3).

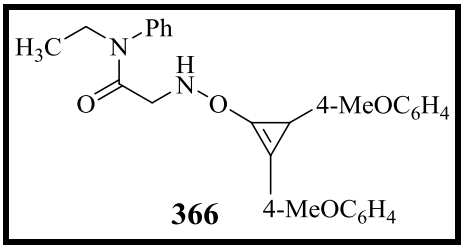
IR υ_{max} (cm^{-1}) 2987, 1731, 1586, 1495, 1445, 1258, 1091, 1070, 907, 750, 728, 690, 669.

MS $(ESI)^+$: m/z [M + H] 367.2.

HRMS: [M] for $C_{25}H_{22}N_2O$ calculated 366.1732, found 366.1756.

New Compound.

3.109. 2-(((2,3-Bis(4-methoxyphenyl)cycloprop-1-en-1-yl)oxy)amino)-*N*-ethyl-*N*-phenylacetamide



366

To a stirred solution of 2-azido-*N*-ethyl-*N*-phenyl-acetamide **363** (0.15 g; 0.79 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.31 g; 1.18 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **237** (0.21 g; 0.75 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.29 (ethyl acetate/petroleum ether = 1:1); white solid 0.19 g, 56 % yield; mp 128-129 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 (1H, s, C<u>H</u>), 7.43 - 7.37 (3H, m, Ar), 7.17 (2H, d, *J* = 8.3 Hz, Ar), 7.13 (2H, d, *J* = 7.2 Hz, Ar), 6.97 (2H, d, *J* = 8.3 Hz, Ar), 6.93 (2H, d, *J* = 8.4 Hz, Ar), 6.63 (2H, d, *J* = 8.4 Hz, Ar), 6.51 (1H, br. s, N<u>H</u>), 3.69 - 3.60 (4H, m, 2 x C<u>H</u>$_2$), 3.64 (3H, s, C<u>H</u>$_3$), 3.66 (3H, s, C<u>H</u>$_3$), 1.17 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.7 (C=O), 167.4 (C), 159.7 (C), 159.6 (C), 140.0 (C), 136.5 (CH), 132.0 (CH), 131.7 (C), 131.1 (CH), 130.1 (CH), 128.8 (CH), 128.3 (CH), 128.0 (C), 127.7 (C), 115.1 (CH), 113.6 (CH), 55.2 (CH_3), 55.1 (CH_3), 44.3 (CH_2), 42.8 (CH_2), 12.9 (CH_3).

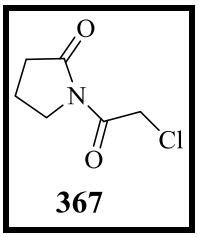
IR υ_{max} (cm^{-1}) 3369, 3029, 2929, 1653, 1606, 1507, 1489, 1416, 1286, 1250, 1171, 1022, 832, 767, 699, 555.

MS $(ESI)^+$: m/z [M + H] 445.2.

HRMS: [M] for $C_{27}H_{28}N_2O_4$ calculated 444.2049, found 444.2047.

Previously unreported.

3.110. 1-(2-Chloroacetyl)pyrrolidin-2-one



367

To a stirred solution of 2-pyrrolidinone (1.11 g; 0.99 mL; 12.93 mmol) in dry benzene (5 mL), was added chloroacetyl chloride (1.75 g; 1.23 mL; 15.51 mmol) dropwise over 0.5 h at 0 ºC under an inert N_2 atmosphere and the reaction mixture was left to stir at the same temperature for 1 h. After completion of this time, the reaction mixture was allowed to warm to ambient temperature and then left for 24 h with stirring at the same temperature. The resulting reaction mixture was filtered free of pyrrolidone hydrochloride and solvents were removed *in vacuo* to obtain the desired compound as a colorless oil (1.4 g, 67 %).

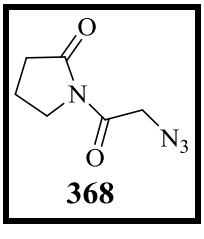
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.25 (2H, s, C$\underline{H}_2$), 3.79 (2H, t, *J* = 7.2 Hz, C$\underline{H}_2$), 2.56 (2H, t, *J* = 8.1 Hz, C$\underline{H}_2$), 2.12-2.01 (2H, m, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.8 (C=O), 165.9 (C=O), 44.6 (CH_2), 44.2 (CH_2), 32.0 (CH_2), 16.5 (CH_2).

IR υ_{max} (cm^{-1}) 2986, 2947, 1720, 1643, 1412, 1372, 1273, 1225, 1186, 1153, 1091, 992, 922.

Previously reported.[123]

3.111. 1-(2-Azidoacetyl)pyrrolidin-2-one



368

To a stirred solution of 1-(2-chloroacetyl)pyrrolidin-2-one **367** (0.91 g; 5.59 mmol) in dry dimethylformamide (10 mL), was added sodium azide (0.54 g; 8.38 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was heated at 90 ºC for 1 h. After this, the reaction mixture was allowed to cool to rt and the organic layer was extracted with dichloromethane (25 mL x 3). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.34 (ethyl acetate/petroleum ether = 1:3); colorless oil 0.7 g, 89 % yield.

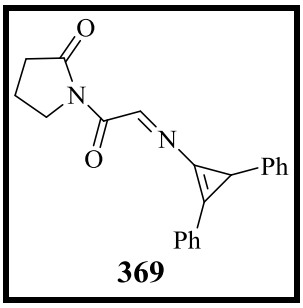
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.42 (2H, s, C$\underline{H}_2$), 3.82 (2H, t, *J* = 7.2 Hz, C$\underline{H}_2$), 2.58 (2H, t, *J* = 8.1 Hz, C$\underline{H}_2$), 2.15-2.05 (2H, m, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.9 (C=O), 168.7 (C=O), 53.8 (CH_2), 45.1 (CH_2), 32.9 (CH_2), 17.6 (CH_2).

IR υ_{max} (cm^{-1}) 2983, 2943, 2094, 1715, 1634, 1417, 1289, 1259, 1198, 1063, 993, 789, 683, 495.

Previously reported.[124]

3.112. 1-(2-((2,3-Diphenylcycloprop-1-en-1-yl)imino)acetyl)pyrrolidin-2-one



369

To a stirred solution of 1-(2-azidoacetyl)pyrrolidin-2-one **368** (0.07 g; 0.49 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.19 g; 0.74 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, diphenylcyclopropenone (0.09 g; 0.46 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same

temperature. The reaction mixture was left overnight at rt and then the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.16 (ethyl acetate/petroleum ether = 1:2); white solid 0.1 g, 46 % yield; mp 154-155 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48 (2H, dd, *J* = 8.1 and 1.5 Hz, Ph), 7.43 - 7.37 (3H, m, C<u>H</u> and Ph), 7.35 - 7.25 (4H, m, Ar), 7.20 - 7.18 (2H, m, Ph), 7.17 (1H, s, C<u>H</u>), 3.47 (2H, t, *J* = 7.2 Hz, C<u>H</u>$_2$), 2.55 (2H, t, *J* = 8.2 Hz, C<u>H</u>$_2$), 2.16 - 2.07 (2H, m, C<u>H</u>$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.3 (C=O), 153.6 (C=O), 144.9 (C), 139.1 (C), 136.8 (C), 134.6 (CH), 129.0 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 112.4 (CH), 46.3 (CH_2), 31.0 (CH_2), 18.5 (CH_2).

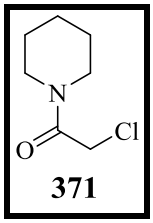
IR υ_{max} (cm^{-1}) 2980, 2359, 1711, 1587, 1487, 1458, 1407, 1226, 760, 726, 649.

MS $(ESI)^+$: m/z [M + H] 331.1.

HRMS: [M] for $C_{21}H_{18}N_2O_2$ requires 330.1368, found 330.1355.

Previously unreported.

3.113. 2-Chloro-1-(1-piperidin-1-yl)ethan-1-one



371

To a stirred solution of chloroacetyl chloride (1.75 g; 1.23 mL; 15.51 mmol) in dry dichloromethane (100 mL), were added piperidine (1.11 g; 1.33 mL; 12.93 mmol) and tetrabutylammonium hydrogen sulfate (0.72 g; 4.59 mmol) in dry dichloromethane (100 mL) at rt under an inert N_2 atmosphere. A solution of potassium carbonate (2.68 g; 19.39 mmol) in water (50 mL) was added slowly in small portions. After this, the reaction mixture was stirred for 45 min at rt, and then the mixture was washed with 5 % aqueous HCl (100 mL x 2), 10 % aqueous NaOH (100 mL x 2) and brine (100 mL). The organic layers were dried ($MgSO_4$) and

then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.53 (ethyl acetate/petroleum ether = 1:1); colourless oil 1.7 g, 82 % yield.

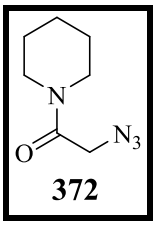
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.06 (2H, s, C$\underline{H}_2$), 3.47 (2H, t, *J* = 5.7 Hz, C$\underline{H}_2$), 3.37 (2H, t, *J* = 5.7 Hz, C$\underline{H}_2$), 1.61 - 2.1.56 (4H, m, C$\underline{H}_2$), 1.50 - 1.46 (2H, m, C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.7 (C=O), 47.3 (CH_2), 43.2 (CH_2), 41.2 (CH_2), 26.2 (CH_2), 25.3 (CH_2), 24.2 (CH_2).

IR (neat) υ_{max} 2936, 2856, 1637, 1443, 1277, 1249, 1222, 1132, 1119, 1022, 953, 852, 785, 651, 563.

Consistent with the previously reported data.[145]

3.114. 2-Azido-1-(1-piperidin-1-yl)ethan-1-one



372

To a stirred solution of 2-chloro-1-(1-piperidin-1-yl)ethan-1-one **371** (0.85 g; 5.28 mmol) in dry dimethylformamide (10 mL), was added sodium azide (0.51 g; 7.92 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was heated at 90 ºC for 1 h. After this, the reaction mixture was allowed to cool to rt and the organic layer was extracted with dichloromethane (25 mL x 3). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/petroleum ether = 1:1); colourless oil 0.7 g, 85 % yield.

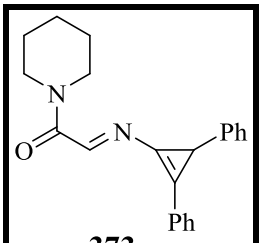
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.76 (2H, s, C$\underline{H}_2$), 3.38 - 3.35 (2H, m, C$\underline{H}_2$), 3.14 - 3.11 (2H, m, C$\underline{H}_2$), 1.48 - 1.45 (2H, m, C$\underline{H}_2$), 1.40 - 1.36 ((4H, m, 2 x C$\underline{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.2 (C=O), 50.4 (CH_2), 45.8 (CH_2), 42.9 (CH_2), 26.1 (CH_2), 25.3 (CH_2), 24.1 (CH_2).

IR υ_{max} (cm^{-1}) 2937, 2857, 2099, 1644, 1443, 1427, 1281, 1249, 1222, 1138, 1016, 953, 920, 852, 787, 552.

Consistent with the previously reported data.[145]

3.115. (*E*)-2-((2,3-dipheylcycloprop-1-en-1-yl)imino)-1-(piperidin-1-yl)ethan-1-one



373

To a stirred solution of 2-azido-1-(1-piperidin-1-yl)ethan-1-one **372** (0.15 g; 0.97 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.38 g; 1.45 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, diphenylcyclopropenone (0.21 g; 0.97 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51(ethyl acetate/petroleum ether = 1:1); yellow solid 0.2 g, 63 % yield; mp 137-138 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.50 (2H, dd, *J* = 8.1 and 1.5 Hz, Ph), 7.43 - 7.31 (5H, m, Ph), 7.28 - 7.20 (3H, m, Ph), 7.06 (1H, s, C<u>H</u>), 6.15 (1H, s, C<u>H</u>), 2.93 - 2.90 ((4H, m, 2 x C<u>H</u>$_2$), 1.62 - 1.52 (6H, m, 3 x CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.6 (C=O), 152.6 (C), 139.9 (C), 137.2 (C), 132.7 (CH), 129.6 (C), 129.0 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.4 (CH), 103.2 (CH), 48.8 (2 x CH_2), 24.7 (2 x CH_2), 23.9 (CH_2).

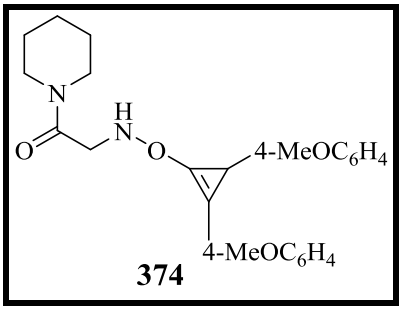
IR υ_{max} (cm^{-1}) 2939, 2359, 1644, 1594, 1444, 1250, 905, 725, 693, 645.

MS $(ESI)^+$: m/z [M + H] 331.2.

HRMS: [M] for $C_{22}H_{22}N_2O$ calculated 330.1732, found 330.1736.

Previously unreported.

3.116. 2-(((2,3-Bis(4-methoxyphenyl)cycloprop-1-en-1-yl)oxy)amino-1-(piperidin-1-yl)ethan-1-one



374

To a stirred solution of 2-azido-1-(1-piperidin-1-yl)ethan-1-one **372** (0.15 g; 0.97 mmol) in dry tetrahydrofuran (5 mL) was added triphenylphosphine (0.31 g; 1.18 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one **239** (0.26 g; 0.97 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.31 (ethyl acetate/petroleum ether = 1:1); white solid 0.14 g, 36 % yield; mp 127-128 ºC.

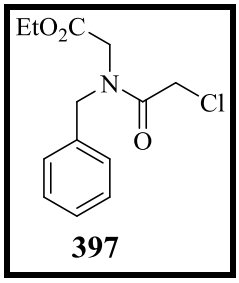
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28 (2H, d, *J* = 8.7 Hz, Ar), 7.01 (2H, d, *J* = 8.7 Hz, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (1H, s, CH), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.04 (1H, s, N<u>H</u>), 3.74 (3H, s, C<u>H</u>$_3$), 3.72 (3H, s, C<u>H</u>$_3$), 3.66 (2H, s, C<u>H</u>$_2$), 2.87 - 2.84 (4H, m, 2 x C<u>H</u>$_2$), 1.51-1.46 (6H, m, 3 x CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.4 (C=O), 158.9 (C), 157.5 (C), 153.1 (C), 132.8 (C), 130.3 (CH), 129.8 (C), 129.1 (CH), 127.2 (C), 113.7 (CH), 113.5 (CH), 103.2 (CH), 55.4 (CH_3), 55.3 (CH_3), 48.9 (2 x CH_2), 29.7 (CH_2), 24.7 (2 x CH_2), 23.9 (CH_2).

IR υ_{max} (cm^{-1}) 3321, 2934, 2359, 1644, 1604, 1512, 1463, 1247, 1176, 1033, 903, 723, 648, 539.

Previously unreported.

3.117. *N*-Chloroacetyl-*N*-benzylglycine ethyl ester



397

To a stirred solution of chloroacetyl chloride (0.70 g; 0.49 mL) in dry dichloromethane (20 mL), were added *N*-benzylglycine ethyl ester (1.00 g; 0.97 mL) and tetrabutyl ammonium hydrogen sulfate (0.20 g; 0.60 mmol) in dry dichloromethane (20 mL) at rt under an inert N_2 atmosphere. A solution of potassium carbonate (1.07 g; 7.74 mmol) in water (20 mL) was added slowly in small portions. After this, the reaction mixture was stirred for 45 min at rt, and then the mixture was washed with 5 % aqueous HCl (40 mL x 2), 10 % aqueous NaOH (40 mL x 2) and brine (40 mL). The organic layers were dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.51 (ethyl acetate/petroleum ether = 1:4); yellow oil 1.20 g, 86 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 - 7.32 (2 x rotamers, 6H, m, Ph), 7.28 - 7.24 (2 x rotamers, 4H, d, *J* = 7.0 Hz, Ph), 4.70 (1 x rotamer, 2H, s, PhC$\underline{H}_2$), 4.67 (1 x rotamer, 2H, s, PhC$\underline{H}_2$), 4.21 - 4.12 (2 x rotamers, 6H, s, C$\underline{H}_2$), 4.12 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.05 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.04 (1 x rotamer, 2H, s, C$\underline{H}_2$), 1.29 - 1.23 (2 x rotamers, 6H, m, C$\underline{H}_3$).

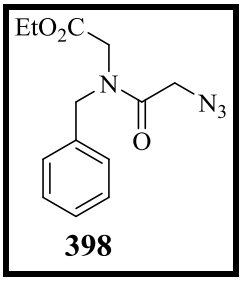
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.7 (C=O), 168.6 (C=O), 167.4 (C=O), 167.2 (C=O), 135.7 (C), 135.1 (C), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.0

(CH), 61.8 (CH_2), 61.3 (CH_2), 52.4 (CH_2), 50.2 (CH_2), 48.5 (CH_2), 47.2 (CH_2), 41.1 (CH_2), 41.0 (CH_2), 14.1 (CH_3), 14.0 (CH_3).

IR υ_{max} (cm^{-1}) 2981, 2943, 1739, 1657, 1450, 1374, 1194, 1023, 952, 749, 732, 698, 497.

Previously reported in the literature.[73]

3.118. *N*-Azidoacetyl-*N*-benzylglycine ethyl ester



398

To a stirred solution of *N*-chloroacetyl-*N*-benzylglycine ethyl ester **397** (1.44 g; 5.34 mmol) in dry dimethylformamide (20 mL), was added sodium azide (0.87 g; 13.35 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was heated at 90 ºC for 1 h. After this, the reaction mixture was allowed to cool to rt and the organic layer was extracted with dichloromethane (50 mL x 3). The combined organic extracts were dried ($MgSO_4$) and then solvents were removed *in vacuo.* The crude product was purified by flash chromatography affording the title compound.

R_f 0.30 (ethyl acetate/petroleum ether = 1:1); yellow oil 1.0 g, 78 % yield.

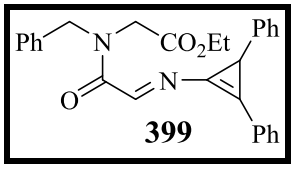
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 - 7.28 (2 x rotamers, 6H, m, Ph), 7.27 (1 x rotamer, 2H, d, *J* = 8.0 Hz, Ph), 7.20 (1 x rotamer, 2H, d, *J* = 7.4 Hz, Ph), 4.68 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.57 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.23 - 4.14 (2 x rotamers, 4H, m, C$\underline{H}_2$), 4.11 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.04 (1 x rotamer, 2H, s, C$\underline{H}_2$), 3.95 (1 x rotamer, 2H, s, C$\underline{H}_2$), 3.88 (1 x rotamer, 2H, s, C$\underline{H}_2$), 1.29 - 1.23 (2 x rotamers, 6H, m, C$\underline{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.7 (C=O), 168.5 (C=O), 168.3 (C=O), 167.9 (C=O), 135.7 (C), 135.0 (C), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 126.6

(CH), 61.9 (CH_2), 61.4 (CH_2), 51.6 (CH_2), 50.7 (CH_2), 50.4 (CH_2), 50.3 (CH_2), 47.9 (CH_2), 47.3 (CH_2), 14.1 (CH_3), 14.0 (CH_3).

Previously reported in the literature.[73]

3.119. Ethyl (*E*)-*N*-benzyl-*N*-(2-((2,3-diphenylcycloprop-1-en-1-yl)imino)acetyl)glycinate



399

To a stirred solution of *N*-azidoacetyl-*N*-benzylglycine ethyl ester **398** (0.15 g; 0.58 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.23 g; 0.84 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, diphenylcyclopropenone (0.11 g; 0.52 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.31 (ethyl acetate/petroleum ether = 3:1); orange yellow oil 0.140 g, 56 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56 – 7.53 (2H, m, Ph), 7.44 – 7.32 (8H, m, Ph), 7.28 – 7.24 (5H, m, Ph), 7.25 (1H, d, *J* = 6.8 Hz, Ph), 7.09 (1H, s, C<u>H</u>), 6.18 (1H, s, C<u>H</u>), 4.33 (2H, s, PhC<u>H</u>$_2$), 4.18 (2H, q, *J* = 7.2 Hz, C<u>H</u>$_2$), 3.66 (2H, s, C<u>H</u>$_2$), 1.28 (3H, t, *J* = 7.2 Hz, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.5 (C=O), 155.8 (C=O), 151.9 (C), 139.8 (C), 137.2 (C), 136.1 (C), 132.8 (CH), 129.4 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 102.5 (CH), 61.1 (CH_2), 54.1 (CH_2), 49.6 (CH_2), 14.2 (CH_3).

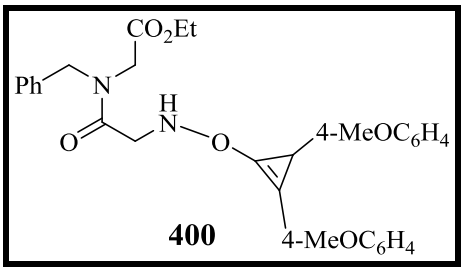
IR υ_{max} (cm^{-1}) 2979, 1739, 1596, 1193, 1158, 754, 693.

MS $(ESI)^+$: m/z [M + H] 439.2.

HRMS: [M] for $C_{28}H_{26}N_2O_3$ calculated 438.1943, found 438.1961.

Previously unreported.

3.220. Ethyl *N*-benzyl-*N*-(2-((2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-ylidene)amino)acetyl)glycinate



400

To a stirred solution of ethyl 2-((2-azidoethyl)(benzyl)amino)acetate **398** (0.15 g; 0.58 mmol) in dry tetrahydrofuran (5 mL), was added triphenylphosphine (0.23 g; 0.84 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, 2,3-bis(4-methoxyphenyl)cycloprop-2-en-1-one (0.14 g; 0.52 mmol) in acetonitrile (2.5 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.31 (ethyl acetate/petroleum ether = 1:5); orange yellow oil 0.14 g, 48 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 – 7.41 (2 x rotamers, 6H, m, Ar), 7.39 – 7.27 (2 x rotamers, 8H, m, Ar), 7.20 – 7.12 (2 x rotamers, 8H, m, Ar), 7.05 – 7.01 (2 x rotamers, 4H, m, Ar), 4.51 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.47 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.22 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.21 (1 x rotamer, 2H, s, C$\underline{H}_2$), 4.06 – 3.97 (2 x rotamers, 4H, m, C$\underline{H}_2$), 3.92 (1 x rotamer, 2H, s, C$\underline{H}_2$), 3.82 (1 x rotamer, 2H, s, C$\underline{H}_2$), 3.74 (1 x rotamer, 3H, s, OC$\underline{H}_3$), 3.73 (1 x rotamer, 3H, s, OC$\underline{H}_3$), 3.61 (1 x rotamer, 3H, s, OC$\underline{H}_3$), 3.60 (1 x rotamer, 3H, s, OC$\underline{H}_3$), 1.27 – 1.21 (2 x rotamers, 6H, m, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.7 (C=O), 168.5 (C=O), 168.4 (C=O), 168.0 (C=O), 167.2 (C), 167.1 (C), 159.5 (C). 159.4 (C), 159.3 (C), 159.2 (C),157.9 (C), 157.1 (C), 136.5 (CH), 135.3 (C), 134.4 (C), 131.7 (CH), 131.6 (CH), 131.3 (CH), 131.1 (C), 131.0 (C), 130.7 (CH), 129.6 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.5 (C), 127.3 (C),

126.5 (CH), 114.8 (CH), 114.7 (CH), 113.2 (CH), 61.4 (CH_2), 60.9 (CH_2), 54.9 (OCH_3), 54.8 (OCH_3), 54.7 (OCH_3), 54.6 (OCH_3), 50.6 (CH_2), 49.5 (CH_2), 46.6 (CH_2), 46.4 (CH_2), 41.6 (CH_2), 41.5 (CH_2), 13.7 (CH_3), 13.6 (CH_3).

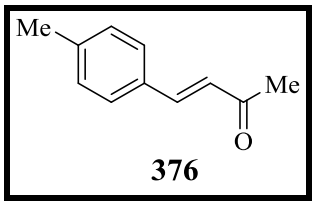
IR υ_{max} (cm^{-1}) 3460, 2987, 1740, 1605, 1602, 1506, 1463, 1244, 1172, 1022, 831, 699.

MS $(ESI)^+$: m/z [M + H] 517.2.

HRMS: [M] for $C_{30}H_{32}N_2O_6$ calculated 516.2287, found 516.2279.

Previously unreported.

3.221. (*E*)-4-(*p*-Tolyl)but-3-en-2-one



376

To a stirred solution of *p*-tolualdehyde (2.01 g; 1.96 mL; 12.93 mmol) in acetone (5 mL), was added 4 N sodium hydroxide (3.21 g; 20 mL H_2O; 80.81 mmol) at rt and after that the reaction mixture was left to stir at the same temperature for 18 h. After completion of this time, the excess acetone was removed under reduced pressure and then 4 N HCl was added slowly until the pH of the solution reached a value 2.0 and finally the mixture was extracted with dichloromethane (100 mL x 3). The combined organic extracts were dried ($MgSO_4$) and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.28 (ethyl acetate/petroleum ether = 1:6); yellow oil 1.5 g, 56 % yield.

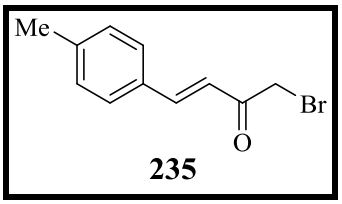
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (1H, d, *J* = 16.2 Hz, C<u>H</u>=CH), 7.45 (2H, d, *J* = 8.0 Hz, Ar), 7.21 (2H, d, *J* = 8.0 Hz, Ar), 6.68 (1H, d, *J* = 16.2 Hz, CH=C<u>H</u>), 2.39 (CH_3), 2.38 (CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 198.5 (C=O), 143.5 (CH), 141.0 (C), 131.6 (C), 129.7 (CH), 128.3 (CH), 126.2 (CH), 27.4 (CH_3), 21.5 (CH_3).

IR υ_{max} (cm^{-1}) 2982, 2934, 1660, 1606, 1512, 1353, 1293, 1260, 1206, 1183, 986, 807, 538.

Previously reported.[125]

3.222. (*E*)-1-Bromo-4-(*p*-tolyl)but-3-en-2-one



235

To a stirred solution of (*E*)-4-(*p*-tolyl)but-3-en-2-one **376** (1.02 g; 6.25 mmol) in dry tetrahydrofuran (60 mL), was added slowly pyrrolidone hydrotribromide (3.71 g; 7.49 mmol) at rt over 1 h under an inert N_2 atmosphere. The reaction mixture was left at rt to stir for 24 h. After this time, excess pyrrolidone hydrotribromide was removed by filtration and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in diethyl ether (20 mL) and then washed with brine (15 mL x 2). The organic layer was dried ($MgSO_4$) and then solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.29 (ethyl acetate/petroleum ether = 2:1); yellow solid 0.9 g, 61 % yield; mp 94-95 ºC.

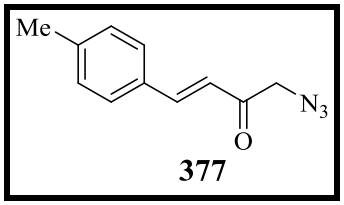
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CH), 7.49 (2H, d, *J* = 7.8 Hz, Ar), 7.23 (2H, d, *J* = 7.8 Hz, Ar), 6.91 (1H, d, *J* = 16.1 Hz, CH=C<u>H</u>), 4.10 (C<u>H_2</u>), 2.40 (C<u>H_3</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.0 (C=O), 145.5 (CH), 141.8 (C), 131.2 (C), 129.8 (CH), 128.7 (CH), 121.3 (CH), 33.2 (CH_2), 21.6 (CH_3).

IR υ_{max} (cm^{-1}) 2983, 2933, 1685, 1667, 1564, 1511, 1386, 1326, 1182, 1153, 1063, 976, 891, 860, 840, 710, 643, 517.

Previously reported.[126]

3.223. (*E*)-1-Azido-4-(*p*-tolyl)but-3-en-2-one



377

To a stirred solution of (*E*)-1-bromo-4-(*p*-tolyl)but-3-en-2-one **235** (0.51 g; 0.21 mmol) in dry dimethylformamide (2 mL), was added sodium azide (0.013 g; 0.21 mmol) under an inert N_2 atmosphere at rt. The reaction mixture was left at rt for 6 h. After completion of reaction, the organic layer was extracted with dichloromethane (10 mL x 3). The combined organic extracts were washed with brine (15 mL x 3) and then dried ($MgSO_4$). The solvents were removed *in vacuo* to obtain the titled compound as a yellow solid (0.4 g, 95 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CH), 7.39 (2H, d, *J* = 8.0 Hz, Ar), 7.14 (2H, d, *J*= 8.0 Hz, Ar), 6.68 (1H, d, *J* = 16.1 Hz, CH=C<u>H</u>), 4.11 (C<u>H</u>$_2$), 2.31 (C<u>H</u>$_3$).

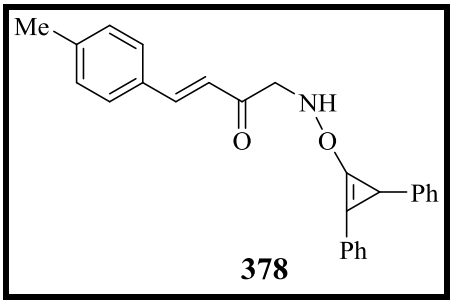
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 193.1 (C=O), 144.7 (CH), 141.9 (C), 131.1 (C), 129.8 (CH), 128.6 (CH), 120.9 (CH), 56.6 (CH_2), 21.6 (CH_3).

IR υ_{max} (cm^{-1}) 2989, 2942, 2097, 1692, 1613, 1599, 1566, 1347, 1285, 1270, 1179, 1084, 998, 909, 799.

MS $(ESI)^+$: Not obtained.

Previously unreported.

3.224. (*E*)-1-[(2,3-Diphenylcycloprop-2-en-1-yl)oxyamino]-4-(*p*-tolyl)but-3-en-2-one



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To a stirred solution of (*E*)-1-azido-4-(*p*-tolyl)but-3-en-2-one **377** (0.040 g; 0.21 mmol) in dry tetrahydrofuran (4 mL), was added triphenylphosphine (0.08 g; 0.32 mmol) at rt. The reaction mixture was left to stir for 45 min at rt. After this time, diphenylcyclopropenone (0.04 g; 0.21 mmol) in acetonitrile (2 mL) was added dropwise under an inert N_2 atmosphere at the same temperature. The reaction mixture was left overnight at rt and then the solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound as a yellow solid (0.04 g, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (1H, s, Ar), 7.56 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CH), 7.48 - 7.36 (5H, m, CH & Ar), 7.26 - 7.23 (2H, m, Ar), 7.13 (2H, d, *J* = 7.9 Hz, Ar), 7.11-7.05 (3H, m, Ar), 6.97 - 6.94 (2H, m, Ar), 6.61 (1H, d, *J* = 16.1 Hz, CH=C<u>H</u>), 6.44 (1H, t, *J* = 4.5 Hz, N<u>H</u>), 4.41 (2H, d, *J* = 4.5 Hz, C<u>H</u>$_2$), 2.31 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 193.7 (C), 167.1(C), 144.4 (CH), 141.8 (C), 137.4 (CH), 135.9 (C), 134.9 (C), 134.1 (C), 131.1 (C), 130.5 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 121.9 (CH), 48.4 (CH_2), 21.6 (CH_3).

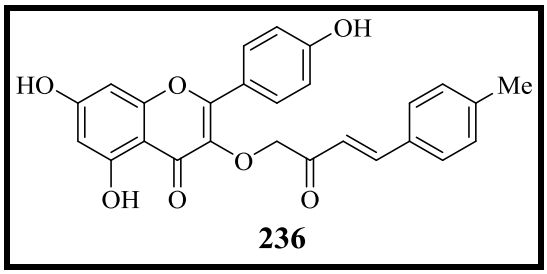
IR υ_{max} (cm^{-1}) 3309, 2980, 1660, 1613, 1504, 1421, 1359, 1179, 1071, 692.

MS $(ESI)^+$: m/z [M + H] 382.2.

HRMS: [M] for $C_{26}H_{23}NO_2$ calculated 381.1729, found 381.1728.

Previously unreported.

3.225. 3-*O*-[(*E*)-(2-Oxo-4-(*p*-tolyl)but-3-en-1-yl] kaempferol.



236

To a solution of kaempferol (0.025 g; 0.09 mmol) in dry 1,4-dioxane (4 mL), was added potassium carbonate (0.013; 0.09 mmol) and the mixture was heated at reflux under an N_2 atmosphere at 80 ºC for 1.5 h. After this time, a solution of (*E*)-1-bromo-4-(*p*-tolyl)but-3-en-2-one **357** (0.04 g; 0.15 mmol) in 1,4-dioxane (2 mL) was added dropwise to the reaction mixture and the reaction mixture was heated at 80 ºC for 48 h. The solvents were removed *in vacuo*. The crude product was purified by flash chromatography affording the title compound.

R_f 0.36 (dichloromethane/methanol = 10:1); yellow solid 0.013 g, 34 % yield.

^{1}H NMR (400 MHz, CD_3OD-d_4) δ ppm 8.01 (2H, d, *J* = 8.7 Hz, Ar), 7.68 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CH), 7.55 (1H, s, O<u>H</u>), 7.53 (1H, s, O<u>H</u>), 7.51 (1H, s, O<u>H</u>), 7.47 (1H, d, *J* = 8.0 Hz, Ar), 7.25 (2H, d, *J* = 8.0 Hz. Ar), 6.97 (2H, d, *J* = 16.1 Hz, CH=C<u>H</u>), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.39 (1H, d, *J* = 1.8 Hz, Ar), 6.18 (1H, d, *J* = 1.8 Hz, Ar), 5.10 (2H, s, C<u>H</u>$_2$), 2.35 (3H, s, C<u>H</u>$_3$).

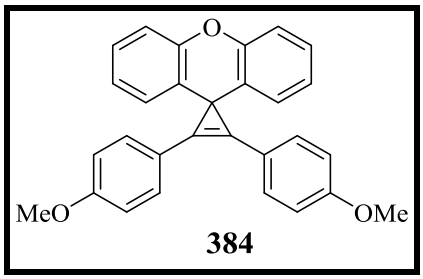
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 195.6 (C), 178.0 (C), 164.5 (C), 161.7 (C), 160.4 (C), 156.9 (C), 156.3 (C), 143.9 (CH), 141.3 (C), 136.5 (C), 131.6 (C), 130.4 (CH), 129.3 (CH), 128.4 (CH), 121.1 (C), 120.5 (CH), 115.1 (CH), 104.4 (C), 98.4 (CH), 93.4 (CH), 75.2 (CH_2), 20.1 (CH_3).

MS $(ESI)^+$: m/z [M + H] 445.1.

HRMS: [M] for $C_{26}H_{20}O_7$ calculated 444.1209, found 444.1204.

Previously reported.[127]

3.226. 2,3-Bis(4-methoxyphenyl)spiro[cyclopropane-1,9'-xanthen]-2-ene



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Cesium fluoride (0.46 g, 3 mmol) was put in a round-bottom flask which was heated for 2 h at 100 ºC and the round bottom flask was allowed to cool to rt under an inert N_2 atmosphere. After that, 2,3-bis(*p*-methoxyphenyl)cycloprop-2-en-1-one (0.09 g, 0.33 mmol), 2-trimethylsilyl)phenyl trifluoromethanesulfonate (0.25 g, 0.20 mL, 0.83 mmole) and acetonitrile (1.5 mL) were added in the round bottom flask under inert atmosphere which contained cesium fluoride and the resulting mixture was left to stir at rt for 24 h. Solvents were removed *in vacuo* and the crude product was purified by flash chromatography affording the title compound.

R_f 0.39 (ethyl acetate/petroleum ether = 1:1); white solid 0.05 g, 38 % yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 - 7.41 (4H, m, Ar), 7.04 - 6.96 (4H, m, Ar), 6.91 - 6.73 (8H, m, Ar), 3.72 (CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 154.4 (C), 138.2 (C), 131.4 (CH), 127.0 (C), 120.8 (C), 126.7 (CH), 124.8 (CH), 122.8 (CH), 115.8 (CH), 114.6 (CH), 55.3 (CH_3), 27.2 (C).

Consistent with previously reported data.[5j]

CHAPTER 4

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