The Synthesis, Attempted Synthesis and Applications of 1,2,4-Oxadiazoles and Isothiazolo-isoxazoles.

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This thesis is dedicated to my son, Edward.

Family is not just an important thing, it is everything.

- *Michael J. Fox.*

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I Acknowledgements

I would like to take this opportunity to express my gratitude and appreciation to those who have supported my years of doctoral and degree education, in both my academic and private lives.

Family & Friends

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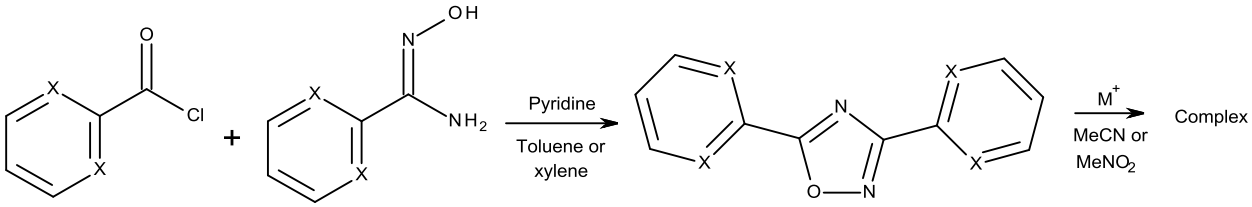
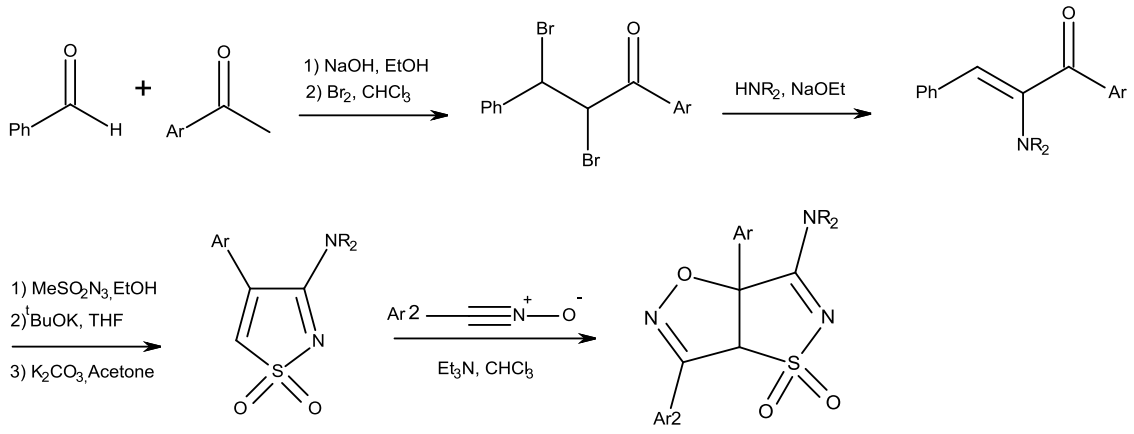
II Abstract

This thesis examines the 1,2,4-oxadiazole heterocyclic unit as a participating structural feature of new ligand systems in supramolecular chemistry. These ligand systems were synthesised by reaction of phenyl, pyridyl or pyrimidyl amidoximes with corresponding acid chlorides to furnish novel, multi-dentate ligand systems featuring at least one 1,2,4-oxadiazole unit. The ability of these heterocycles to form complexes with metal cations was investigated and several novel systems are reported.

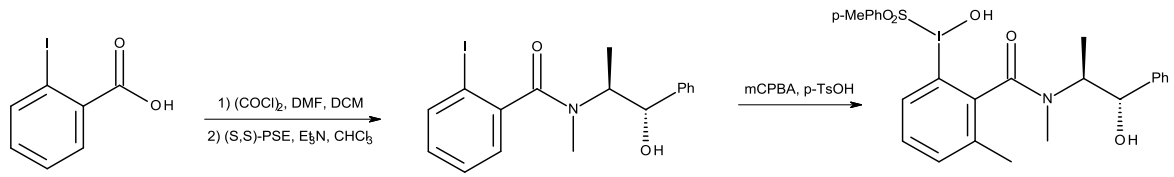


X = N or CH

The synthesis and biological activity of a range of isothiazolo-isoxazoles was also studied. Such compounds were prepared through an eight-step synthesis, the critical reaction involving a 1,3-dipolar cycloaddition of a nitrile oxide to an isothiazole-1,1-dioxide, which acted as an alkenic 1,3-dipolarophile rather than as an iminic 1,3-dipolarophile.



The synthesis of a range of catalytic, (S,S)-pseudoephedrine-containing hypervalent iodine systems is also described. The pre-catalytic iodine(I) systems were synthesised employing Schotten-Baumann conditions. The catalytic iodine(III) systems were achieved via in-situ mCPBA oxidation and the use of p-TsOH as a ligand-type additive. Attempts to produce 1,2,4-oxadiazole analogues of this system are also described in this thesis.



III Abbreviations

DCM	Dichloromethane	**ACN**	Acetonitrile
THF	Tetrahydrofuran	**DMSO**	Dimethylsulfoxide
PE	Petroleum ether	**EtOAc**	Ethyl Acetate
DMF	Dimethylformamide	**TEA**	Triethylamine
DCC	N,N'-Dicyclohexylcarbodiimide	**CDI**	1,1'-Carbonyldiimidazole
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide		
TBTU	(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate		
HBTU	(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate		
HOBt	Hydoxybenzotriazole	**DIPEA**	Diisopropylamine
TBAF	Tetrabutylammonium fluoride	**NCBT**	1-Chlorobenzotriazole
TFA	Trifluoroacetic acid	**mCPBA**	*meta*-Chlorobutylperoxybenzoic acid
mCBA	*meta*-Chlorobenzoic acid	**PIDA**	Phenyliodine diacetate
PIFA	Phenyliodosyl bis(trifluoroacetate)	**IBX**	2-Iodoxybenzoic acid
DMP	Dess-Martin periodinane	**HTIB**	Hydroxyl(tosyloxy)iodobenzene
TMSCN	Trimethylsilyl cyanide	**TBDPS**	*tert*-butyldiphenylsilyl
NHS	N-Hydroxysuccinimide	**NCS**	N-Chlorosuccinimide
DMAP	N,N-Dimethylaminopyridine	**HVI**	Hypervalent iodine
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide		
Me	Methyl	**Et**	Ethyl
Pr	Propyl	**iPr**	Isopropyl
Bu	Butyl	**^{t}Bu**	*tert*-butyl
Ph	Phenyl	**Ar**	Aryl
Ac	Acyl	**Bn**	Benzyl
Bz	Benzoyl	**PCB**	4-Chlorobenzyl
PNB	4-Nitrobenzyl	**Ts**	Toluenesulfonyl
Mes	Methanesulfonyl	**Tf**	Trifluoromethanesulfonic
Pyrr	Pyrrolidinyl	**Py**	Pyridyl
Bipy	Bipyridyl	**Boc**	*tert*-Butyloxycarbonyl
Cbz	Carbobenzyloxy	**NMR**	Nuclear Magnetic Resonance

s	Singlet	**d**	Doublet
dd	Doublet of doublets	**ddd**	Doublet of doublets of doublets
t	Triplet	**tt**	Triplet of triplets
q	Quartet	**qt**	Quintet
sxt	Sextet	**m**	Multiplet
b	Broad	**bs**	Broad singlet
bd	Broad doublet	**Appt**	Apparent
DEPT	Distortionless Enhancement through Polarization Transfer		
HMBC	Heteronuclear Multiple Bond Correlation	**HSQC**	Heteronuclear Single Quantum Coherance
nOe	Nuclear Overhauser Effect	**Hz**	Hertz
MHz	Megahertz	**J**	Coupling Constant
L	Ligand	**Cat**	Catalysts/Catalytic
RT	Room temperature	**b.p**	Boiling point
m.p	Melting point	**HPLC**	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry	**LCMS**	Liquid Chromatography Mass Spectrometry
GCMS	Gas Chromatography Mass Spectrometry	**TLC**	Thin Layer Chromatography
UV	**U**ltraviolet	**IR**	Infrared
XRD	X-Ray diffraction	**MW**	Molecular weight
g	Grams()	**mg**	Miligram(s)
L	Litre(s)	**dm**	Decimetre(s)
nm	Nanometres	**mL**	Mililitre(s)
hr	Hour(s)	**min**	Minute(s)
ppm	Parts per million	**conc**	Concentrated
eq	Equivalent(s)	**(g)**	Gas
(l)	Liquid	**(s)**	Solid
(aq)	Aqueous	**Nu**	Nucleophile
E	Electrophile	**e.e.**	Enantiomeric excess
IC_{50}	Half Maximal Inhibitory Concentration	**EC_{50}**	Half Maximal Effective Concentration
MCF-7	Michigan Cancer Foundation-7	**RPMI**	Roswell Park Memorial Institute Medium
lit	Literature		

1 Introduction

One of the key topics of this thesis is the 1,2,4-oxadiazole. The 1,2,4-oxadiazole is a versatile heterocycle and finds application across almost the entire spectrum of chemistry. This thesis explores these existing applications and attempts to build on them whilst investigating some new, very recent developments in the chemistry and application of the 1,2,4-oxadiazole. This project, like many, deviates from its path at several points with ventures through a broad range of organic chemistries, however the 1,2,4-oxadiazole always remains the heart of the matter and is the ultimate target of the all syntheses detailed.

This introduction details the background chemistry and science which form the foundations for this research project. The chapter is categorised into four subchapters. The first provides a general overview of the 1,2,4-oxadiazole unit, its synthesis and reactivity. This forms a basis for the next three subchapters, each of which considers new investigations into an existing application of the 1,2,4-oxadiazole.

The second of these subchapters introduces the 1,2,4-oxadiazole in supramolecular chemistry- a relatively unexplored area for this heterocycle.

The third subchapter focuses on introducing the 1,2,4-oxadiazoline as a key component in biologically active compounds popular amongst our research group.

The fourth and final subchapter introduces the chemistry of the 1,2,4-oxadiazole with direction towards the development of novel asymmetric catalysts.

1.1 The Chemistry of the 1,2,4-Oxadiazole Heterocyclic Unit

This sub-chapter of the introduction offers a general introduction to the chemistry of the 1,2,4-oxadiazole. This area has been reviewed several times and so only a brief summary is provided here.

Prior to the late 1960's, 1,2,4-oxadiazole research was not popular, with only a handful of articles published. Since the 1962 discovery and 1967 publication of the Boulton-Katritzky rearrangement[1,2,3] (introduced more thoroughly later in this chapter), research interest in 1,2,4-oxadizoles has grown considerably.

In recent decades, the 1,2,4-oxadiazole has found application across much of the chemical spectrum, from critical features of medicinal chemistry to new developments in materials and supramolecular chemistry, through to more peculiar uses such as the novel and insensitive high explosive shown below[4].

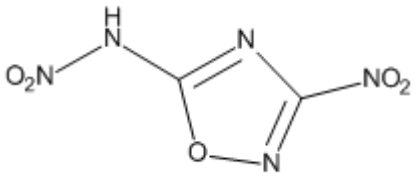


Figure 1.1 - High explosive 1,2,4-oxadiazole, synthesised by Chen and co-workers[4].

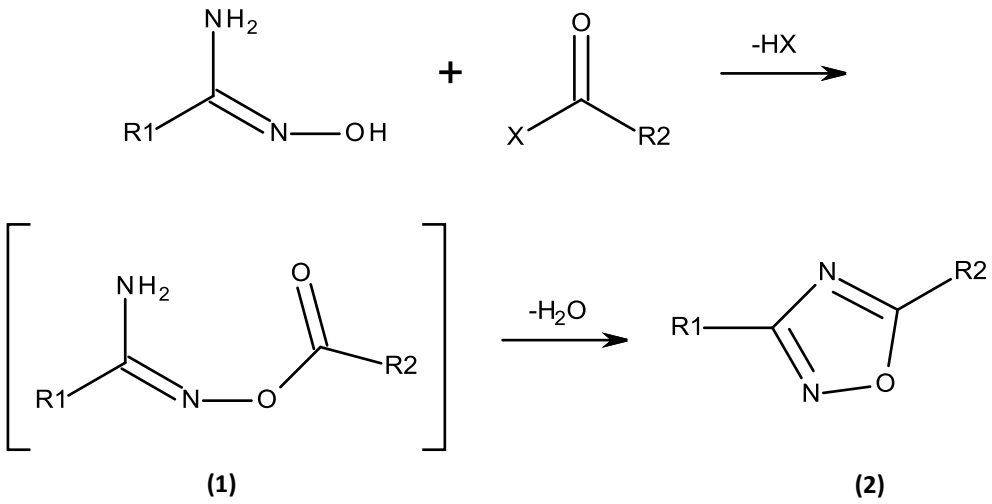
1.1.1 The Synthesis of 1,2,4-Oxadiazoles

The 1,2,4-oxadiazole was first synthesised by the German chemist, Johann Karl Wilhelm Ferdinand Tiemann (1848-1899) in collaboration with a second chemist, Paul Kruger, some 125 years ago[5]. Since the original synthesis of the 1,2,4-oxadiazole, many alternative syntheses have arisen. This section of this sub-chapter focuses only on the most common of these syntheses.

1.1.1.1 The Synthesis of 1,2,4-Oxadiazoles by Reaction of Amidoximes with Reactive Carboxylic Species

The most popular means of synthesising the 1,2,4-oxadiazole unit is through the reaction of an amidoxime with a reactive carboxylic unit[6]. Reaction commences with acylation of the amidoxime oxygen and subsequent loss of the carboxylic activating group or hydrogen halide, thus producing an intermediate *O*-acylamidoxime **(1)** (Scheme 1.1). This intermediate depending on substitution and stability can often be isolated if necessary, however one usually finds cyclodehydration to the

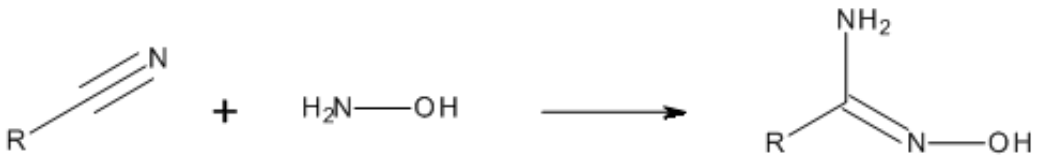
oxadiazole **(2)** a spontaneous process. If isolated, the intermediate can be cyclodehydrated under thermal conditions to the oxadiazole[7].



Scheme 1.1

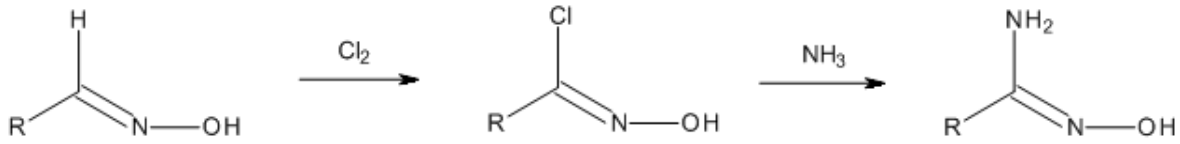
1.1.1.2 Sources of and Variations on the Amidoxime Component

Some compounds with amidoxime functionality are available commercially; however a wide variety of alkyl and aryl amidoximes can easily and inexpensively be achieved from nitriles through reaction with hydroxylamine (Scheme 1.2). This step can be performed in a wide range of organic solvents but is also achievable under aqueous conditions[6].



Scheme 1.1

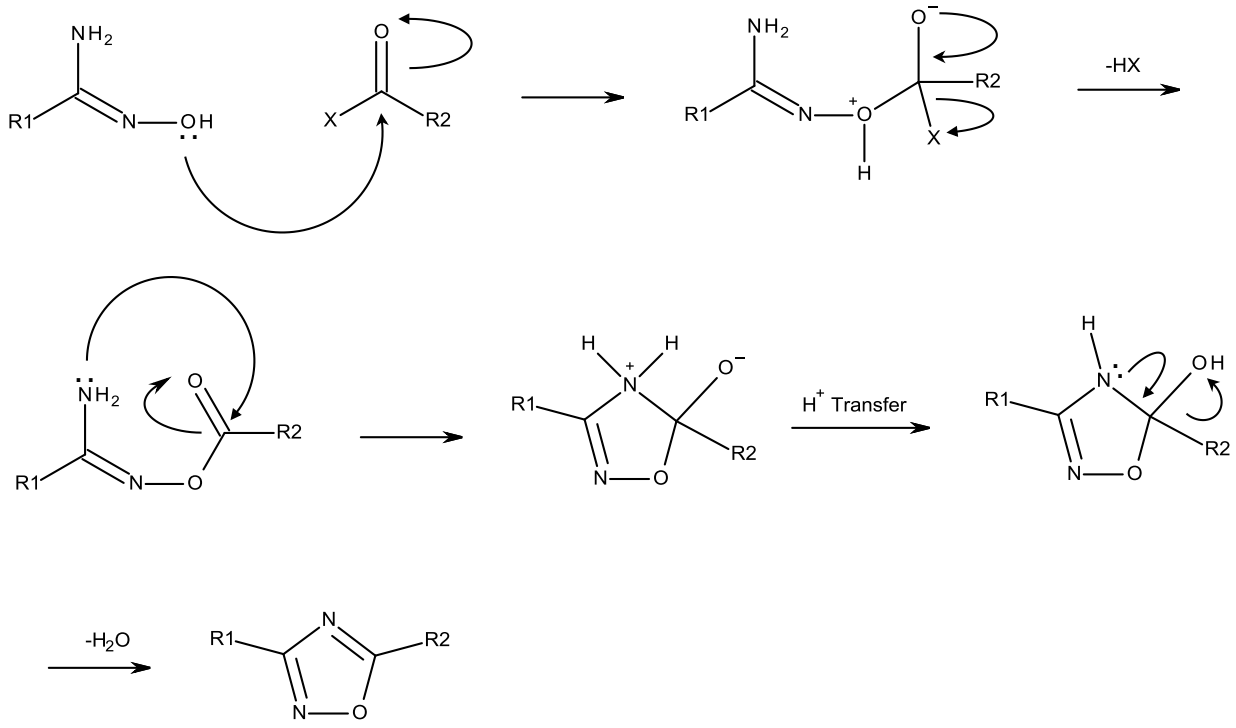
As an alternative, the prerequisite amidoxime can be obtained via reaction of imidoyl halides with ammonia (Scheme 1.3). The imidoyl halides are easily synthesised via chlorination of the corresponding oxime with chlorine gas or a source of cationic chlorine such as N-chlorosuccinimide[8].



Scheme 1.3

1.1.1.3 Sources of and Variations on the Carboxylic Component

Acid halides such as acid chlorides are popular and highly effective reagents in providing the necessary reactive carboxylic fragment for 1,2,4-oxadiazole formation[6]. Synthesis of 1,2,4-oxadiazoles by this means remains popular since the reaction is tolerant of a wide range both alkyl and aryl amidoximes and acid chlorides. The mechanism for the reaction between acid halide and amidoxime is shown below in Scheme 1.4.



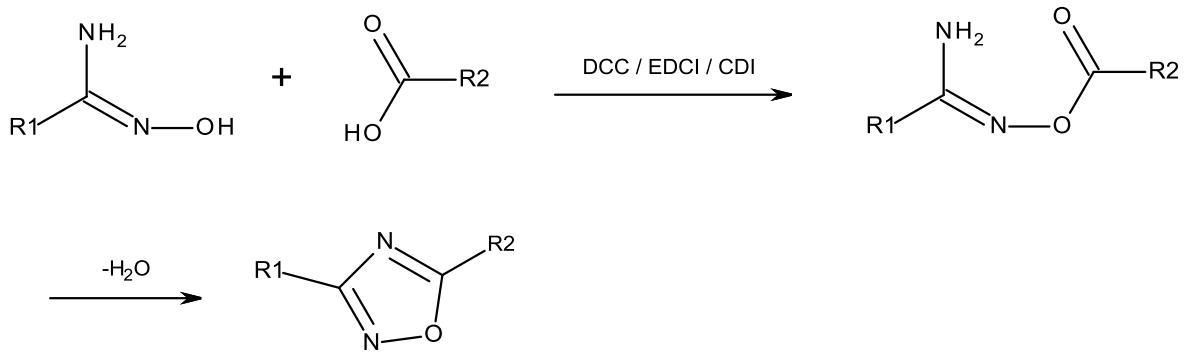
Scheme 1.4

The reaction mechanism proceeds initially with the coupling of acid chloride to amidoxime and with loss of HX followed by cyclodehydration to the 1,2,4-oxadiazole.

Usually, it is necessary to isolate the amidoxime prior to reaction with acid chloride in order to remove any aqueous impurities that would disrupt the coupling to the acid halide. However, the conversion of nitrile to amidoxime and then reaction with an acid chloride to 1,2,4-oxadiazole has been achieved as a one-pot synthesis with magnesia-supported sodium carbonate[9].

In cases where the acid chlorides are inconvenient or simply unavailable, several other alternatives are available- some long-known, some newly discovered.

The carboxylic fragment can also be provided by a variety of carboxylic acids, through use of common coupling agents such as N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1,1'-carbonyldiimidazole (CDI)[10,11] (Scheme 1.5). This is a convenient synthesis since many of these reactions involve mild conditions and are tolerant of a wide range of substituted alkyl and aryl carboxylic acids. Once coupled, a switch to a high boiling solvent is often necessary to promote cyclodehydration of the *O*-acylated intermediate.



Scheme 1.5

Uronium salts such as (1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in the presence of HOBt and DIPEA have also been shown to be strongly efficient coupling agents, particularly when faced with sterically challenging carboxylic acids[12]. They have also demonstrated rapid coupling kinetics and are soluble in polar organic solvents such as DMF[12]. Carboxylic acids have been shown to react with amidoximes under microwave conditions in DMF in the presence of HBTU (the hexafluorophosphate counterion derivative of TBTU) and DIPEA[13].

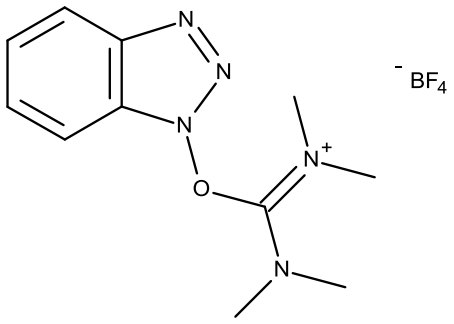
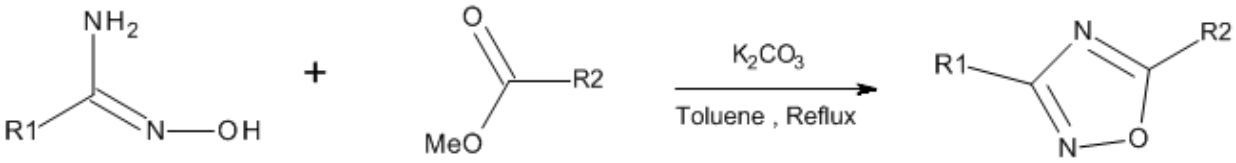


Figure 1.2 – Structure of TBTU.

Esters have also found some appreciable application in providing the carboxylic fragment necessary to react with the amidoxime in 1,2,4-oxadiazole synthesis[14,15]. In the past, the synthesis of the 1,2,4-oxadiazole unit via the ester functional group has suffered from low yields, the necessity for the

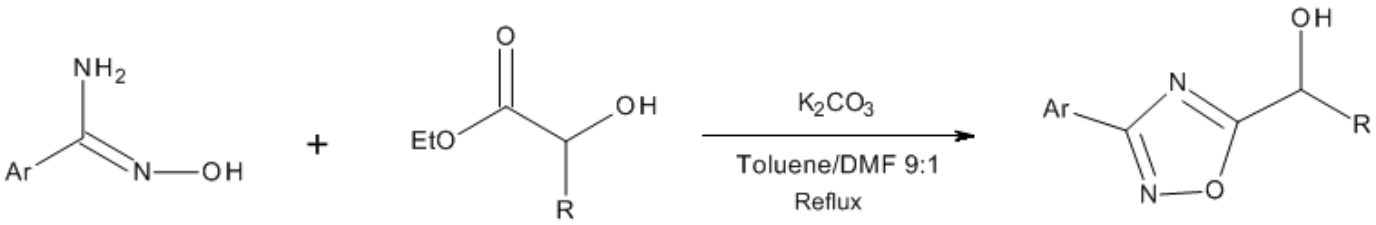
strong bases and harsh general conditions[15]. Recent research has shown that the ester can be a more practical and suitable source of the carboxylic fragment. Reactions involve moderate conditions, weak bases such as potassium carbonate and generally provide good yields (Scheme 1.6). However, this research used only relatively simple aryl esters and amidoximes[15].



R1 = CH_2Ph, 4-MePh, 4-MeOPh, *t*-Butylpropionate R2 = Me, 4-MePh

Scheme 1.6

Very recently, simple ethyl glycolates and ethyl lactates **(3)** have been demonstrated as effective substrates in the *O*-acylation of amidoximes, furnishing 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles in good yields (Scheme 1.7). This was achieved with potassium carbonate at reflux in a 9:1 toluene:dimethylformamide solvent[16].



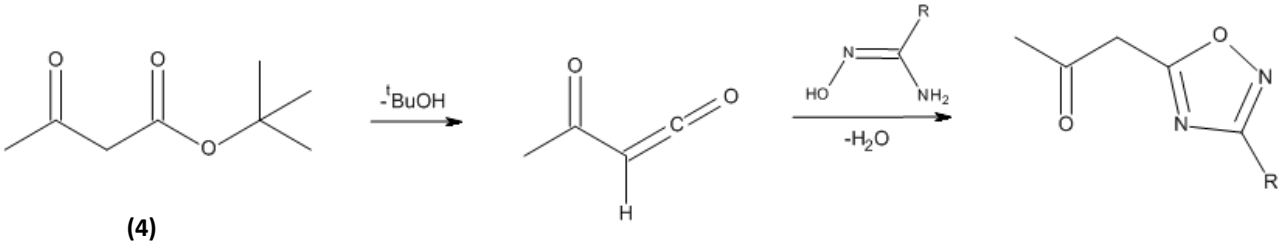
(3)

R = Me, H

Scheme 1.7

Extending from the reactive potential of the ester, it has been shown that β-keto esters are highly satisfactory sources of the carboxylic fragment in the synthesis of 1,2,4-oxadiazoles from reaction with amidoximes, demonstrating simple achievement of 3-substituted-5-β-keto-1,2,4-oxadiazoles. Substitution at the 3-position is highly variable via this method with good yields observed through a wide range of aryl and alkyl amidoximes[17]. The most satisfactory results are obtained through use of *tert*-butyl-β-keto esters **(4)**. The substituted β-keto ester, under thermal conditions, eliminates a molecule of alcohol- this elimination favouring the more hindered alcohols. This elimination yields an acyl ketene **(5)**, a reactive intermediate which subsequently acylates the amidoxime oxygen with

loss of a proton to promote conventional cyclodehydration and formation of the corresponding 1,2,4-oxadiazole[17] (Scheme 1.8).

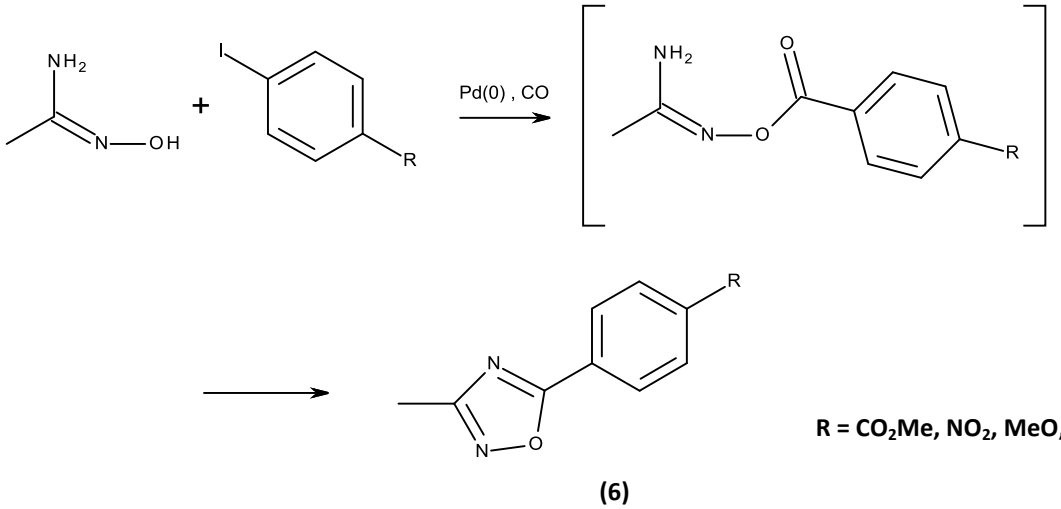


(4) **(5)**

R = ^{i}Pr, CO_2Et, Ph, CH_2OCH_2Ph, 4-FPh, 4-CO_2Ph, 4-CF_3, 3-pyridyl, 4-(CF_3)-3-pyridyl

Scheme 1.8

It has been demonstrated that *O*-acylation of the amidoxime can be achieved following a palladium catalysed coupling of the amidoxime with an aryl iodide in the presence of carbon monoxide. The reaction proceeds through an intermediate acyl-palladium complex which enables subsequent *O*-acylation of the amidoxime (Scheme 1.9). At present the coupling reaction generally applies to methylamidoximes only[18] giving 3-methyl-5-aryl-1,2,4-oxadiazoles **(6)**.

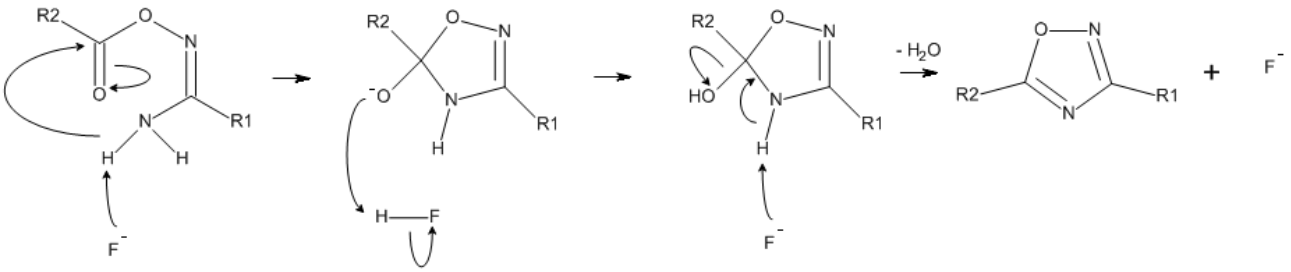


R = CO_2Me, NO_2, MeO, Br

(6)

Scheme 1.9

Recently, the cyclodehydration of *O*-acylated amidoximes has been improved with the catalytic use of TBAF[19]. Whilst in many cases cyclodehydration to the oxadiazole is spontaneous, this synthesis offers a mild alternative to the otherwise impractical high boiling solvent-switch and potentially time consuming reflux conditions. The catalytic role of fluoride is shown in Scheme 1.10 below[19]. This synthesis has been further developed to tolerate solvent free conditions[20].

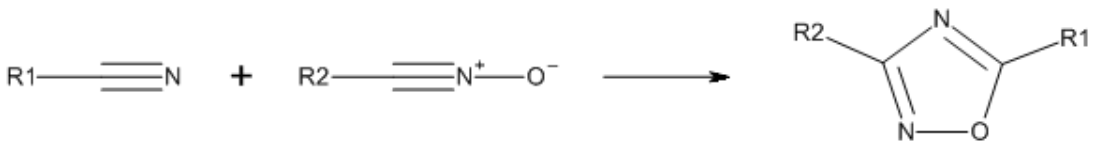


R1 = Ph, Me
R2 = Ph, Me

Scheme 1.10

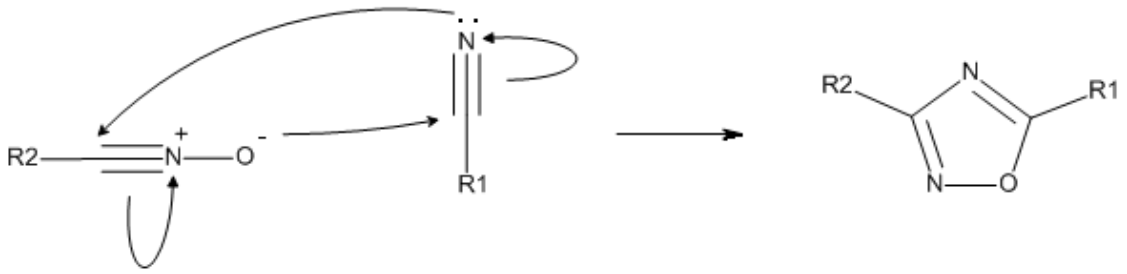
1.1.2 The Synthesis of 1,2,4-Oxadiazoles Through the Cycloaddition of Nitrile Oxides with Nitriles

The 1,3-dipolar cycloaddition reaction between (the 1,3-dipolar) nitrile oxides and (the dipolarophilic) nitriles is a well-established route to 1,2,4-oxadiazoles (Scheme 1.11) and is second in popularity only to the cyclisation of *O*-acylamidoximes described earlier[6,21,22].



Scheme 1.11

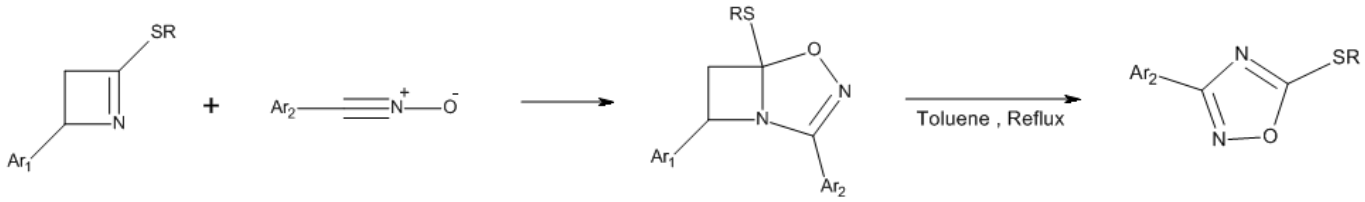
Nitrile oxides are a class of chemical species with a zwitterionic, propargyl-type structure. This nature gives them both nucleophilic and electrophilic properties, the reactive effects of which are demonstrated in the reaction mechanism below (Scheme 1.12).



Scheme 1.12 – Mechanism of the 1,3-dipolar cycloaddition reaction of nitrile oxides to nitriles.

The synthesis of 1,2,4-oxadiazoles via this route is popular due to the mild conditions and the wide range of synthetic options available for acquiring the precursors to the nitrile oxides.

In a recent piece of research, our group have demonstrated that the 1,3-dipolar cycloaddition of nitrile oxides with 4-aryl-1-azetines **(7)** generates oxadiazabicyclo[3.2.0]heptenes. These bicyclic compounds can then undergo a thermal [2+2] cycloreversion to yield 5-alkylthio-1,2,4-oxadiazoles[23] (Scheme 1.13), the 1-azetine therefore acting as a nitrile equivalent.

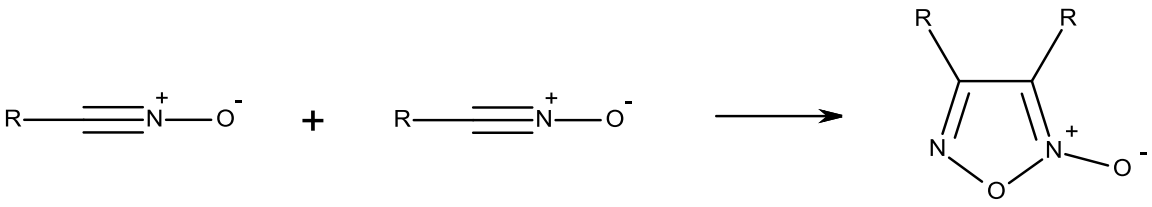


(7)

Scheme 1.13

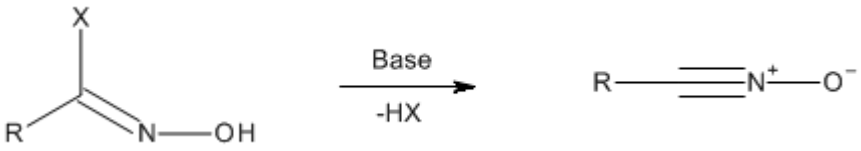
1.1.2.1 Sources of the Nitrile Oxide Component

Nitrile oxides readily dimerise (Scheme 1.14); a process which occurs should the nitrile oxide not hastily react by the desired means[24]. Some stabilised nitrile oxides have been synthesised and occasionally isolated, however, the vast majority are better handled as *in-situ* reactive intermediates.

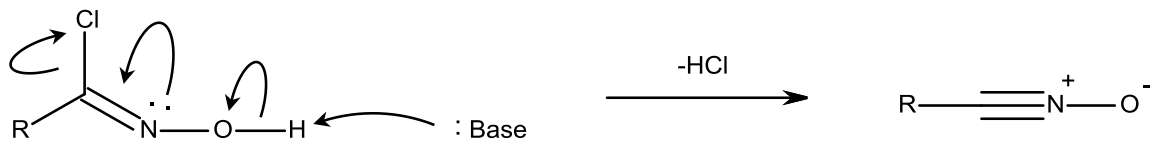


Scheme 1.14

The most common means of accessing nitrile oxides is via the base mediated dehydrohalogenation of imidoyl halides[6] (Schemes 1.15 and 1.16).

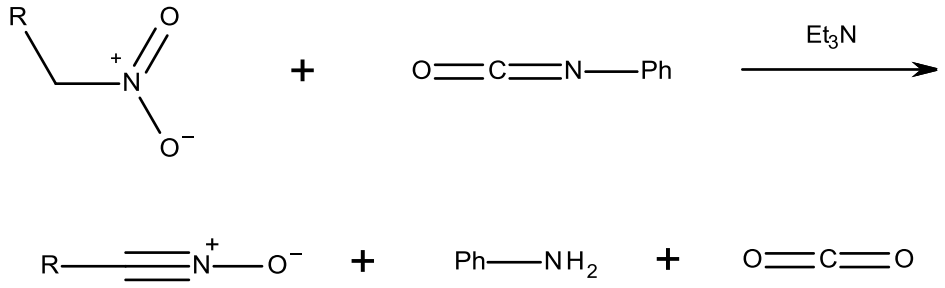


Scheme 1.15

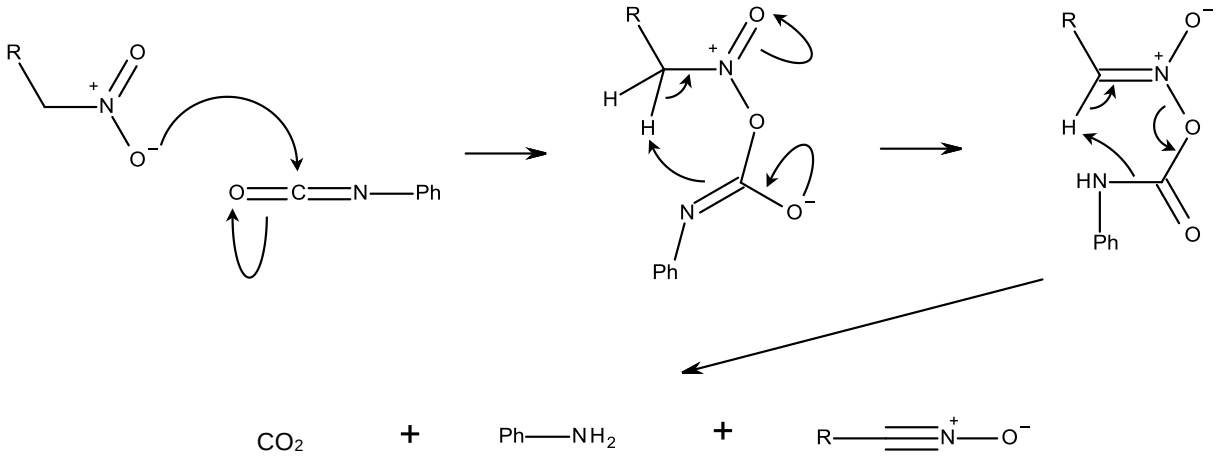


Scheme 1.16 - Mechanism of the base mediated synthesis of nitrile oxides from imidoyl halides (chloroximes).

Sourcing the nitrile oxide from imidoyl halide species is not without issue. Since the imidoyl halide is synthesised through treatment of the precursor oxime with electrophilic halide, some multi-functionalised substrates which may be sensitive to halogenation or oxidation may be produced, such as alkenes and the more electron rich arenes[25]. An alternative route to nitrile oxides is available through the Mukaiyama-Hoshino method (Scheme 1.17). This method involves reaction of a phenylisocyanate with a nitroalkane. The Mukaiyama-Hoshino method is widely used and tolerant of a wide range of conditions and reagents. The only limiting factor is the acquisition of potentially troublesome nitro precursors[26].



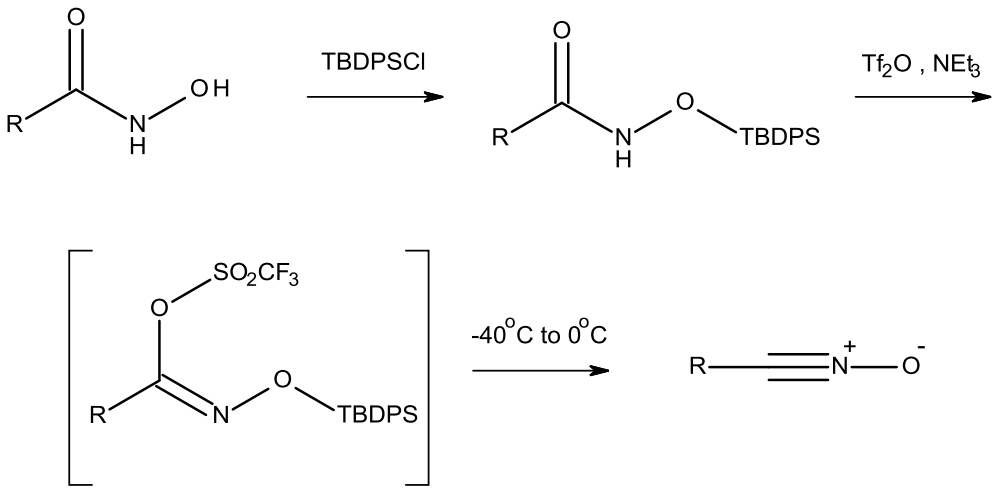
Scheme 1.17 – The Mukaiyama-Hoshino method.



Scheme 1.18 – Suggested mechanism of the Mukaiyama-Hoshino method of nitrile oxide synthesis.

The generally accepted mechanism shown in Scheme 1.18 suggests initiation of the reaction with nucleophilic attack at the isocyanate from the nitroalkane. The resulting intermediate then undergoes intramolecular transfer of H_2O, one atom at a time. The mechanism concludes with the expulsion of aniline and carbon dioxide and the synthesis of the desired nitrile oxide[6,26].

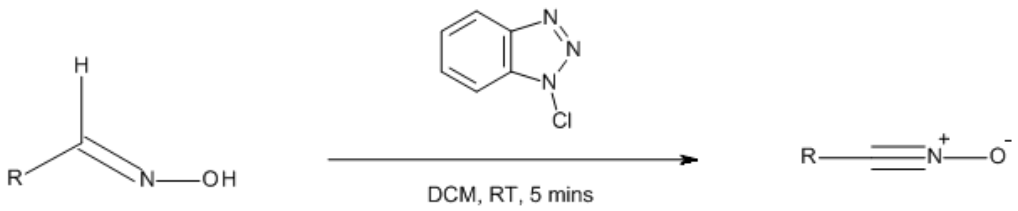
The nitrile oxide unit is also accessible via the dehydration of *O*-silylated hydroxamic acids. Prior to recent redevelopments, this route had previously been of poor comparative value, mainly due to the tendency for hydroxamic acids to suffer rearrangement to the isocyanate in conditions similar to those that promote dehydration. In a study by Carreira and co-workers, it has been demonstrated that *O*-silylated hydroxamic acids, following carbonyl activation by triflic anhydride and treatment with a deprotecting agent, can be converted to the corresponding nitrile oxide[25] (Scheme 1.19).



R = Ph, CH=CHPh, $(CH_2)_2$Ph

Scheme 1.19

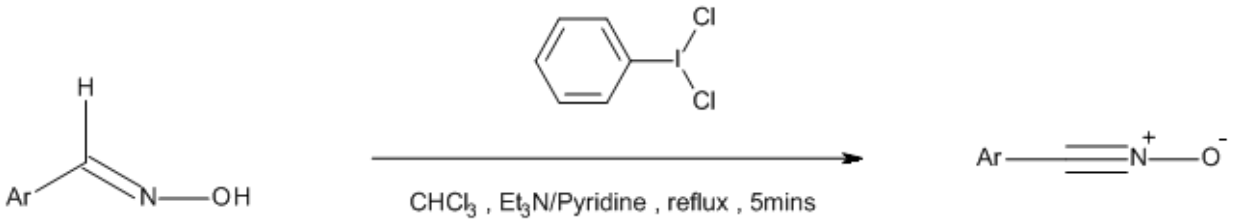
Further alternative routes to nitrile oxides are available. The conversion of a several halo- and methyl substituted aryl aldoximes to the corresponding nitrile oxide has been achieved[27] without the necessity for base via the treatment of the aldoxime with 1-chlorobenzotriazole (NCBT) which affords the nitrile oxide product in near quantitative yield at room temperature in minutes (Scheme 1.20). Whilst this reaction avoids the use of base, it was limited to a small range of aryl aldoximes only[27].



R = 2,6-Cl_2Ph, 2,4,6-Me_3Ph

Scheme 1.20

The hypervalent iodine(III) reagent iodobenzene dichloride has been reported as an effective reagent for the synthesis of nitrile oxides[28] (Scheme 1.21). The treatment of a range of methoxy- and vinyloxy- aryl aldoximes with iodobenzene dichloride in the presence of triethylamine or pyridine in chloroform yields the corresponding nitrile oxide in strong yields[28].



Ar = Ph, 4-MeOPh, 3,4,5-$(MeO)_3$Ph, 2-OCH_2CH=CH

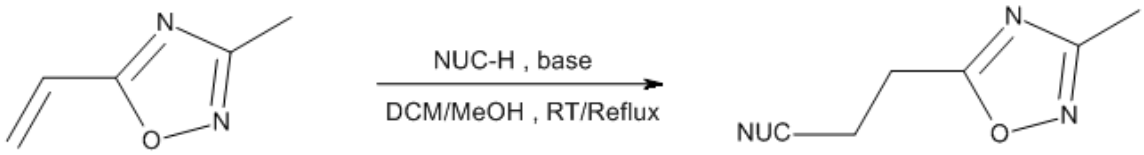
Scheme 1.21

1.1.3 The Reactivity of 1,2,4-Oxadiazoles

The 1,2,4-oxadiazole unit, relatively speaking, is highly stable and is thus a largely inert heterocycle. Whilst functional group manipulations of the oxadiazole unit are possible, these will not be considered in this thesis due to their standard nature. Instead this introduction will specifically focus on more interesting and unique reactions of the 1,2,4-oxadiazole unit.

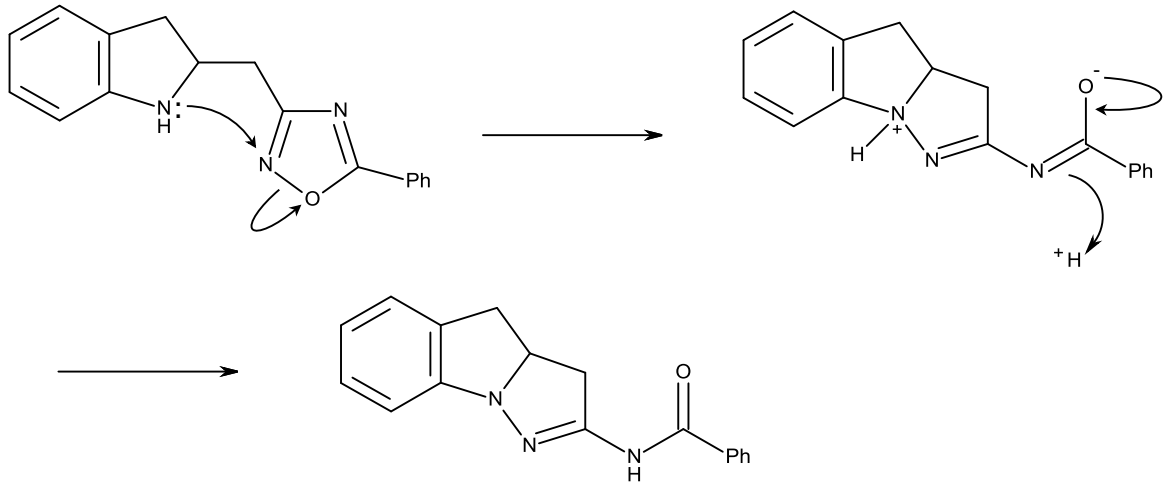
The 1,2,4-oxadiazole is almost completely inert towards attack from electrophiles. Nucleophilic displacement at the 3-position is also very uncommon. However, the nucleophilic displacement of suitable leaving groups at the 5-position is a commonly observed method of functionalisation in 1,2,4-oxadiazoles. For example, it is well known that trichloromethyl groups can be displaced by oxygen and nitrogen nucleophiles at the 5-position[29].

Some 5-vinyl-1,2,4-oxadiazoles have been demonstrated to be very good Michael acceptors. Reaction of these derivatives with a good range of nucleophiles including primary and secondary amines, thiols and alcohols in the presence of a range of bases generates Michael addition products in strong yields[30] (Scheme 1.22).



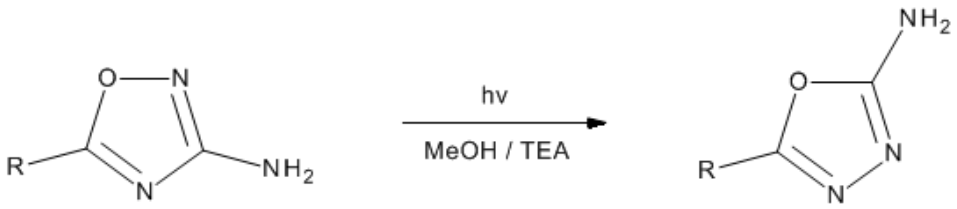
Scheme 1.22

One of the most well-known reactions of the 1,2,4-oxadiazole is the monocyclic rearrangement reaction of certain 5-membered heterocycles into other 5-membered heterocycles. This can occur via treatment with acid or base or under photoirradiative conditions[1]. This reaction is known commonly as the Boulton-Katritzky Rearrangement[2]. The reaction is observed with a wide range of 5-membered heterocycles, however it is typically applied to isoxazoles and 1,2,4-oxadiazoles[31]. The mechanism for this popular reaction, applied to an example 1,2,4-oxadiazole is shown[32].



Scheme 1.23 – Example Boulton-Katritzky Rearrangement.

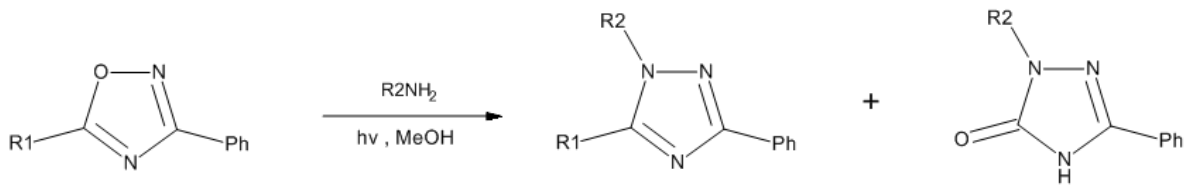
Other rearrangement reactions of 1,2,4-oxadiazoles are possible under photoinduction. Vivona and co-workers have demonstrated the photo-rearrangement of certain 5-alkyl-3-amino-1,2,4-oxadiazoles into the isomeric 1,3,4-oxadiazoles[33] (Scheme 1.24).



R = C_6H_{17}, $C_{11}H_{23}$

Scheme 1.24

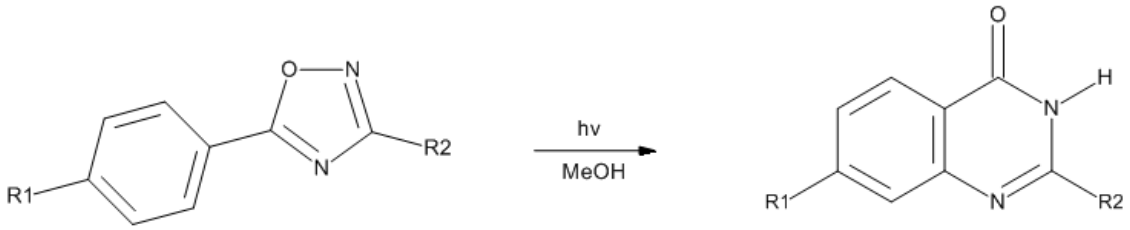
Further exploration of this work has seen the photo-rearrangement of 3-phenyl-1,2,4-oxadiazoles into 1,2,4-triazoles, indazoles and benzimidazoles through treatment with nitrogen nucleophiles[34] (Scheme 1.25).



R1 = NH_2, NHMe, NMe_2
R2 = H, Me, Pr, Bu, NH_2

Scheme 1.25

This research has subsequently led to the synthesis of 1,2,4-thiadiazoles when 3-phenyl-5-amino-1,2,4-oxadiazoles were treated with various sulfur nucleophiles[35]. Extending this work further, Vivona has shown that a range of 5-aryl-1,2,4-oxadiazoles **(22)** can rearrange under similar conditions to form quinazolin-4-ones[36] **(23)** (Scheme 1.26).

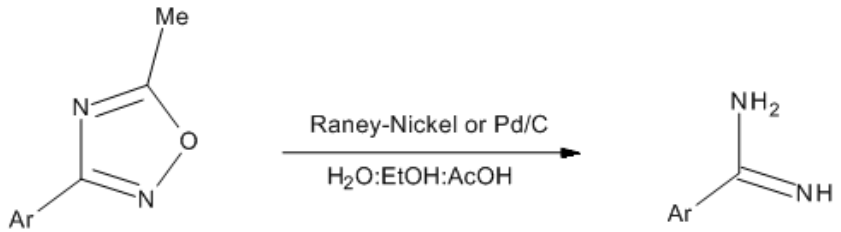


(22) **(23)**

Scheme 1.26

R1 = H, Me, CN, Cl
R2 = MeO, Ph

During the synthesis of Conotoxin MVIIA, the venom from the cone shell, the hydrogenation of a 3-aryl-5-methyl-1,2,4-oxadiazole over Raney Nickel catalyst in an ethanol/acetic acid/water solvent mix was shown to generate amidines in good yields (78%)[37] (Scheme 1.27).



Scheme 1.27

Additionally, in a synthesis of some new antithrombotics, hydrogenation of 3-methyl-5-aryl-1,2,4-oxadiazoles to the corresponding amidoxime has been shown to proceed effectively with catalytic palladium on carbon[38]. The ring-opening hydrogenation of such substituted 1,2,4-oxadiazoles is an interesting reaction and was observed experimentally during this project and is discussed further in section 3.3.2.2. It has also been observed that other standard reducing agents such as lithium aluminium hydride in THF can ring-open the heterocycle to the produce N-substituted amidoximes[39].

1.2 The Supramolecular Chemistry of Ligand Systems Featuring the 1,2,4-Oxadiazole Unit

This subchapter introduces the fundamentals that inspired an investigation into the 1,2,4-oxadiazole unit as a key feature of ligand systems and its subsequent significance in potential supramolecular structures that may form. A brief introduction to relevant research of supramolecular chemistry follows.

1.2.1 Defining Supramolecular Chemistry

Modern supramolecular chemistry, is truly a multidisciplinary field[40,41]. The versatility and growth of supramolecular chemistry was exemplified in 1987 with the award of the Nobel Prize for Chemistry to Cram, Lehn and Pederson for their early and pioneering work in this field[42].

A supermolecule can be defined as a multi-molecular chemical species in which the individual molecules are held together by non-covalent forces. These non-covalent bonding interactions, predictably, are significantly weaker than covalent bonds, can be of different types and often provide significant stability to the supramolecular structure. The major types of such bonding are discussed below.

1.2.2.1 Hydrogen Bonding

With an approximate strength of 4-30 $KJmol^{-1}$, the hydrogen bond may be regarded amongst the stronger non-covalent interactions. Natural supramolecular systems commonly feature the hydrogen bond due to this strength along with the high levels of directionality the interaction offers. The hydrogen bond is often regarded as the most important non-covalent interaction of all[57].

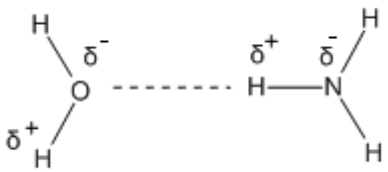


Figure 1.3 – Popular illustration of Hydrogen Bonding.

1.2.2.2 Electrostatic Interactions

Electrostatic interactions encompass interactions between two ions, or between two molecules with dipole moments, or, between an ion and a molecule with a dipole moment. An ion-ion interaction is the strongest electrostatic interaction, with an approximate strength between 200-300 $KJmol^{-1}$[1,40]. The interaction between two ions is non-directional. An example of this is the stabilising interaction between a halide anion and an ammonium cation.

The interaction between an ion and a dipole on the other hand, does require some directionality and orientation. In order to sufficiently stabilise the complex, the interaction will only occur if both substrates are in the correct geometry. This is demonstrated in the example below (Figure 1.4), which shows a potassium ion interacting with the electronegative nitrogen and oxygen atoms of the polyetherial macrocycle in which it sits[43,44].

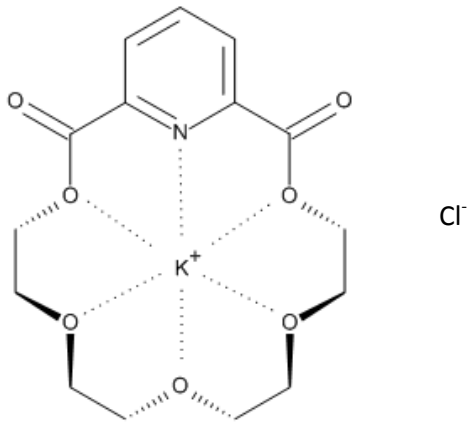


Figure 1.4

1.2.2.3 π-Interactions

Interactions involving π-bonding electrons are also commonly observed in supramolecular chemistry. There are two distinct, π-interactions observed in supramolecular chemistry that involve π-electron systems. These are cation-π interactions and π-π interactions. Interactions between cations and π-electrons are often observed in organometallic chemistry, for example the interactions between π-electrons of two cyclopentadiene rings and an iron centre as observed in ferrocene[45] (Figure 1.5).

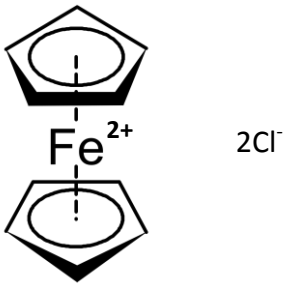


Figure 1.5

Non-covalent interactions between two π-electron systems are encountered often throughout supramolecular chemistry largely due to the abundance of aromatic rings in many ligand systems. Two types of π-π interaction are encountered (Figure 1.6). *Face-to-face* π-π interactions are those in which π-ring systems orientate in a parallel, offset fashion. These interactions are between the corner of one π-ring system and the centre of the other. In addition to this orientation, there exists the *edge-to-face* setup, whereby one of the hydrogen atoms of one ring forms a perpendicular interaction with the second ring[45].

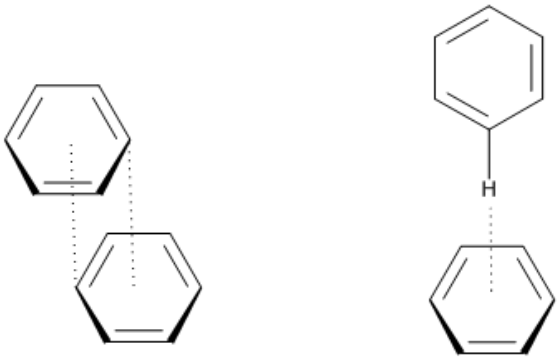


Figure 1.6 - Face to face *(left)* and edge to face *(right)* π-π interactions.

π-π Interactions result from the unique, conjugated attraction between the π-electron cloud of one ring system and the σ-framework of the second ring system, which are negatively charged and positively charged, respectively[45-48].

1.2.2.4 Van der Waals Interactions

Van der Waals interactions are the weakest of all non-covalent interactions with approximate strength of less than 5 $KJmol^{-1}$. Van der Waals interactions are attractive forces which occur between atoms which have experienced, at a given moment, a minute fluctuation in the transient location of their electron clouds. The instantaneous, uneven distribution of electrons about a nucleus creates a minor dipole which has the power to induce a momentary dipole on a neighbouring atom[45].

1.2.2.5 Hydrophobic Effects

The hydrophobic effect describes the expulsion of hydrophobic molecules from aqueous solution. Polar molecules form an interaction more readily with other polar molecules than they do with non-polar molecules. Likewise non-polar molecules interact more favourably with other non-polar molecules. This process is energetically favourable. The hydrophobic effect is observed commonly in supramolecular assemblies within living systems.

1.2.3 The Common and Major Themes within Supramolecular Chemistry

Supramolecular chemistry has become an all-encompassing field. However, one can attempt to categorise supramolecular chemistry and subsequent structures into two separate fields; host-guest chemistry and self-assembly.

1.2.3.1 Host-Guest Chemistry

Host-guest chemistry describes the formation of a supramolecular complex by the specific association of two molecules of suitable size and shape. The interaction is signified by one of the two molecules, usually the largest, acting as the *host*. This host molecule is able to encompass and effectively wrap around a second molecule of suitably smaller size and complementary shape. An excellent definition of the host and the guest was offered by Cram[45]:

The host is defined as an organic molecule or ion whose binding sites converge in the complex..... The guest component is any molecule or ion whose binding sites diverge in the complex[45].

1.2.3.2 Self-Assembly

Self-assembled systems can form by utilising any number of the non-covalent interactions described earlier. The supramolecular products of self-assembly are always the most thermodynamically stable products. In terms of enthalpy, the process is highly favourable, due to the high stability of the self-assembled systems. However, the formation of self-assembled species does not proceed via an entropically favourable pathway due to the creation of an ordered, uniform system from disordered components. Self-assembly is therefore a seemingly reverse-entropy process. However, it is argued that the displacement of solvent molecules via hydrophobic interactions from the binding sites of dissembled ligand strands compensates for the entropic disfavourability of the assembly process[45].

1.2.3.3 Metallosupramolecular Chemistry

The use of metal ions in devising potential self-assembling systems is a popular tactic in supramolecular chemistry. The term metallosupramolecular chemistry is now reserved for this study. The use of metal ions in supramolecular chemistry is popular since metal ions, particularly those of the *d*-block, have strict coordination parameters. This offers the opportunity to postulate some structures based on these strict coordinations.

1.2.4 Common Structural Descriptions of Metallosupramolecular Systems

Amongst the most popular metallosupramolecular themes are racks, ladders, grids and helicates. These are only considered *themes,* since many self-assembled systems adopt structures that feature some overlap between these structural descriptives.

1.2.4.1 Racks

Racks consist of a single polytopic ligand strand, coordinated by metal ions at multiple ligand binding sites. The metal ions form the junction or *joints* of the rack. Further coordination of this metal ion to another ligand forms the 'spoke' or 'shelf' of the rack[62]. An example of a rack-type metallosupramolecular system is shown below, which was synthesised by Lehn and co-workers in 1995[48]. This example has ruthenium(II) ions as the joints of the rack with the terpyridine units forming the spokes.

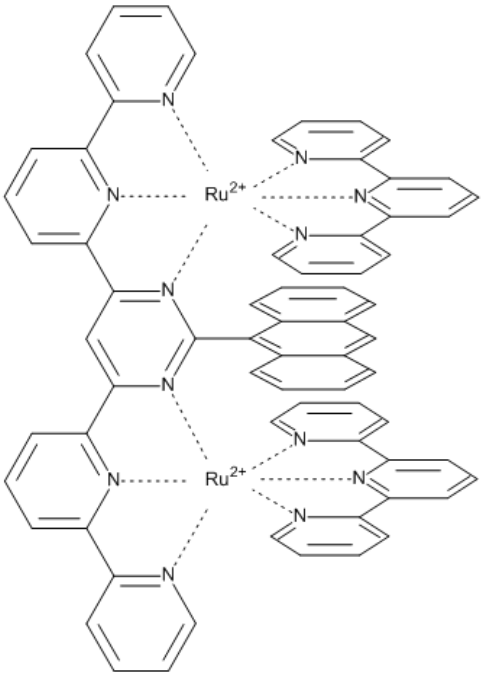


Figure 1.7 – Simple *Rack* System.

1.2.4.2 Ladders

Ladder-type supramolecular structures are closely related to racks; however, ladders incorporate a second polytopic ligand strand roughly parallel to the other. The polytopic ligands are linked by a further ligand which is bound to the parallel chains by metal ions. These central ligands and metal ions form the rungs of the ladder[45].

In the below 2-runged and 3-runged systems, reported by Lehn in 1996, the 2,2'-bipyrdine chains form the vertical supports for the ladder with the bipyrimidine units forming the rungs. These are held together by the 4-coordinate copper(I) ions which act as the joints[49].

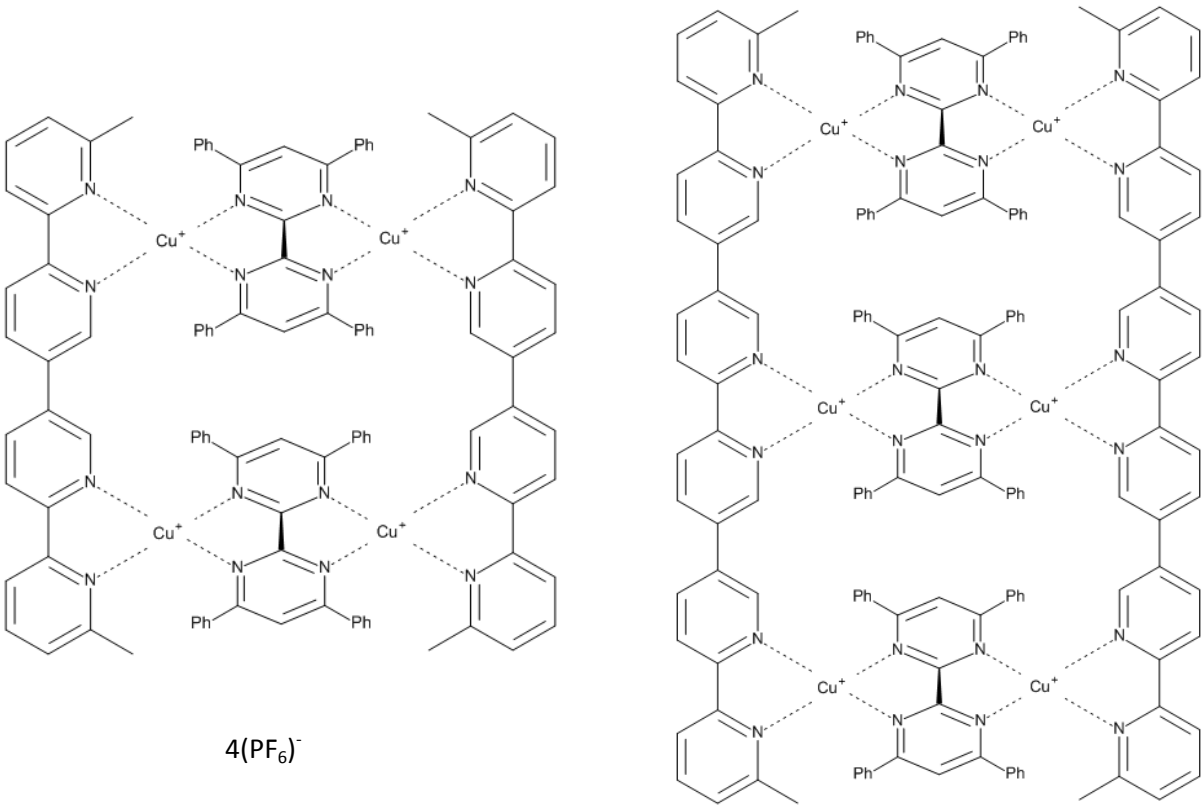


Figure 1.8 – Two-runged *(left)* and three-runged *(right) ladder* systems.

1.2.4.3 Grids

Grids are observed when polytopic ligand strands coordinate to metal ions in such a manner that orthogonal, linear assemblies are produced. For example, grids can exist as square grids, which are observed when 4-coordinate metal ion such as Cu^{2+} bind to certain polytopic ligands with linear binding sites.

The polymeric square grid below (Figure 1.9), reported by Fujita and co-workers in 2004, comprises 4,4'-bipyridine units coordinated by Cd^{2+} ions in square planar geometry[50].

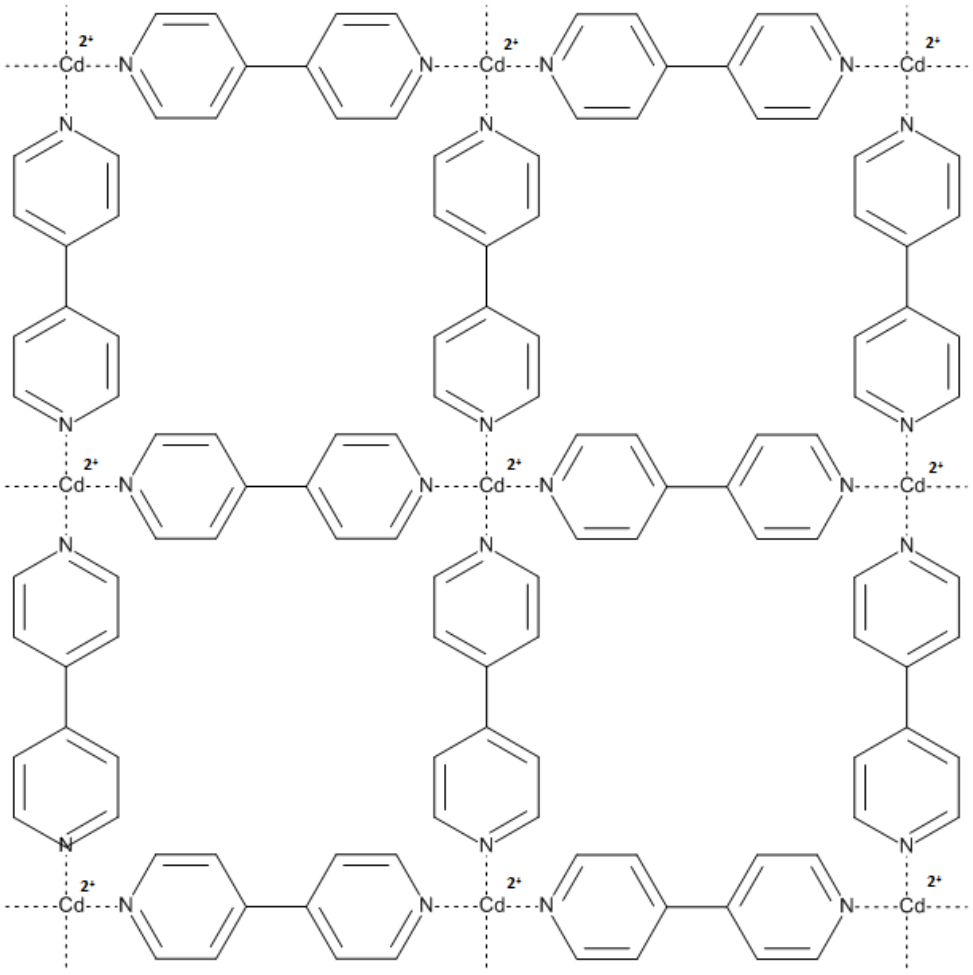


Figure 1.9 – Example *grid* system.

1.2.4.4 Helicates

The helicates are a form of metallosupramolecular structure that have adopted helical character in their geometry. This helical nature is observed as multidentate ligand strands wrap around metal ions, forming an effect similar to that of a thread of a screw[45]. Classifying and defining helicates is challenging since helicating supramolecular structures are can be extremely varied in their nature. Current helicate nomenclature enables one to formulate only an approximate image of a supramolecular complex. The nuclearity of a helicate describes the number of metal ion centres within the structure. A mononuclear structure contains one metal centre, a *dinuclear* structure contains two, *trinuclear* structures contain three etc. Two ligand strands (or threads) are described as *double* helicates and three ligand strands as *triple* helicates etc. and those that form an eventual loop are described as *cyclic* or *circular* helicates[45,51]. Some helicate structures contain ligand strands of differing composition. Helicates containing consistent ligand strands are termed *homostranded* helicates whereas those containing more than one different ligand strand are termed *heterostranded* helicates[51].

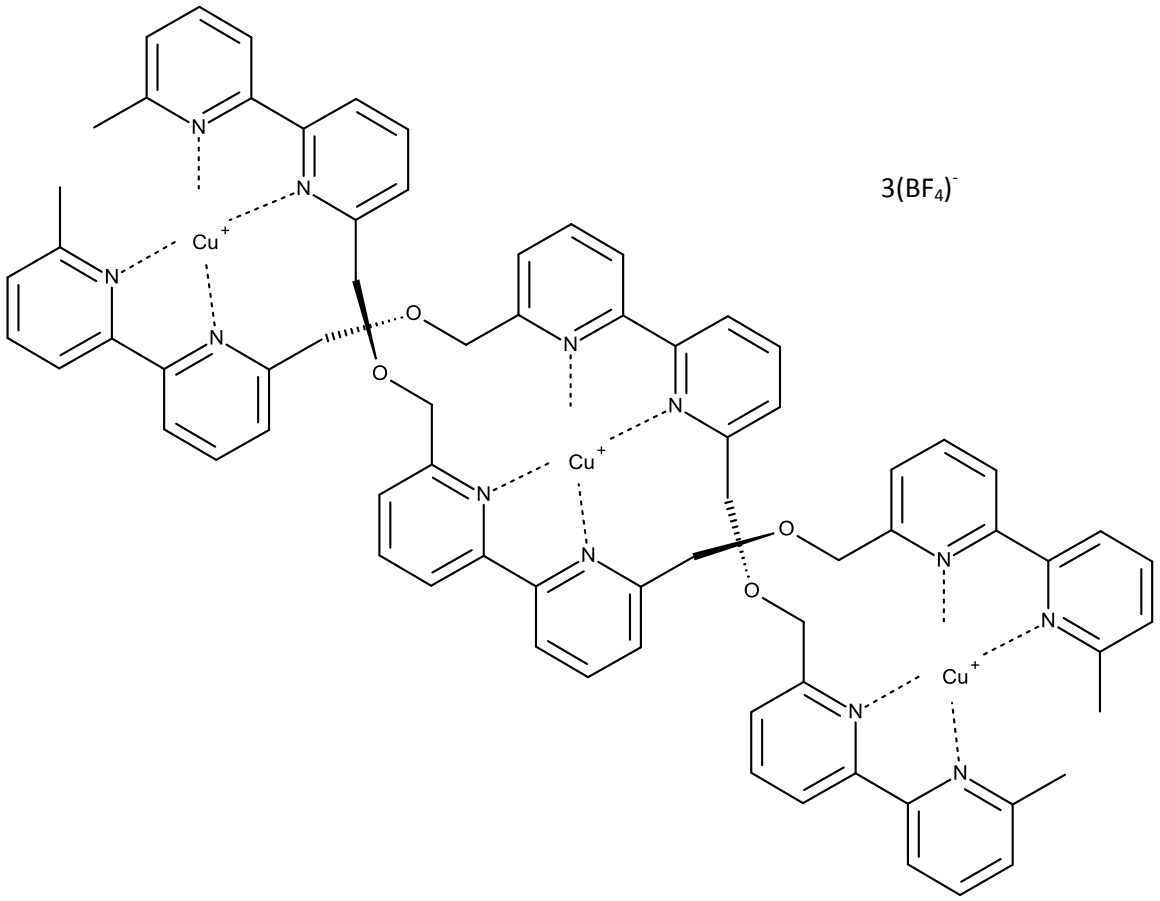


Figure 1.10 – Example *helicate* structure, synthesised by Lehn[52].

The example in Figure 1.10 first reported by Lehn in 1993, demonstrates the helicating effect of the ligand strands, spiralling down as they do in a screw-thread like manner[52]. In this example the copper(I) ions coordinate in a square planar geometry. The helicating effect is not observed around the metal ions due to this geometry; the effect is entirely observed in the ligands strands at non-coordinating sites.

1.2.5 Recent Advances in Supramolecular Chemistry Featuring the 1,2,4-Oxadiazole Unit

The 1,2,4-oxadiazole is virtually unknown in supramolecular chemistry. There have been a handful of articles reported that describe the 1,2,4-oxadiazole as a coordination unit with metal ions. This is highly surprising, since as a highly nitrogenous heterocyclic unit, the 1,2,4-oxadiazole at a glance offers great potential in metallosupramolecular chemistry.

The 1,2,4-oxadiazole offers three potential binding sites. The research into metal ion coordination at these sites is described herein.

1.2.5.1 Coordination via the Imine, N4 Atom

This site is the strongest candidate for metal ion coordination. This is due to the marginal, but significantly higher basicity of this nitrogen atom over the oxime N2 nitrogen atom[54]. Very few examples of 1,2,4-oxadiazoles acting as coordinating units in ligands, exist in the literature. However, of the very few examples that do exist, the vast majority demonstrate coordination through this N4 imine site.

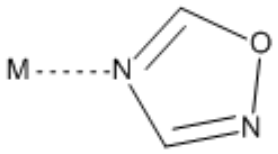
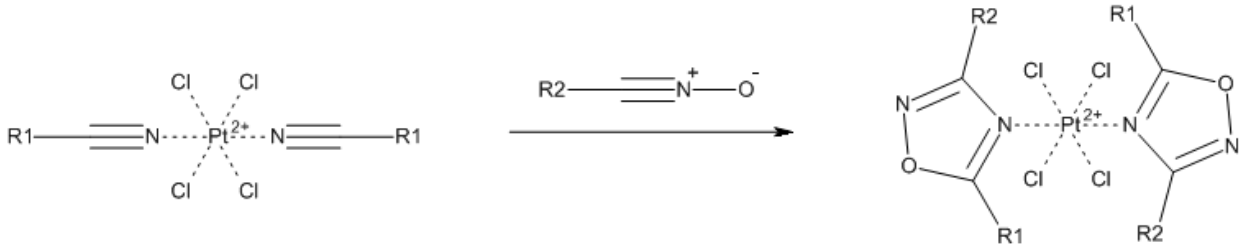


Figure 1.11 – 1,2,4-Oxadiazole coordination through N4.

Reported in 2003 and 2005, Bokach and co-workers synthesised two mononuclear, 1,2,4-oxadiazole structures, one featuring a platinum(IV) and the other a platinum(II) centre[55,56] (Scheme 1.28). These

complexes were not resultant from metallosupramolecular self-assembly however since both complexes were synthesised by 1,3-dipolar cycloaddition of a nitrile oxide with a pre-obtained platinum-nitrile complex.

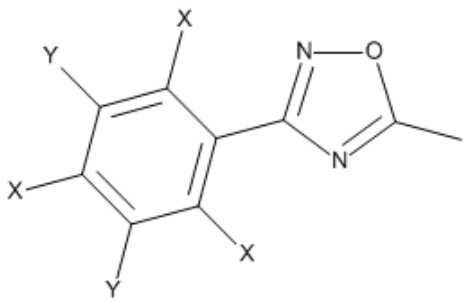


R1 = Me, Et, CH_2Ph

R2 = 2,4,6-Me_3Ph, 2,4,6-$(MeO)_3Ph$

Scheme 1.28

The first 1,2,4-oxadiazole complex was reported in 1985[57]. Massacesi and co-workers synthesised a number of very simple 3-aryl-5-methyl-1,2,4-oxadiazoles and synthesised some simple complexes with metal ions[57]. Notably however, the group did not examine any 3-heteroaryl-1,2,4-oxadiazole systems, nor were any crystal structures of their materials published.



A: X = MeO, Y = H
B: X = Me, Y = Cl
C: X = Me, Y = H

Figure 1.12 – Massecesi's simple 1985 1,2,4-oxadiazole ligand.

Massacesi and co-workers determined, largely through I.R spectroscopy, that ligand A formed simple mononuclear *cis* square planar complexes with a range of divalent metal ions, with coordination

presumably through the methoxy oxygen[57]. Whilst ligands B and C also formed simple complexes, the lack of crystal data limits definitive information regarding specific coordination modes.

In 1999, Goodwin and co-workers synthesised a tridentate 3-(2,2'-biyridine)-5-methyl-1,2,4-oxadiazole system and investigated its supramolecular potential. It was found that the ligand formed a simple, attractive and interesting mononuclear grid-type system with Fe^{2+} ions. Coordination about the 1,2,4-oxadiazole was observed solely through the N4 nitrogen atom[58]. To this day, it appears that this remains the only example of the 1,2,4-oxadiazole unit acting as part of a successful tridentate binding domain.

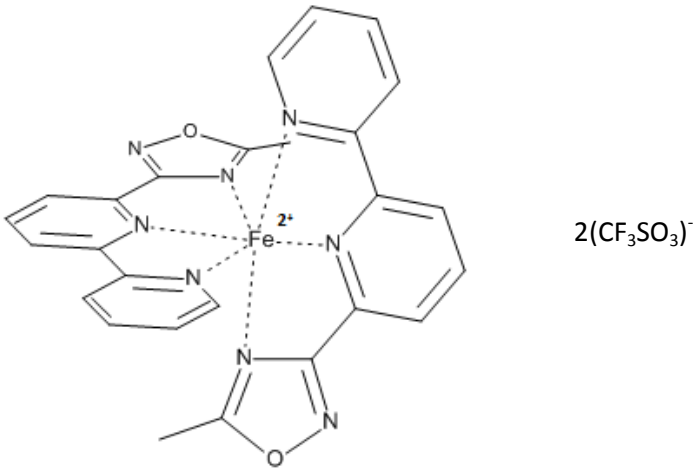


Figure 1.13 – Goodwin's 1999 1,2,4-oxadiazole complex[58].

Brinn and co-workers were also amongst the first to demonstrate that the 1,2,4-oxadiazole unit is capable of acting as an effective binding site in more conventional ligand systems and showed that 3-phenyl-5-(2-oxyphenyl)-1,2,4-oxadiazole was able to coordinate to Cu^{2+} ions to form a simple mononuclear complexes. The 1,2,4-oxadiazole coordinates to Cu^{2+} through only the imine N4 atom along with the phenolic oxygen atom which yielded two isomeric complexes[59], an interesting result in its own right, since oxygen atoms acting as donor atoms in coordination chemistry is rarely seen with transition metals[60].

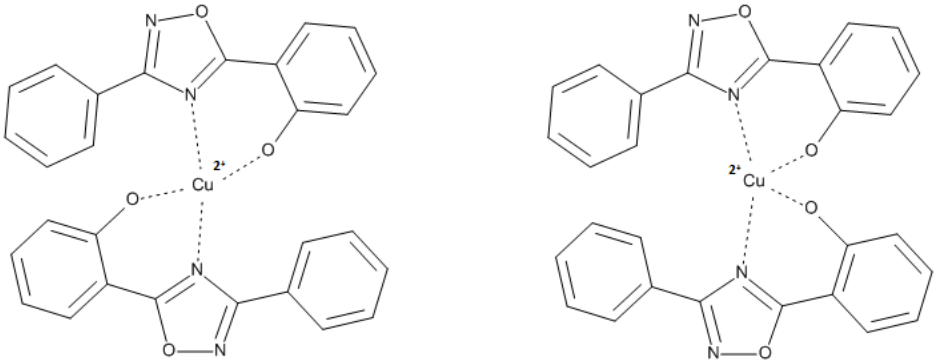


Figure 1.14 – Brinn's isomeric 1,2,4-oxadiazole complexes[59].

In 2007, Steel and co-workers published the coordination chemistry and complexes of a simple bis-oxadiazole ligand[53]. This work offered a greater insight into the coordination chemistry of the 1,2,4-oxadiazole unit. Steel's research group descrbed their ligand in their 2007 publication as *'a curiously ignored ligand*[53]*.*

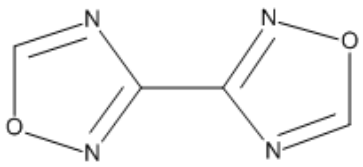


Figure 1.15 – Steel's 2007 bis-oxadiazole ligand.

Due to bond rotation about the 3,3'-linking positions of the oxadiazole units, a total of five coordination modes were potentially offered by this simple ligand leading to three possible mononuclear species and two possible dinuclear species. Steel reported that reaction of the bis-oxadiazole with Li_2PdCl_4 produced a simple mononuclear complex through only one specific binding mode, shown below in Figure 1.16.

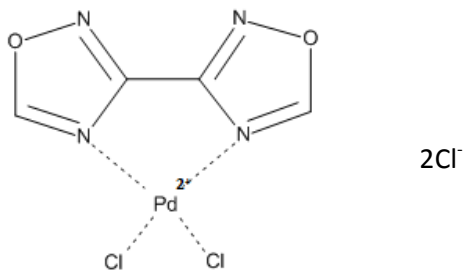


Figure 1.16

Further exploration of this ligand with alternative metal ions was conducted and reaction with silver nitrate generated a highly interesting, one-dimensional coordination polymer. The Ag^{+} ions are three-coordinate, existing in a slightly distorted trigonal geometry, coordinating as they do through the imine N4 nitrogen atoms of two bis-oxadiazole ligands and a monodentate nitrate molecule[53].

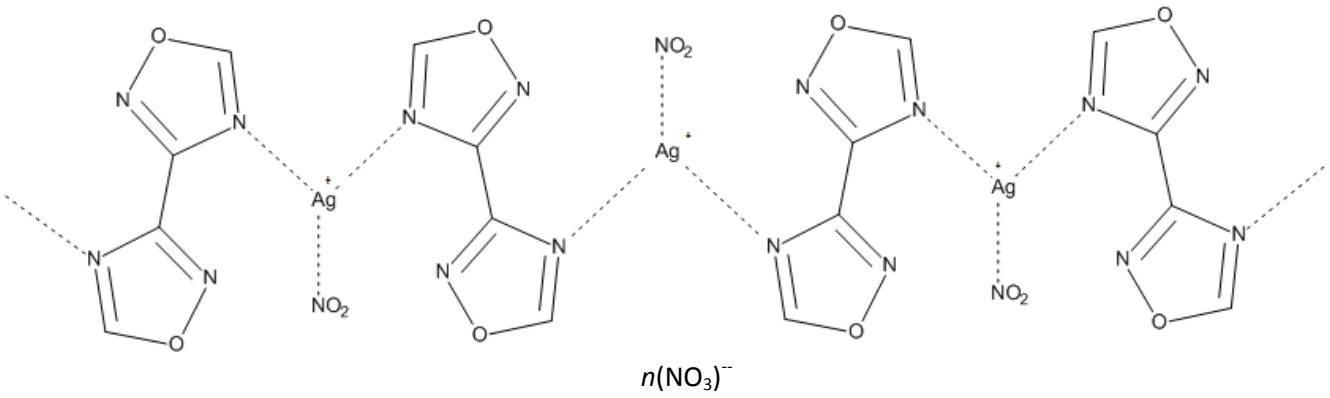


Figure 1.17 – Steel's 1D, 1,2,4-oxadiazole coordination polymer**.**

Once again, this metallosupramolecular structure demonstrates the seemingly highly preferential imine N4 coordination tendency.

Though still simple, the most extensive 1,2,4-oxadiazole containing ligands have been synthesised by Pace and co-workers. Reported in 2011, Pace found that 3,5-bis-(2-pyridyl)-1,2,4-oxadiazole systems form simple mononuclear complexes with Cu^{2+}, Ni^{2+} and Zn^{2+} ions[61] (Figure 1.18). Coordination was again observed through the oxadiazole N4 atom and the 3-(2-pyridyl) nitrogen.

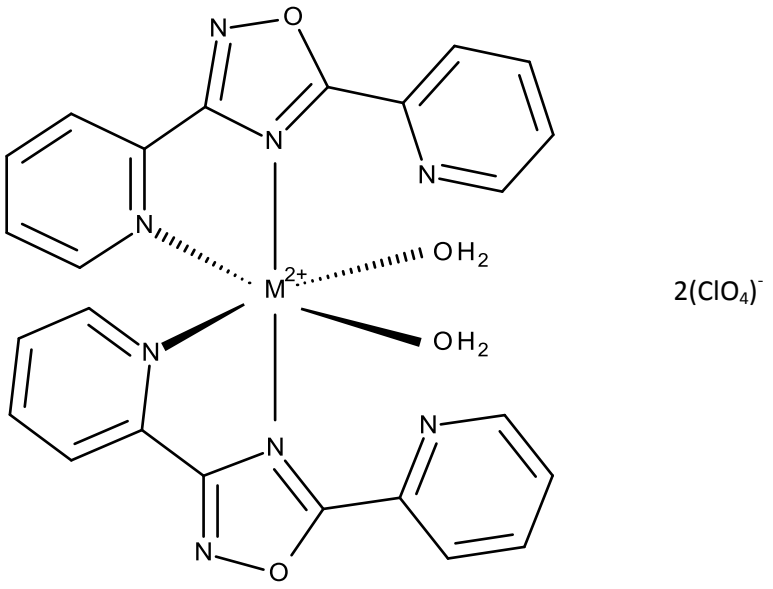


Figure 1.18

1.2.5.2 Coordination via the Oxime, N2 Atom

The second plausible means of coordination at the disposal of the 1,2,4-oxadiazole unit is via the oxime N2 atom.

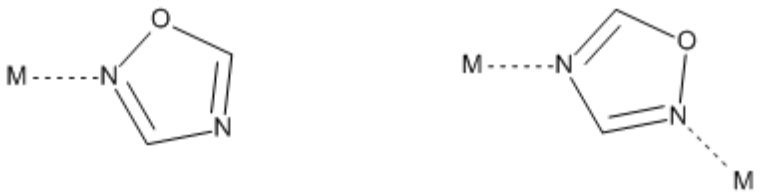


Figure 1.19 – The monodentate *(left)* and bidentate *(right)* potential 1,2,4-oxadiazole binding modes involving N2 coordination.

As mentioned earlier, coordination via this atom is less promising than with N4, due to the electronic nature of the heterocycle. The lower basicity of this N2 nitrogen atom is caused by the electron withdrawing effect of the more electronegative, neighbouring oxygen atom. This shift in electron density towards the oxygen atom in the N-O bond reduces the nucleophilicity/basicity of the N2 nitrogen atom. Thus the likelihood of preferential coordination over the imine N4 nitrogen is drastically reduced. To the best of our knowledge, coordination through the N2 has only ever been

observed once. This was again by Pace and co-workers, who in 2011 reported a 3-(2-pyridyl)-5-phenyl-1,2,4-oxadiazole system which coordinated to Cu^{2+}, Ni^{2+} and Zn^{2+} ions via the oxadiazole N2 atom and the 3-(2-pyridyl) nitrogen[61] (Figure 1.20).

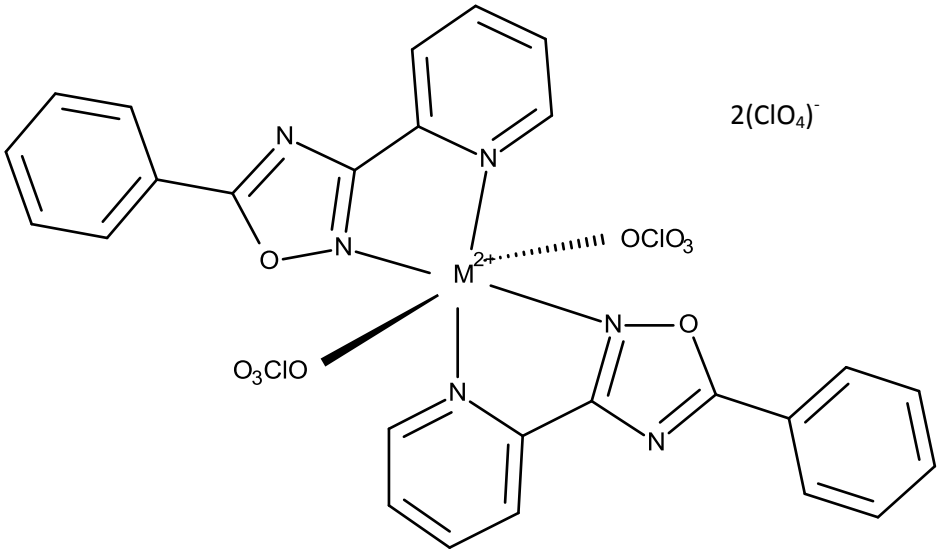


Figure 1.20

1.2.5.3 Coordination via the Oxygen Atom

Coordination via the oxygen atom remains the least likely coordination prospect of the three heteroatoms comprising the 1,2,4-oxadiazole. Coordination of oxygen with alkali metals and alkali earth metals has been observed in oxygenated heterocycles on many occasions, particular since the discovery of crown ethers in 1967[60,62]. Though coordination of O-sites to transition metals is possible[63], is it rarely observed[60]. Early work in coordination chemistry predicted that oxygen coordination was just as likely as nitrogen coordination[58,64]. Since this is now widely accepted as a rarity, one should consider the 1,2,4-oxadiazole unit as primarily monodentate (through N4), with realistic bidentate potential (through N2), but with only theoretical tridentate potential (through O).

1.2.6 Recent Advances in the Supramolecular Chemistry of the Thiazole

The research conducted in this thesis on the use of 1,2,4-oxadiazoles as ligands in supramolecular chemistry was carried out in collaboration with Rice. Rice has had huge success with thiazoles and due to its relevance to this thesis, a brief survey of Rice's thiazoles follows.

Rice and co-workers reported in 2000 a pyridine-thiazole-thiazole-pyridine ligand strand **(24)**, which was shown to demonstrate great versatility with a variety of metal ions[65]. In reaction with first row divalent transition metal ions as such as Cu^{2+} ions this ligand self-assembles to form a dinuclear triple helicate[65] (Figure 1.21). The helicating effect is mostly observed about the central thiazole-thiazole bond.

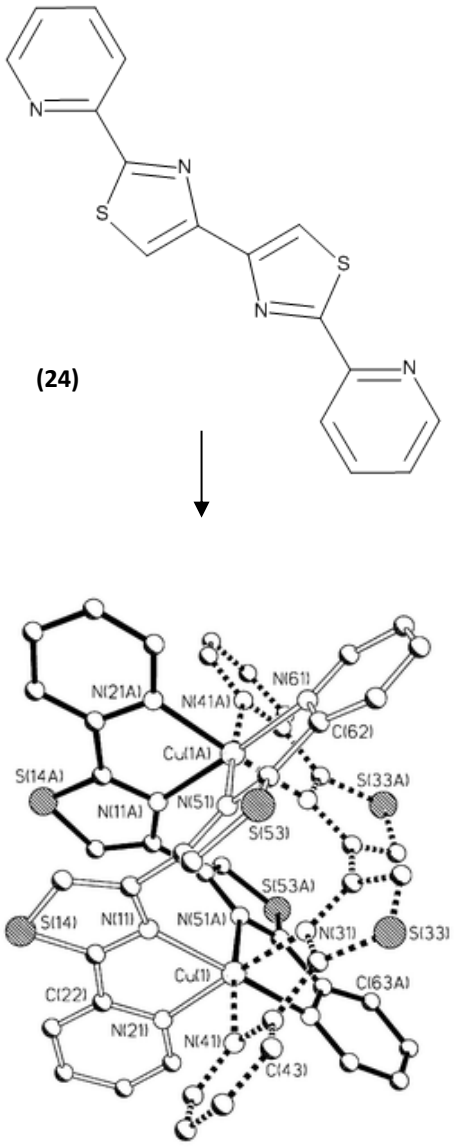


Figure 1.21

Exploring the reactivity of this ligand further, this time towards second row transition metal ions, the formation of a dinuclear triple helicate complex with Cd^{2+} ions was observed[66]. However, one subtle difference in the assembled metallosupramolecular structure was noticed. The thiazole-pyridine partitioning was observed in accordance with the previous complex, but not in all three strands. This was observed in just two of the strands. The third ligand is partitioned into a bidentate thiazole-pyridine unit on one side and a monodentate pyridyl domain on the other[66]. A water molecule completes the six-coordinate geometry of the lone pyridyl coordinated cadmium ion, resulting in a non-symmetric dinuclear triple helicate, shown in Figure 1.22.

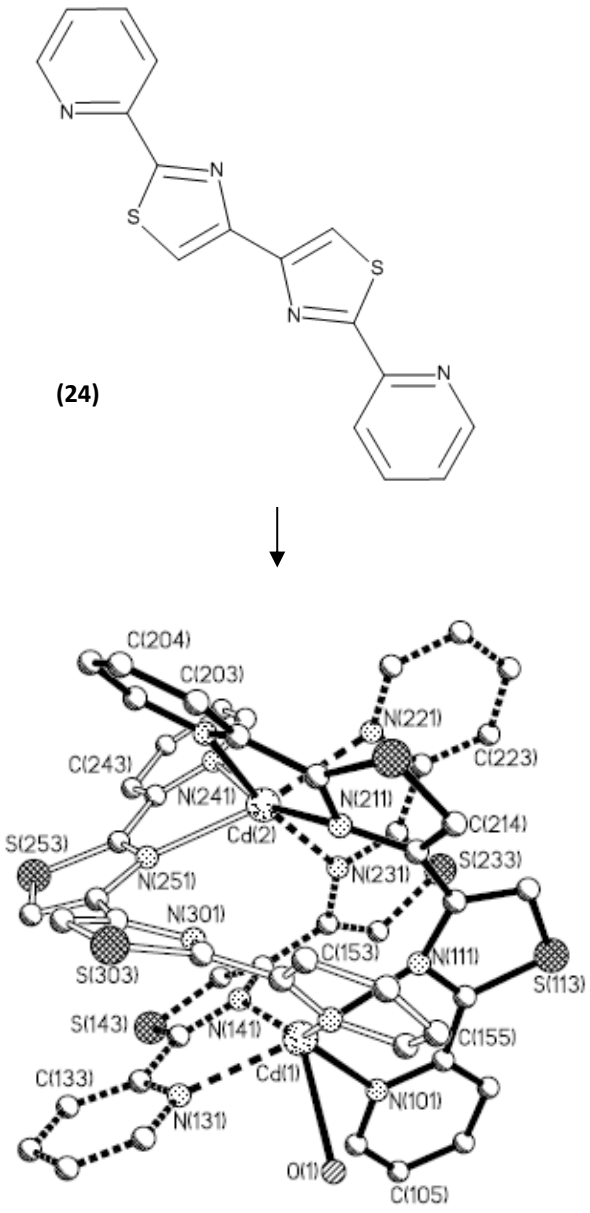
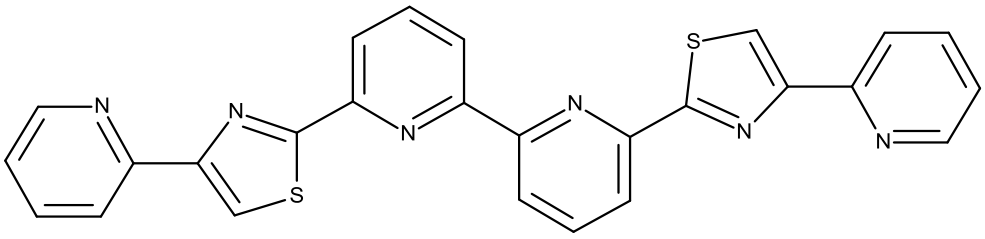


Figure 1.22

In 2001, Rice and co-workers synthesised a bipyridyl-centred ligand **(26)**, flanked by thiazole-pyridine domains at both sides[67]. A dinuclear double helicate with Cu^{2+} and Zn^{2+} ions was observed, but the ligand did not partition into two tridentate domains, rather into two bidentate pyridine-thiazole domains, forming a complex with four-coordinate metal ions[67] (Figure 1.23). The central bipyridine unit does not coordinate in these conditions[67].



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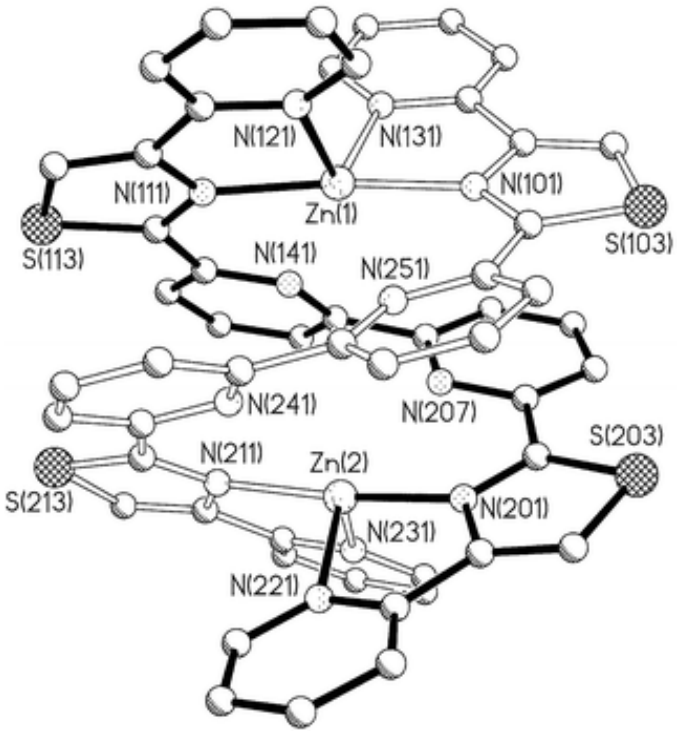
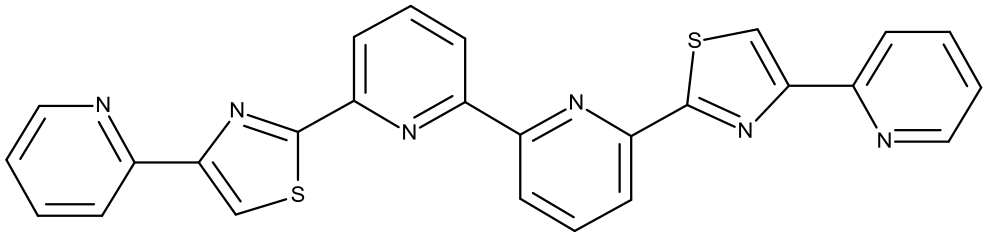


Figure 1.23

Interestingly, this ligand formed a slightly different dinuclear double helicate in reaction with Ni^{2+} ions. The terminal pyridine-thiazole unit expands from a bidentate domain to a tridentate domain through additional coordination with one of the pyridine nitrogens of the inner bipyridine unit[67] (Figure 1.24). Each Ni^{2+} ion in this system is in six coordinate state.



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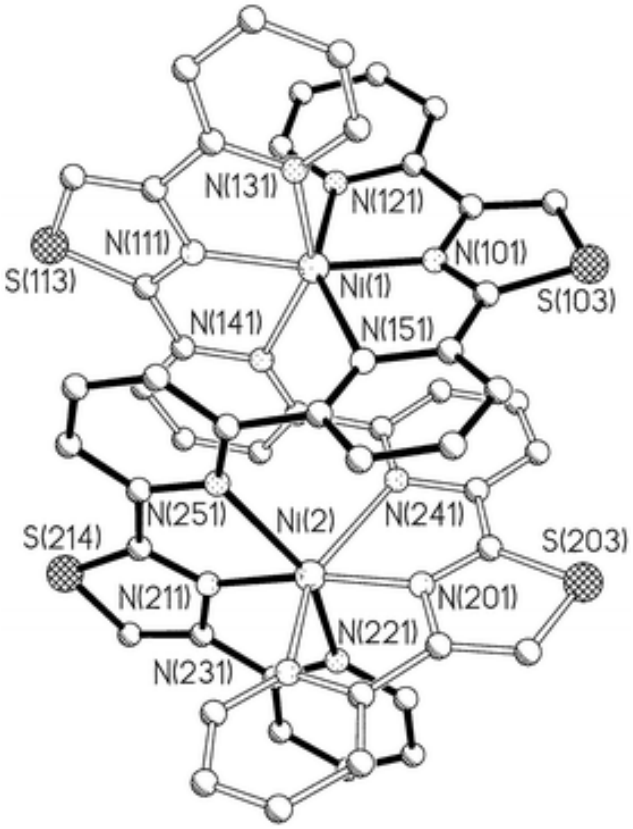
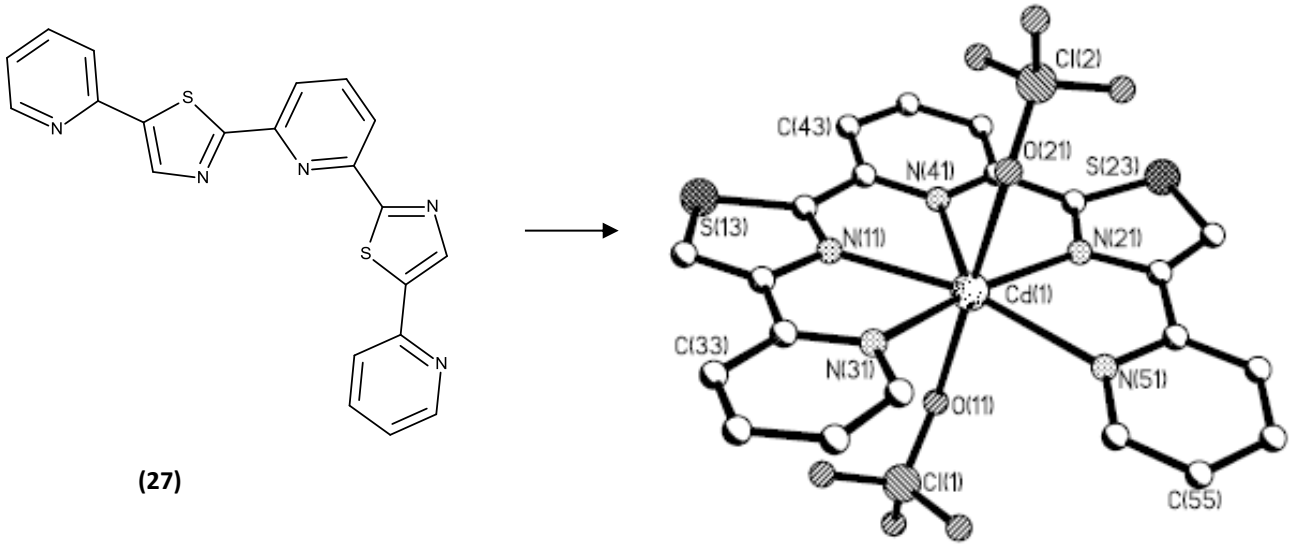


Figure 1.24

Other successful thiazole ligands synthesised by the Rice group include the pyridine-thiazole-pyridine-thiazole-pyridine system **(27)**, which was reported to behave as a full pentadentate ligand[66]. Reaction with Cd^{2+} ions led to the formation of mononuclear complex with a very slight helical twist, with coordination from all five ligand nitrogen atoms in a near planar fashion. Coordination from perchlorate anions both above and below the ligand in an axial fashion resulted in the Cd^{2+} ions adopting a seven-coordinate nature[66] (Figure 1.25).



(27)

Figure 1.25

Following the success of several thiazole based ligands, in 2010 Rice and co-workers synthesised a seven-ringed, highly elaborate, bipyridine-thiazole-phenyl-thiazole-bipyridine system[68] **(28)**. This complex ligand, in reaction with Cd^{2+} ions, self-assembled into a dinuclear double helicate with the ligand partitioned by the phenylene spacer unit into two pyridine-pyridine-thiazole tridentate units with the Cd^{2+} ions residing in pseudo-octahedral geometries[68] (Figure 1.26).

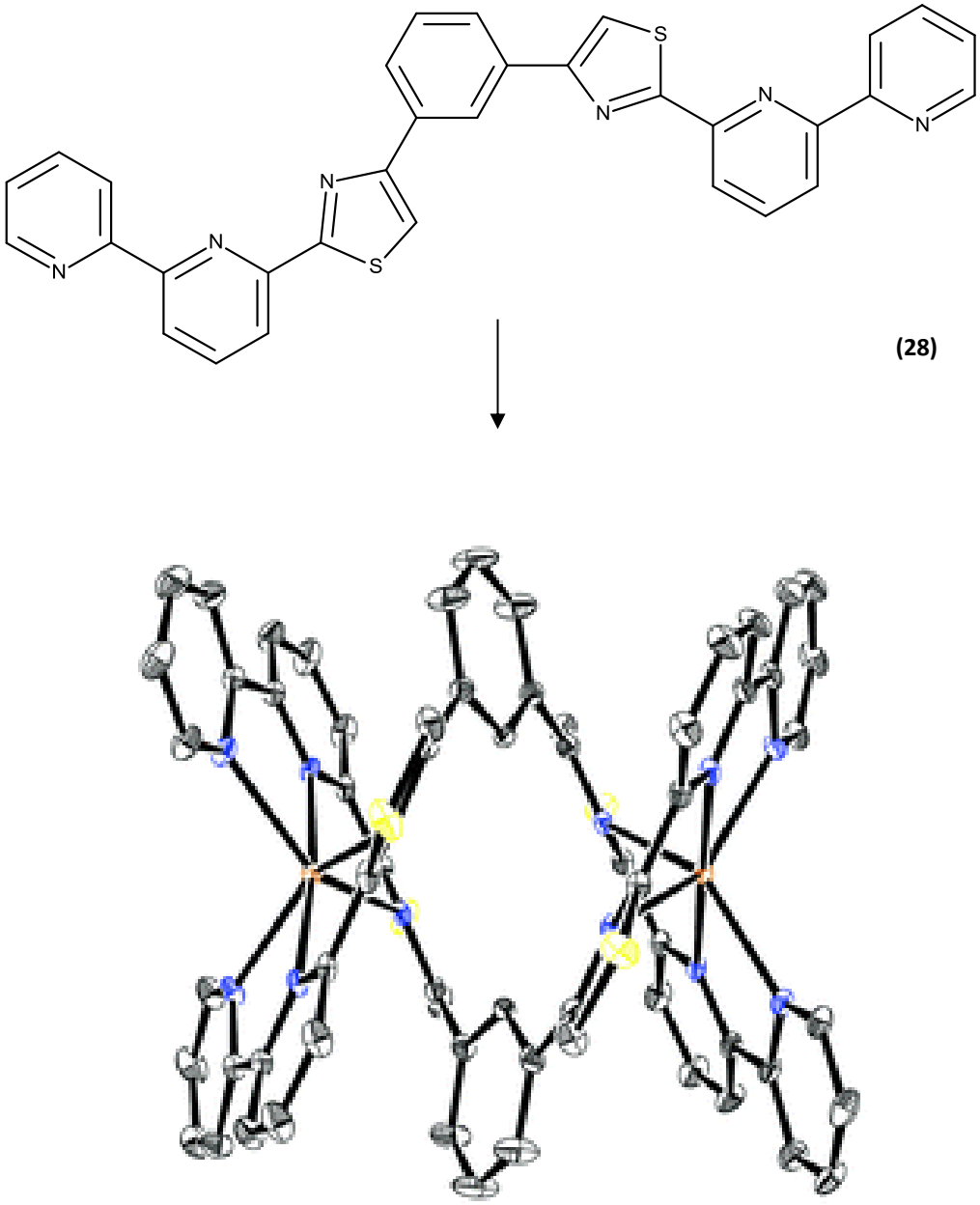
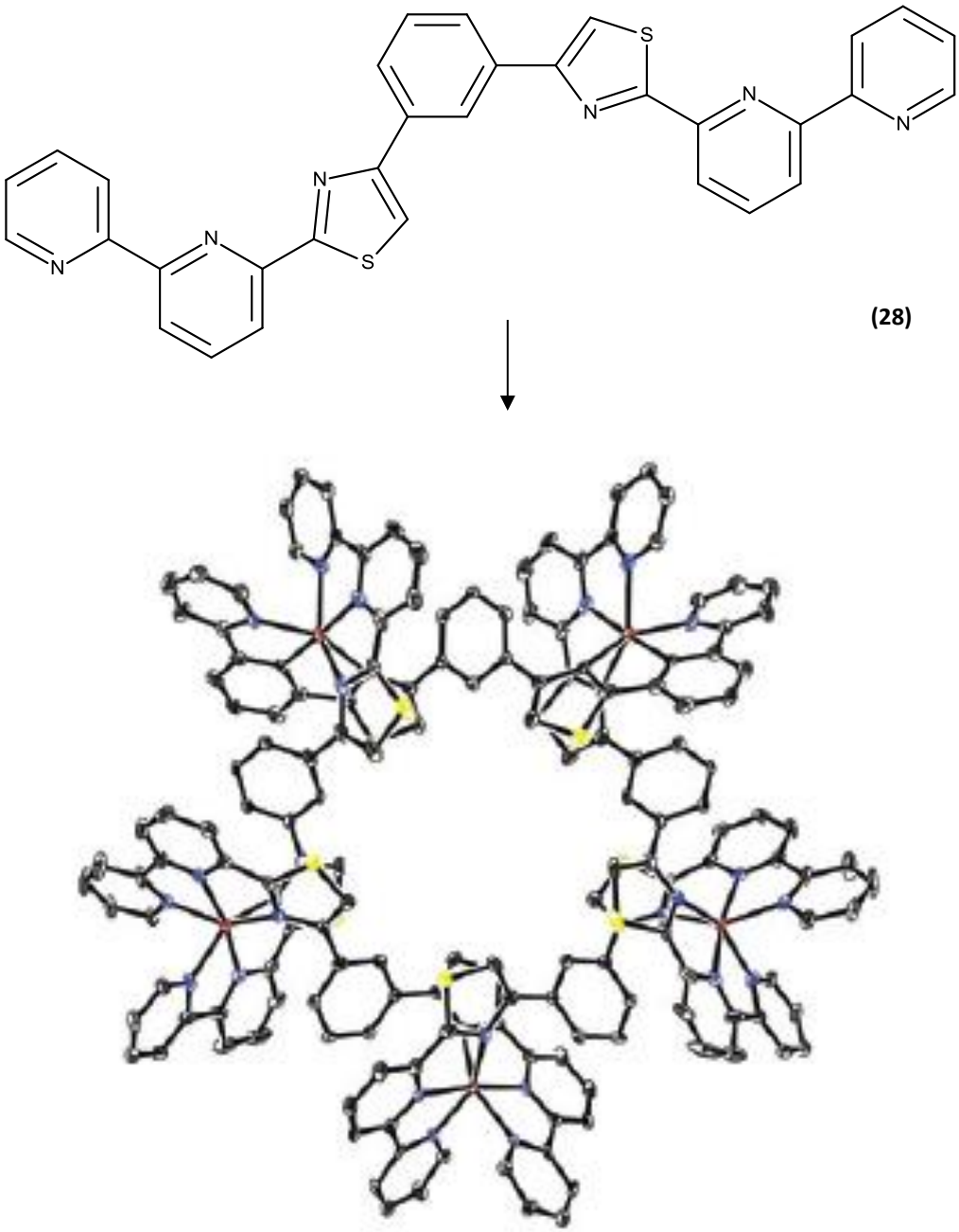


Figure 1.26

Additionally, this ligand produced one of the most significant metallosupramolecular systems developed by Rice. In 2010 it was reported that this seven-ringed ligand self-assembled in reaction with Zn^{2+} ions to form a pentanuclear, quintuple cyclic helicate[68]. The Zn^{2+} ions are six-coordinate and octahedral in geometry, coordinating to the pyridine-pyridine-thiazole tridentate domains of two ligand strands[68] (Figure 1.27).

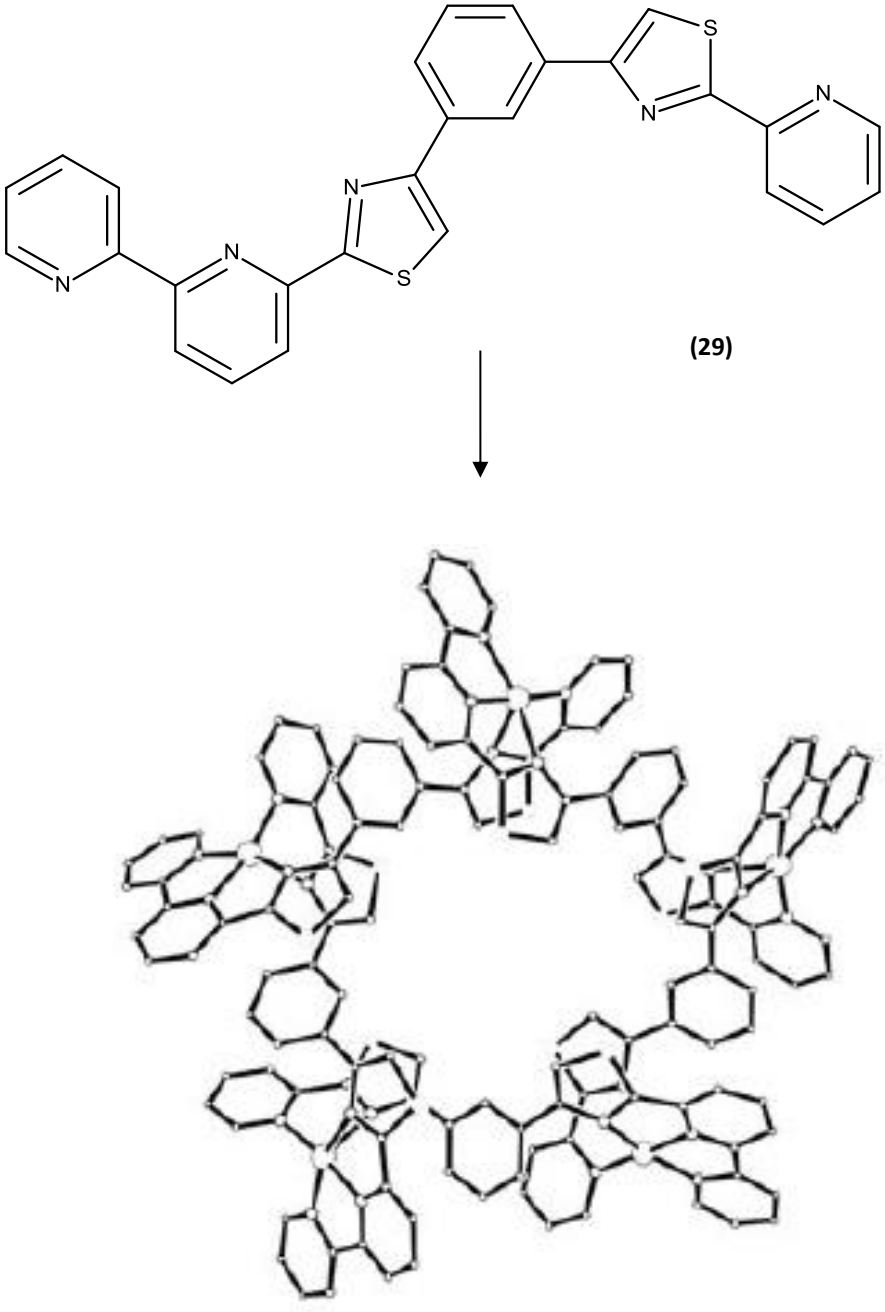


(28)

Figure 1.27

In 2010, Rice also reported the synthesis of another pentanuclear cyclic helicate, this time from the same ligand described above with one of the terminal pyridine units removed, rendering a potentially tridentate-bidentate partitioned system[69] **(29)**. This ligand self-assembled in reaction with Cu^{2+} ions into a pentanuclear cyclic helicate with the ligands adopting a head-to-tail arrangement

about the five-coordinate Cu^{2+} ions (Figure 1.28). That is, each Cu^{2+} ion coordinates a bidentate domain from one ligand and a tridentate domain from another[69].



(29)

Figure 1.28

Extending this work by capitalising on the pentanuclear systems observed, Rice and co-workers synthesised a heteroleptic pentanuclear, cyclic helicate through deliberate selection of a pyridine-thiazole-phenyl-thiazole-pyridine ligand **(30)** and the bipyridine-thiazole-phenyl-thiazole-bipyridine ligand **(28)** in reaction with Cu^{2+} ions[69]. This elaborate complex features three of the bipyridine-type ligands and two of pyridine-type ligands. Four of the copper(II) ions of this pentanuclear complex are in a five-coordinate state, binding to the tridentate pyridine-pyridine-thiazole domain of one ligand and the bidentate pyridine-thiazole domain of another (Figure 1.29). One of the five ions however, exists in a six coordinate state, bound to the tridentate pyridine-pyridine-thiazole domains of two bipyridine-thiazole-phenyl-thiazole-bipyridine ligand strands[69].

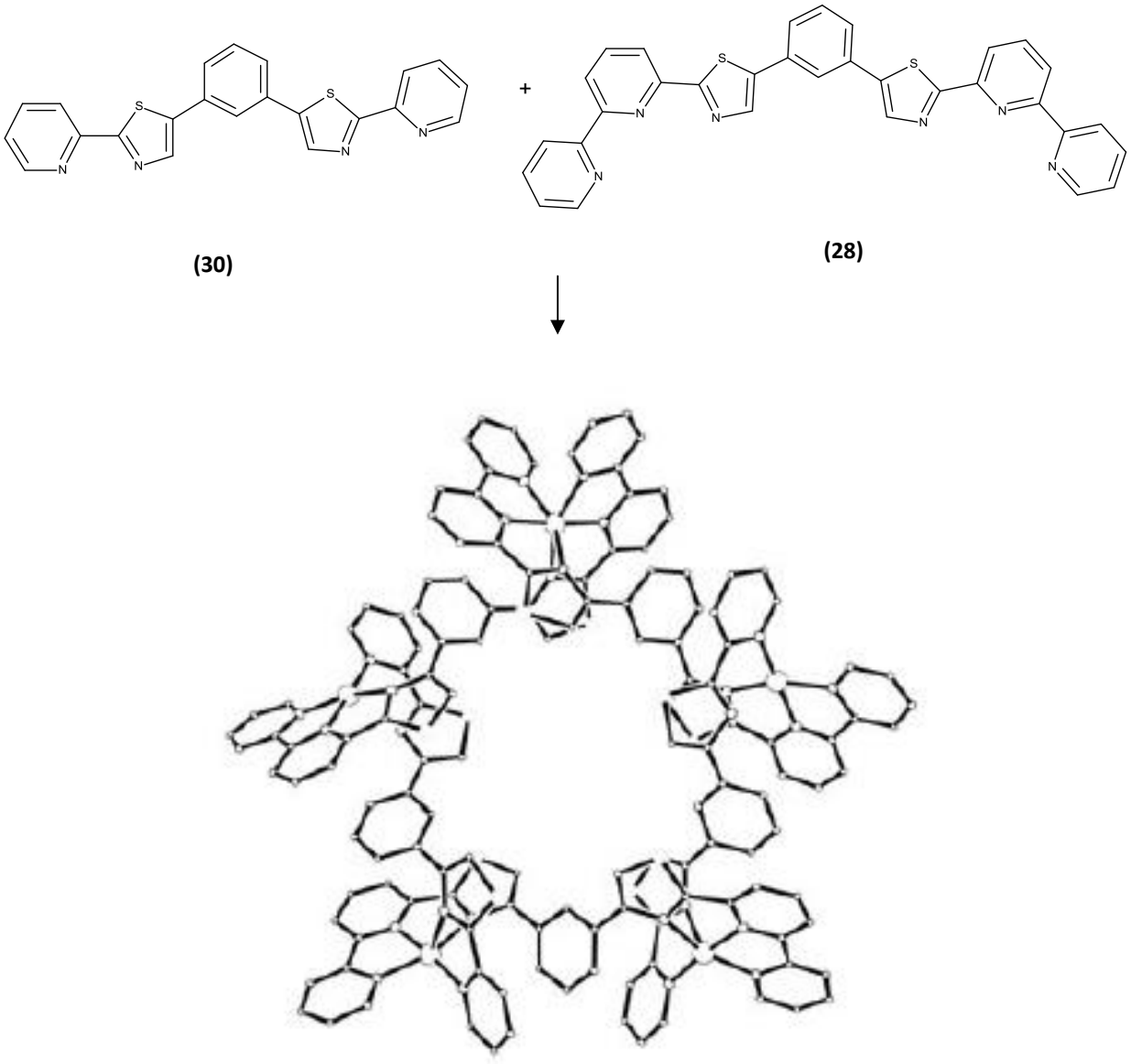


Figure 1.29

1.3 The 1,2,4-Oxadiazole Unit in Medicinal Chemistry

The 1,2,4-oxadiazole unit is commonly observed throughout medicinal chemistry. It is also popular in agrochemistry, polymer science and also materials chemistry[70]. A 2012 study by AstraZeneca demonstrates the increasing extent to which the 1,2,4-oxadiazole unit has featured in patent applications in the last ten years- from approximately 180 applications in 2000 to 370 applications in 2008. This illustrates an enormous increase in interest towards the 1,2,4-oxadiazole in medicinal chemistry alone[70].

The increased interest in the 1,2,4-oxadiazole unit has led to the heterocycle being exploited in a vast number of drug development programs. There are several reasons for this popularity. Often, the 1,2,4-oxadiazole unit forms a critical part of the pharmacophore of the molecule and as such is crucial in favourable ligand-receptor binding in some molecules[70,71]. In other situations, the regiochemistry of the 1,2,4-oxadiazole has been capitalised upon, since the unit has been utilised as an aromatic and planar linking scaffold, installed to ensure that certain substituents are present in the drug candidate in desired orientation[72]. The most frequently encountered reason why the 1,2,4-oxadiazole unit has gained such popularity in recent years is the close structural and geometric relationship with esters and amides[70]. The 1,2,4-oxadiazole unit is thus deployed as a highly stable, hydrolysis resistant, bioisostere with such ester and amide functionalities.

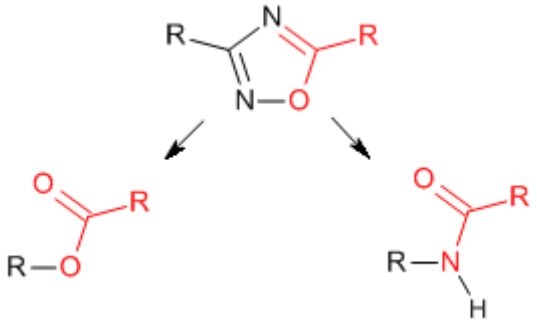


Figure 1.30 – The isosteric relationship between 1,2,4-oxadiazoles and esters/amides.

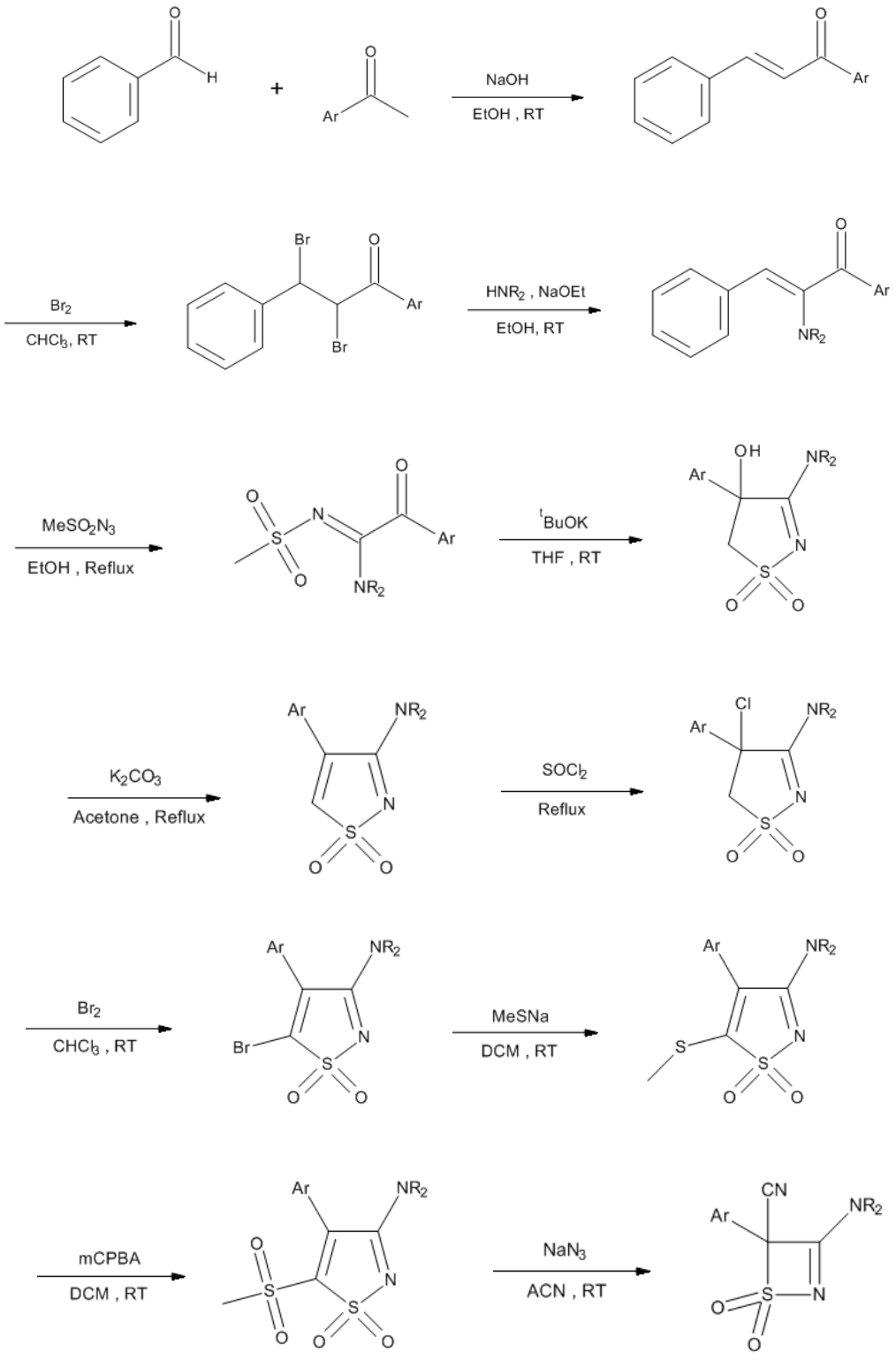
The growing popularity of the 1,2,4-oxadiazole in industry has prompted an explosion of research, focussing on these unique medicinal properties. This topic has been extensively reviewed[3,6,73,74,75], and will not be detailed further here.

1.3.1 The Medicinal Chemistry of the β- and γ-Sultams and Their Bicyclic Derivatives

Our group have previously synthesised a limited range of thiazete-1,1-dioxide derivatives and isothiazole-1,1-dioxide derivatives, also known as β-sultams and γ-sultams, respectively[76]. The major objective of this project was to extend this work by incorporating the 1,2,4-oxadiazole nucleus in a bid to boost activity.

Various syntheses of sultams exist, however the synthesis that our group have particularly been interested in was pioneered by Clerici and co-workers[77,78,79], as it offers several points at which the synthesis can be intercepted to install the 1,2,4-oxadiazole unit.

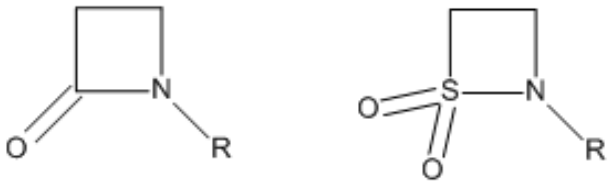
The synthesis (Scheme 1.29) begins with a simple aldol reaction between an acetophenone derivative and benzaldehyde. The α,β-unsaturated ketone is then dibrominated and the α,β-dibrominated ketone is treated with a secondary amine to yield the corresponding enamine[80,81]. Following reaction with methanesulfonyl azide the enamine is converted to the amidine, which is then cyclised through treatment with base to yield the 4-hydroxyisothiazoline[79]. This heterocycle is then chlorinated using thionyl chloride and then subsequently dehydrochlorinated by treatment with sodium carbonate[79]. The resultant isothiazole is α-brominated, which enables the substitution of bromide by thiomethoxide to yield the methyl thioether. Oxidation with mCPBA yields the methyl sulfone which, following treatment with sodium azide undergoes a ring contraction to the thiazete-1,1-dioxide.



Scheme 1.29 – Synthetic Route to β-sultams and γ-sultams.

1.3.2 The Thiazete and Thiazetidine-1,1-dioxides and Extensions with 1,2,4-Oxadiazoles

β-Sultams **(32)** are four-membered sulfonamide heterocycles[82]. They are analogous with the well-known β-lactams **(31)** [76,82].



(31) **(32)**

Figure 1.31 - Comparison of β-lactam and β-sultam heterocycles.

The chemical and biological reactivity of the β-lactam has been very well explored throughout the last century. These heterocycles find broad use in several divisions of medicine, most prominently to combat bacterial infections[83,84].

The analogous β-sultam was first synthesised in 1960[85]. This heterocycle has been well explored and is a popular feature of much research at the University of Huddersfield[84,86,87], most notably with interesting roles as inhibitors of serine proteases[86].

There are a number of synthetic routes to the β-sultam heterocycle. These have been reviewed extensively[76,82,88] and will not be discussed at length in this thesis. The synthesis outlined in Scheme 1.29 is the major synthetic focus for this project, with several extensions planned. To the best of our knowledge, the only thiazete-1,1-dioxide that has seen its anticancer activity explored is that which was studied by our group previously[76] (Figure 1.32).

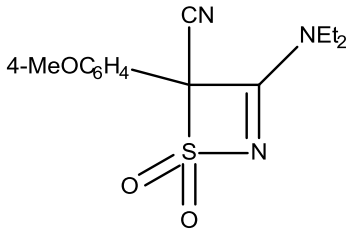
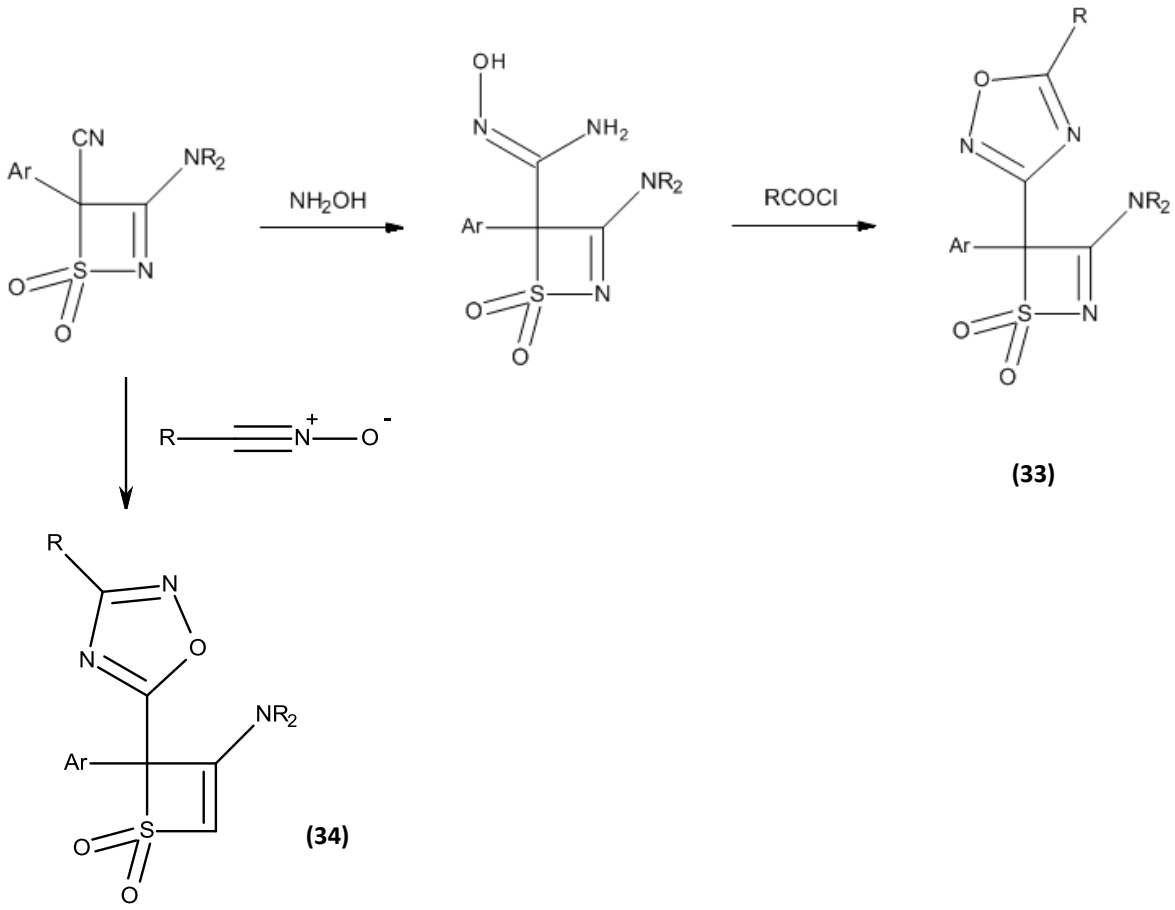


Figure 1.32

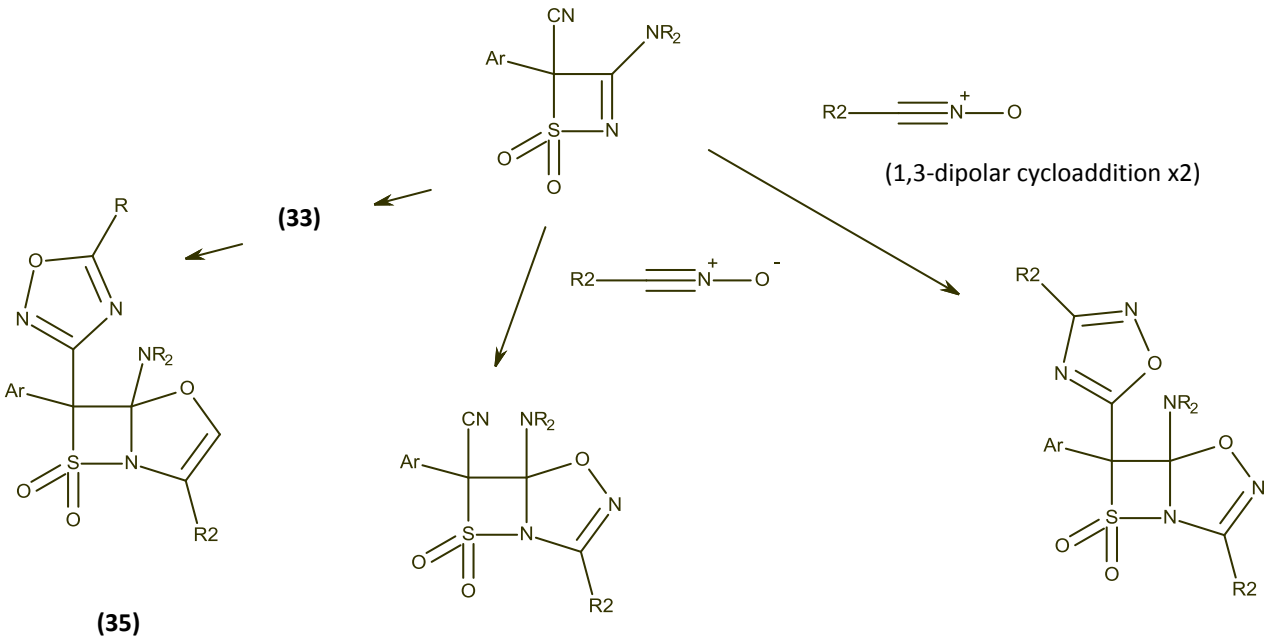
This β-sultam was yielded by the synthetic protocol in Scheme 1.29. This synthesis is versatile and enables several significant, yet simple changes to be made. The arene substituent can be varied in the initial aldol step. The amino functionality is also introduced early in the synthesis during the third step from which the enamine is generated. The nitrile is a static feature of the β-sultam and is resultant from the previous ring contraction reaction. Throughout this work our group hopes to vary these substituents and create an extensive library of such 3-amino-4-aryl-4-cyano-thiazete-1,1-dioxides and explore their anticancer activity, in addition to incorporating the 1,2,4-oxadiazole unit.

The most attractive means of expanding the molecule to include the 1,2,4-oxadiazole nucleus sits with the nitrile. Reaction with hydroxylamine should generate the corresponding amidoxime. Reaction of the amidoxime with an activated carboxylic unit completes the 1,2,4-oxadiazole introduction and adds a further variable **(33)** to the structure (Scheme 1.30).



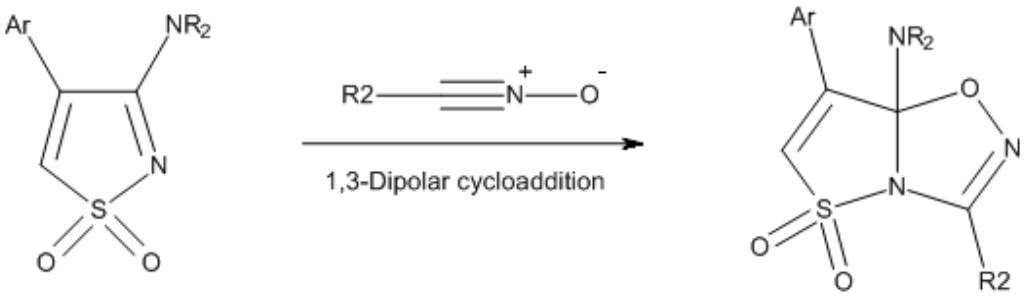
Scheme 1.30

We anticipated that the thiazete imine bond present in the starting material (see Figure 1.32) and products **(33)** and **(34)** may also offer potential roles as dipolarophiles, leading, as shown in Scheme 1.31, to bicyclic β-sultams **(35-37)**.



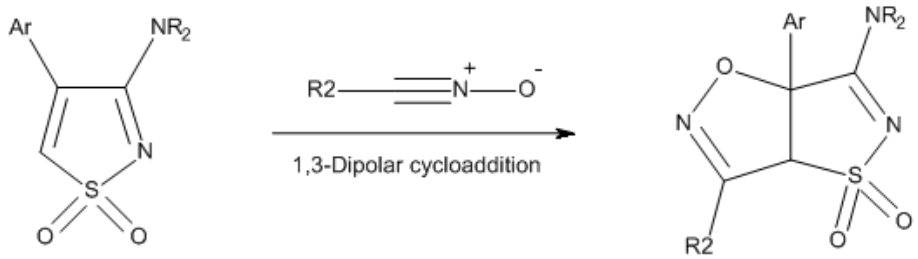
Scheme 1.31

With reference to Scheme 1.41, there is potential to incorporate the 1,2,4-oxadiazoline system at various points, with a 1,3-dipolar cycloaddition to the imine bond of the isothiazoles, which are candidate dipolarophiles. An example is shown in Scheme 1.32, giving the isothaizolo-1,2,4-oxadiazoline **(38)**.



Scheme 1.32

Our group have previously explored the possibility of synthesising a bicyclic isothiazolo-oxadiazole system via a 1,3-dipolar cycloaddition reaction at this imine bond. The substrate for this reaction was the 3-diethylamino-4-(4-methoxyphenyl)-isothiazole-1,1-dioxide that the previously described β-sultam (Figure 1.32) was synthesised from. The desired product was not achieved, as the competing alkene of the isothiazole acted as a stronger dipolarophile. Interestingly, cycloaddition did not occur at the imine at all, with the isothiazolo-isoxazole **(39)** the only product[76] (Scheme 1.33). It was one of the aims of this thesis to explore this process further.



(39)

Scheme 1.33

This reaction was initially reported by Clerici in 2006, though with a narrow range of isothiazole substrates explored[78]. Thus it was felt that the chemistry in Scheme 1.29 offered a lot of scope with a wide range of isothiazoles and β-sultams being available which could function as dipolarophiles. The biological activity of these systems could also be investigated.

1.4 The Asymmetric Catalytic Potential of Chiral 1,2,4-Oxadiazole-containing Systems

Asymmetric synthesis is one of the most fundamental aspects of organic chemistry.

One of the aims of this thesis is to explore novel, chiral, catalytic systems that contain the 1,2,4-oxadiazole system. Despite the stability, isosteric and potential substituent geometry benefits of the system, the 1,2,4-oxadiazole unit has not been a popular structural feature in the field of asymmetric organocatalysis. In fact a thorough review of the literature does not reveal any reports of any organic catalytic systems featuring the 1,2,4-oxadiazole heterocycle. This bodes well for our research plans, the primary goal of which is to study existing organocatalysts which feature similar heterocyclic or ester or amide functionalities and exchange the ester/amide/heterocyclic functionality for the 1,2,4-oxadiazole heterocycle. The specific systems focussed upon in this preliminary study were L-proline based systems and chiral hypervalent iodine(III) systems. These are reviewed briefly below.

1.4.1 L-Proline Mediated Asymmetric Synthesis

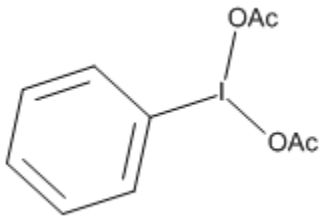
L-Proline is a popular selection for enriching organic systems with chirality, not only due to its low cost and high commercial availability, but its chemistry also. L-Proline possesses secondary amine functionality and is the only common natural amino acid to do so. Relative to other amino acids, L-proline is of stronger nucleophilicity and has a higher pKa[89]. This makes L-proline a useful tool in asymmetric chemistry since it is able to react with Michael acceptors or carbonyls to form enamines, imines or iminium ions[89]. In this thesis, the synthesis of an L-proline containing 1,2,4-oxadiazole will be described together with the attempted development of chiral hypervalent iodine (III) systems designed to eventually contain the L-proline-1,2,4-oxadiazole unit.

1.4.2 Hypervalent Iodine Systems

1.4.3 Significant Breakthroughs in Hypervalent Iodine

The first hypervalent iodine compound was prepared in 1886 (iodobenzene dichloride by German chemist Conrad Willgerodt (1841 – 1930))[90]. Their first practical origin can be traced back to the early sixties and originated with iodobenzene diacetate or phenyliodine diacetate (PIDA),

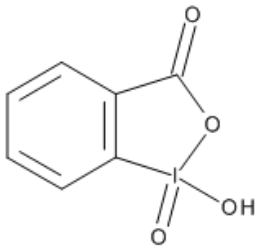
synthesised originally by Alcock and Waddington[91] (Figure 1.34), inspired by Conrad Willgerodt's early work on iodobenzene dichlorides and diesters[92].



(40)

Figure 1.34

One of the most useful hypervalent iodine(V) reagents utilised in recent times is 2-iodoxybenzoic acid (IBX) (Figure 1.35), a potent oxidising agent, particularly useful for converting primary and secondary alcohols to the corresponding carbonyls with little over-oxidation to the acid[93,94].

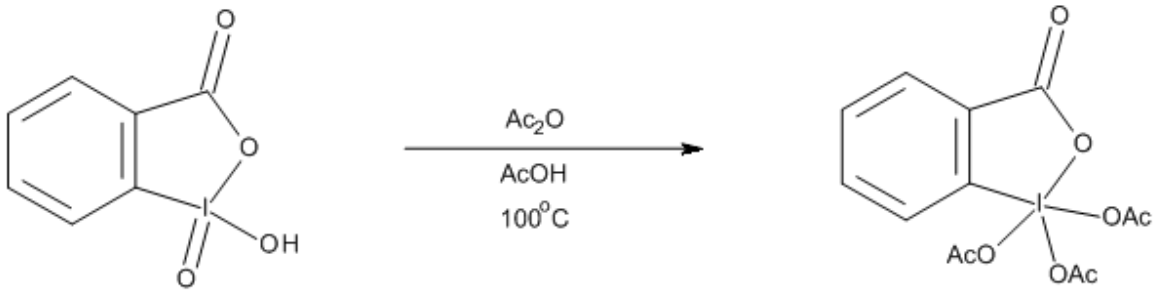


(41)

Figure 1.35

One of the major drawbacks of IBX was its limited solubility in organic solvents[94,95]. Several successful, clean oxidations have been reported with DMSO as solvent[96,97], however little else exists amongst the literature due to insolubility in the more practical organic solvents.

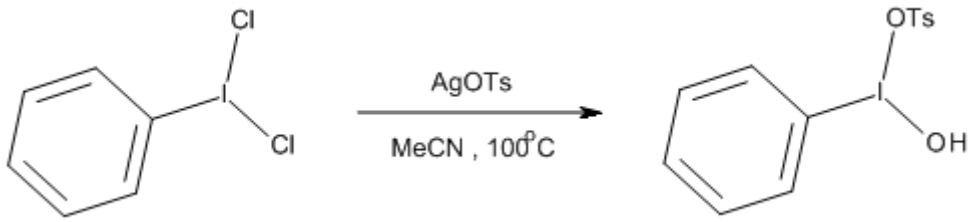
Dess and Martin made what is probably the most significant discovery in the history of hypervalent iodine chemistry. Dess and Martin treated IBX **(40)** with acetic anhydride in acetic acid, which yielded the triacetate[98] (Scheme 1.34). This compound proved to be much more soluble in organic solvents than the predecessor IBX and remained a highly significant oxidising agent, broadly tolerant of high functional group densities and capable of successfully reacting in the most tricky oxidation circumstances[99]. This reagent is known as the Dess-Martin Periodinane **(41)** (DMP).



Scheme 1.34 – The synthesis of DMP.

1.4.4 Iodine(III) Reagents

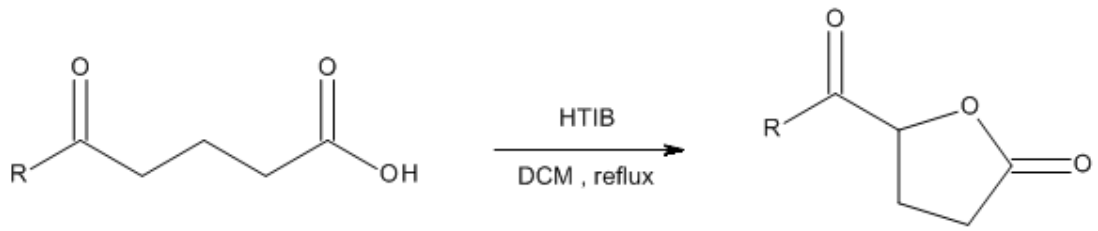
In 1977, Gerald F. Koser and co-workers attempted to synthesise the ditosylate from iodobenzene dichloride (Scheme 1.35)[100]. Instead of synthesising iodobenzene ditosylate, Koser synthesised the mono-tosylated, hydroxyl(tosyloxy)iodobenzene (HTIB) **(42)** which later became known as Koser's reagent[100]. **(40)** **(41)**



(42)

Scheme 1.35

In 1990, Moriarty and co-workers utilised HTIB in the lactonisation of 5-oxo-pentanoic acid derivatives[101] (Scheme 1.36). This reaction will be revisited in detail later in this thesis.



Scheme 1.36

In addition to reporting the synthesis of PIDA, Alcock also reported the first synthesis of phenyliodosyl bis(trifluoroacetate) in 1963[91] (Figure 1.36), a reagent known as PIFA.

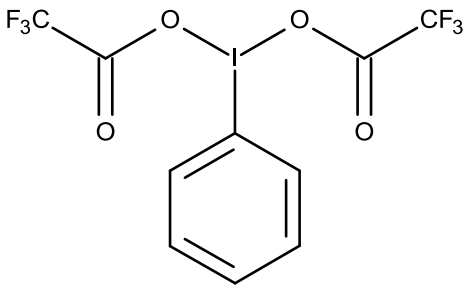
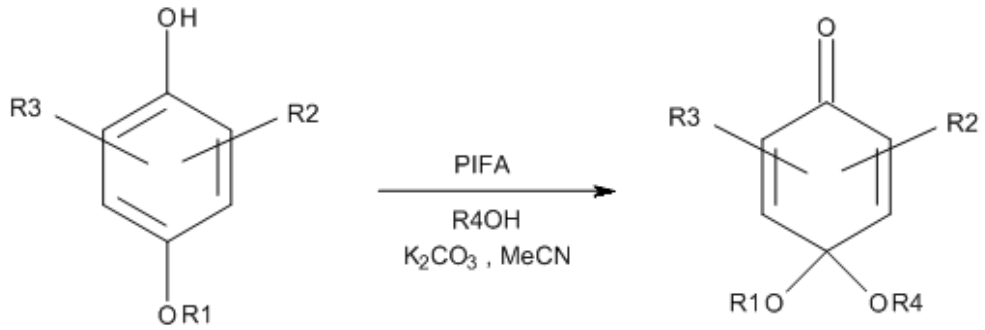


Figure 1.36

Tamura and co-workers reported the reactivity of PIFA towards 4-alkoxyphenols[102]. They found that the reaction of such substrates with PIFA and certain alcohols produced benzoquinone-4-monoacetals[102], shown in Scheme 1.37.

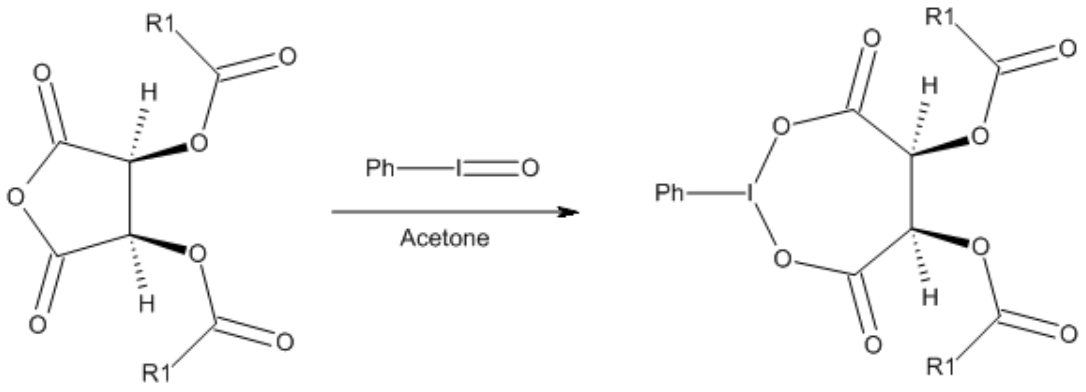


Scheme 1.37

Alcock's PIDA and PIFA and Koser's HTIB form the basis of modern hypervalent iodine(III) (HVI) research.

During the mid 2000s, organoiodine research focussed on an alternative feature of the classic HTIB-type iodine(III) structure. This focus was to vary the compounds, usually at the aryl unit, by enriching them with chirality in a bid to produce reagents capable of inducing asymmetry in synthesis.

In 1986 Imamoto and co-workers reported the first synthesis of a chiral hypervalent iodine(III) reagent by reaction of iodosylbenzene with L-tartaric anhydride derivatives[103] (Scheme 1.38). The catalyst was found to be effective in the asymmetric oxidation of sulfides to sulfoxides, delivering reasonable enantiomeric excesses of up to 53%[103].



R1 = Me, Ph, ^{t}Bu

Scheme 1.38 – Synthesis of early HVI asymmetric reagent.

In 2001, Wirth and co-workers synthesised a series of chiral hypervalent iodine(III) catalysts approximately based around the core structure of HTIB[104,105,106] (Figure 1.37).

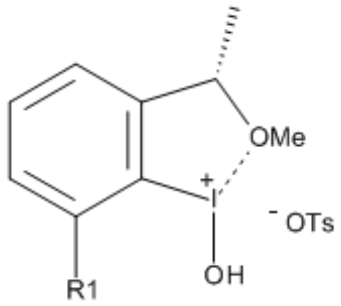
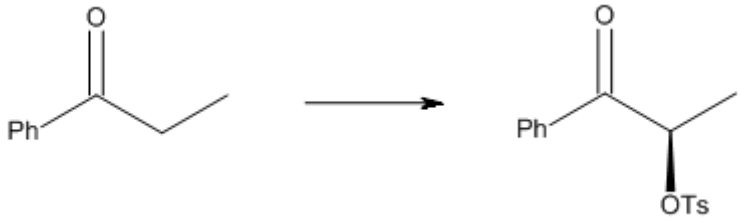
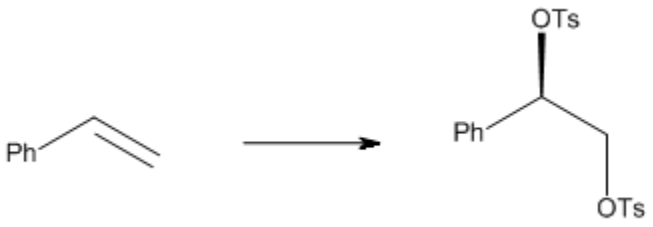


Figure 1.37

Wirth and co-workers found this iodonium salt catalyst to successfully α-oxytosylate ketones[104,106] (Scheme 1.39) and ditosylate alkenes[105,106] (Scheme 1.40) with some asymmetry, albeit minor. The ethyl derivative gave the best e.e's in both cases (40-65%).



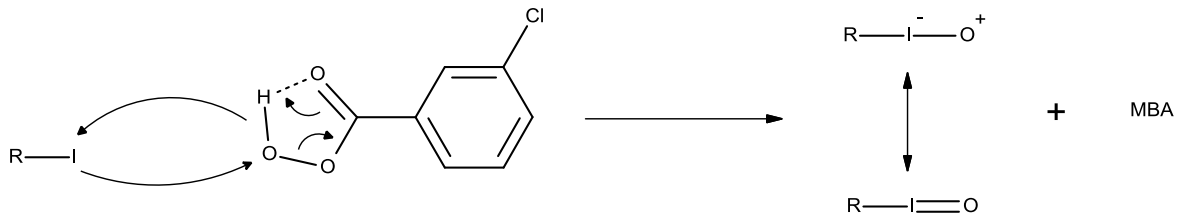
Scheme 1.39



Scheme 1.40

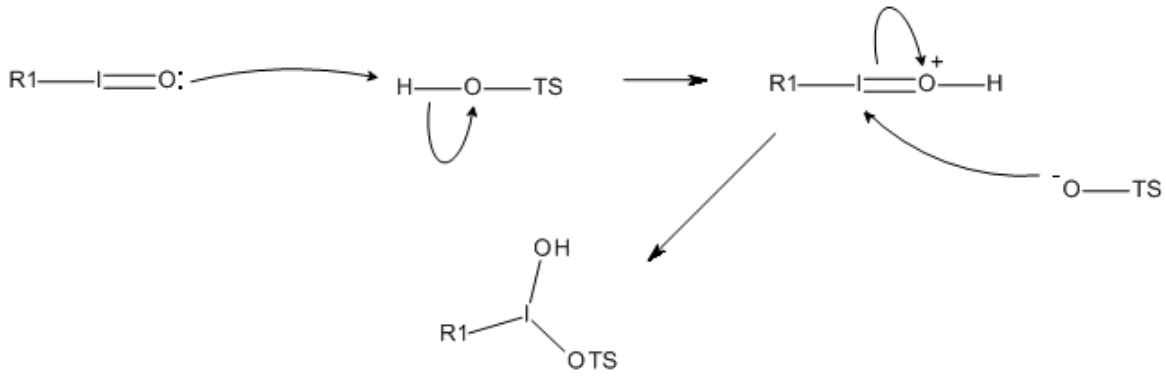
Until the mid-early 2000's, stoichiometric amounts (at least) of hypervalent iodine were required to in order to successfully synthesise the desired product. Soon after this time, it was discovered that only a catalytic amount of a monovalent iodine compound was required, providing there was a stoichiometric amount of oxidant present[107]. Previously, the iodine(III) species had been synthesised and then isolated before its use. The inclusion of a stoichiometric amount of oxidant along with the monovalent iodine compound to the reaction mixture enables the *insitu* generation of the reactive iodine(III) species[107]. The iodine(III) species then reacts accordingly with the substrate to synthesise the oxidised product, regenerating the reduced iodine(I) compound. This is then reoxidised by the stoichiometric oxidant, reproducing the reactive iodine(III) species.

Since its use by Kita and co-workers[108], mCPBA has been a popular co-oxidant for the *in-situ* generation of catalytic hypervalent iodine(III) species. mCPBA oxidises iodine(I) compounds to the hypervalent iodosylbenzene (Scheme 1.41).



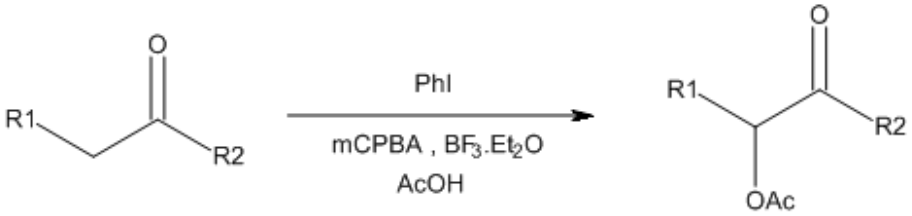
Scheme 1.41 - m-Chloroperoxybenzoic acid mediated in-situ generation of hypervalent iodine(III) species.

In addition to the re-oxidation of iodine(I) back to the iodosylbenzene, it is necessary in many cases to conduct the reaction in the presence of an additive, usually an acid. For example the *in-situ* generation of Koser's reagent (HTIB) would require the presence of *p*-toluenesulfonic acid in addition to an oxidant such as mCPBA (Scheme 1.42). In several reactions utilising HTIB the *p*-toluenesulfonic acid is regenerated also[151,109].



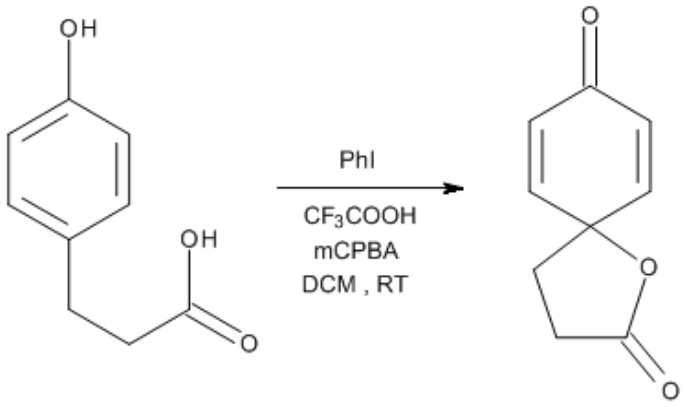
Scheme 1.42

In 2005, Ochiai and co-workers reported the first catalytic α-acetoxylation of ketones[110]. This was achieved through a simple but highly effective return to PIDA as the hypervalent iodine(III) species The use of iodobenzene as precatalyst in the presence of acetic acid with mCPBA as oxidant enables the *insitu* generation of PIDA, which mediates the α-acetoxylation of ketones in good yields across a range of substrates[110] (Scheme 1.43). Ochiai also reported that it was necessary for the reaction to be conducted in the presence of a Lewis acid such as BF_3-Et_2O, which induces enolisation and activates the ketone[110].



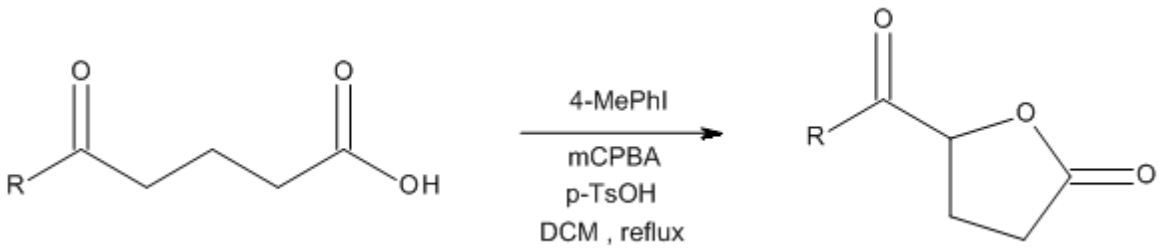
Scheme 1.43

In addition to several other monoaryl iodine(III) species, Kita in 2005[111] reported the use of catalytic PIFA, although with stoichiometric amounts of mCPBA and trifluoroacetic acid, in an adaptation of Tamura's[102] 1987 PIFA mediated spirocyclisation[111] (Scheme 1.44).



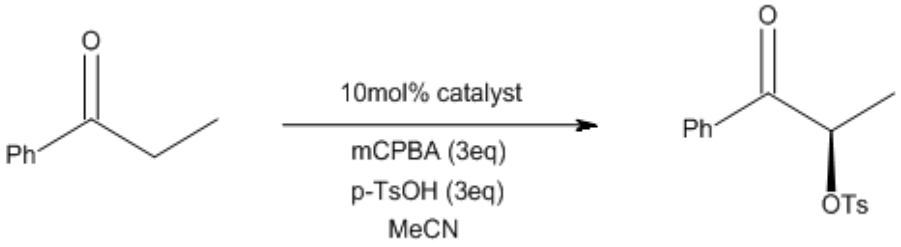
Scheme 1.44

Taking Moriarty's 1990 HTIB mediated lactonisation of 5-oxopentanoic acid derivatives, Ishihara and co-workers utilised Kita's catalytic reagents and successfully converted the reaction to a fully catalytic process using 5mol% iodotoluene, 20mol% *p*-toluenesulfonic acid and 1 equivalent of mCPBA[112] (Scheme 1.45). This latter reaction forms the basis of some of the work reported later in this thesis.



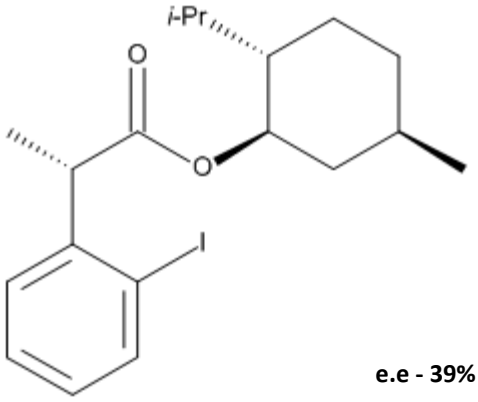
Scheme 1.45

Wirth and co-workers in 2008 synthesised a range of chiral aryl iodides[113] based around their earlier iodine(III) compounds[106] and investigated their enantioselective catalytic properties in the α-oxytosylation of propiophenone[113] (Scheme 1.46), the non-catalytic asymmetric induction of which[106] was described earlier (Scheme 1.39).



Scheme 1.46

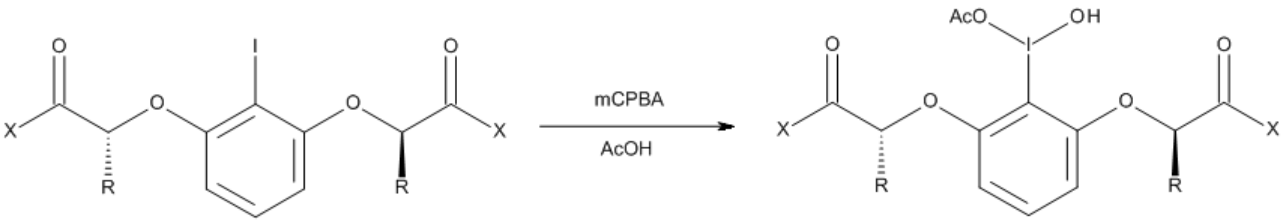
Wirth synthesised a range of 11 chiral catalysts which featured ether functionality and a further 17 which featured ester functionality. Wirth found that the highest enantiomeric excess was generally achieved with ester based catalysts[113] such as that shown in Figure 1.38 below.



e.e - 39% (R), Yield - 42%

Figure 1.38

In 2010, Ishihara revisited Kita's oxidative spirolactonisation as the lead reaction upon which to assess a new breed of chiral iodoarene, pre-hypervalent iodine(III) catalyst, with Ishihara utilising the same conditions as Kita[114]. These catalysts were symmetrical; the inactive iodine(I) and active iodine(III) derivatives are shown in Scheme 1.47 below.

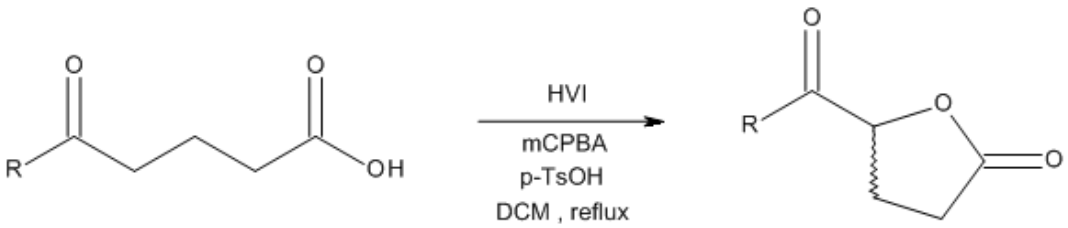


Scheme 1.47

(A) – R = Me, X = OEt, (B) – R = Me, X = OH, (C) – R = Me, X = NH_2, (D) – R = Me, X = NHPh, (E) – R = Me, X = NH[3,5-$(CF_3)_2$Ph], (F) – R = Me, X = NH[3,5-(tBu)$_2$Ph], (G) – R = Me, X = NHMes, (H) – R = Me, X = *N*-pyrr, (I) – R = Me, X = NPh_2, (J) – R = iPr, X = NHMes

Ishihara and co-workers reported good to excellent e.e.s across the range of catalysts, with catalyst F delivering an e.e. of 84% and catalyst G an e.e. of 82%[114]. The latter catalyst was pursued further despite its marginally inferior e.e by virtue of the greatly superior yields it offered (64% vs 36%)[114]. Upon further investigation including solvent and temperature screening, it was determined that lower temperatures (-20 ^{o}C) provided better selectivities, with $CHCl_3$ proving to be the best solvent. Enantioselectivities were boosted to a maximum of 92% under these conditions, a record high enantioselectivity by any hypervalent iodine(III) system[114].

Wirth and co-workers have investigated the asymmetric catalytic potential of hypervalent iodine(III) on Moriarty's 1990 lactonisation. Wirth has not reported any notable enantiomeric excesses for this reaction (Scheme 1.48).



Scheme 1.48

There are no reports of hypervalent iodine catalysts featuring 1,2,4-oxadiazoles. Several HVI catalysts have been synthesised which feature ester or amide functionality. Therefore our research group plan to capitalise on the isosteric nature of 1,2,4-oxadiazoles with such functional groups and synthesise the first chiral, 1,2,4-oxadiazole-containing, hypervalent iodine(III) catalyst. The above lactonisation reaction was chosen as an attractive reaction for screening.

2 Experimental

All reactions monitored and analysed by TLC were done so using Macherey-Nagel 0.2 mm pre-coated Alugram® N/UV_{254} silica gel or alumina gel plates.

Column chromatography was conducted using 60 Å, 70-230 mesh, 63-200 µm silica gel supplied by Sigma-Aldrich. Where necessary, 60 Å, 50-200 µm, basic alumina gel was used and was supplied by Acros.

Analysis by NMR spectroscopy was achieved using Bruker DPX, Bruker AVIII 400 MHz NMR and Bruker AV500 NMR spectrometers.

Analysis by high resolution mass spectrometry was achieved using a Bruker Daltonics micrOTOF-Q Mass Spectrometer.

Infra-red analysis was achieved using a Nicolet 380 FT-IR spectrometer.

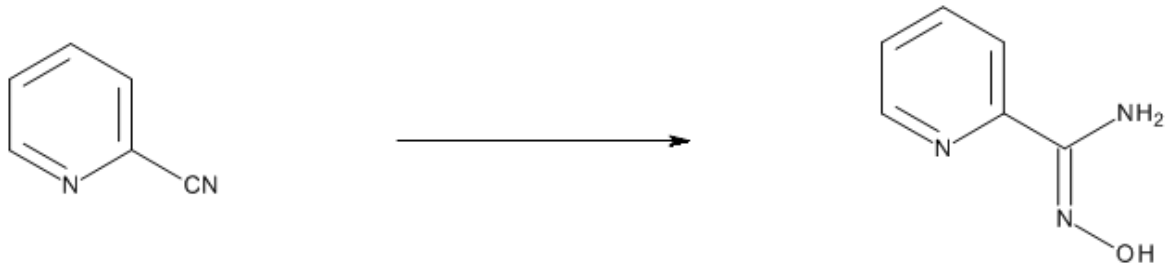
HPLC analysis was determined using a Hewlett-Packard Series 1050 chromatogram with a Chiralpak I-B column.

Melting point determinations were made using a Stuart, SMP10 digital melting point apparatus.

2.1 Experimental Procedures for the Synthesis of Novel 1,2,4-Oxadiazole Containing Ligand Systems

2.1.1 Experimental Procedures for the Synthesis of Ligand Precursor Materials

2.1.1.1 Synthesis of N'-hydroxypyridine-2-carboxamidine



(43)

(44)
$C_6H_7N_3O$
MW = 137.14 g/mol

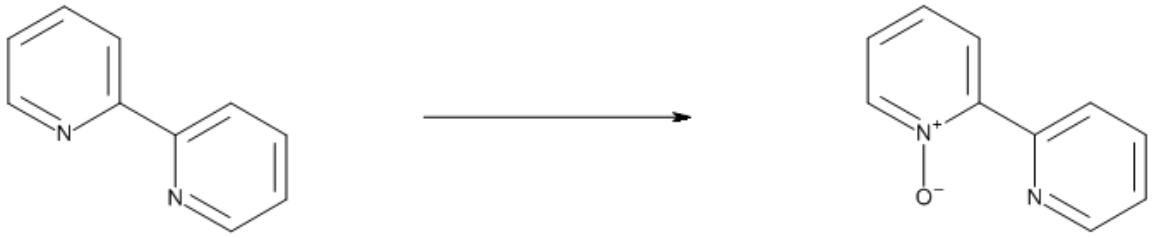
To hydroxylamine hydrochloride (735 mg, 10.57 mmol) in water (25 ml) sodium carbonate (1.12 g, 10.57 mmol) was added in small portions. To this, 2-cyanopyridine **(43)** (1.00 g, 9.61 mmol) in ethanol (25 ml) was added and reaction mixture set to stir at reflux for 24 hours. After this time, the reaction mixture was extracted with dichloromethane (2 x 50 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to yield the product as a white solid (1.01 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ5.67 (2H, broad, N**H**$_2$); δ7.24 (1H, ddd, J=6.0Hz, 3.9Hz, 0.9Hz, Ar**H**); δ7.64 (1H, ddd, J=6.4Hz, 6.4Hz, 1.4Hz, Ar**H**); δ7.84-7.87 (1H, m, Ar**H**); δ8.48-8.51 (1H, m Ar**H**); δ8.58 (1H, broad O**H**).

M.p.: 118-120 ^{o}C (Literature value 115-119 ^{0}C)[92,167,168].

This data is consistent with that reported in the literature[92,167,168].

2.1.1.2 Synthesis of 1-oxido-2-(2-pyridyl)pyridin-1-ium



(45)

(46)
$C_{10}H_8N_2O$
MW = 172.18 g/mol

To 2,2'-bipyridyl **(45)** (2.00 g, 12.80 mmol) in dichloromethane (30 ml) was added in small portions m-chloroperoxybenzoic acid (1.99 g, 11.52 mmol) over 8 hours. After this time the reaction mixture was concentrated by rotary evaporation. The crude product was purified by gravity column chromatography with a 100:1 dichloromethane:methanol solvent system to yield the pure product as a white solid (1.11 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.05 (1H, *appt*. td, J=6.8Hz, 2.2Hz, Ar**H**); δ7.10-7.16 (2H, m, Ar**H**); δ7.60 (1H, *appt.* td, J=7.8Hz, 1.8Hz, Ar**H**); δ7.95 (1H, dd, J=8.1Hz, 2.1Hz, Ar**H**); δ8.11 (1H, d, J=6.4Hz, Ar**H**); δ8.49-8.52 (1H, m, Ar**H**); δ8.69 (1H, d, J=8.0Hz, Ar**H**).

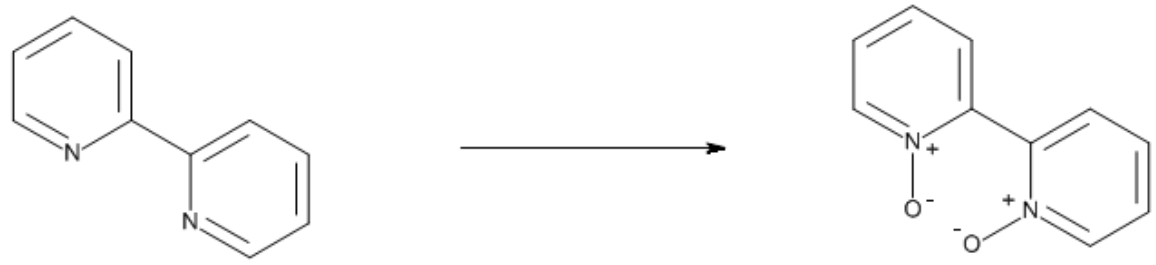
^{13}C NMR (100 MHz, $CDCl_3$): δ123.45 (Ar), 124.55 (Ar), 124.59 (Ar), 124.92 (Ar), 127.02 (Ar), 135.38 (Ar), 139.77 (Ar), 146.35 (Ar), 148.55 (Ar), 148.78 (Ar).

micrOTOF-Q MS m/z $C_{10}H_8N_2O$+Na, calculated 195.0529, observed 195.0536.

IR (cm^{-1}): 760, 848, 1031, 1233, 1249, 1416, 1440, 1461, 1567, 1582, 1615, 3068.

This data is consistent with that reported in the literature[92,167,168].

2.1.1.3 Synthesis of 1-oxido-2-(1-oxidopyridin-1-ium-2-yl)pyridin-1-ium



(45)

(47)
$C_{10}H_8N_2O_2$
MW = 188.18 g/mol

To 2,2'-bipyridyl **(45)** (2.00 g, 12.80 mmol) in glacial acetic acid (16 ml) was added 36% hydrogen peroxide (2 ml). The reaction mixture was stirred at 80^0C for 3 hours after which time a second amount of 36% hydrogen peroxide (5 ml) was added. The reaction mixture was heated for a further 4 hours, cooled to room temperature, poured into acetone (150 ml) and stored at refrigerated temperature overnight. After this time, the precipitates were filtered, washed with acetone and dried under vacuum at RT with no further purification to yield the product as a white crystalline solid (2.25 g, 93%).

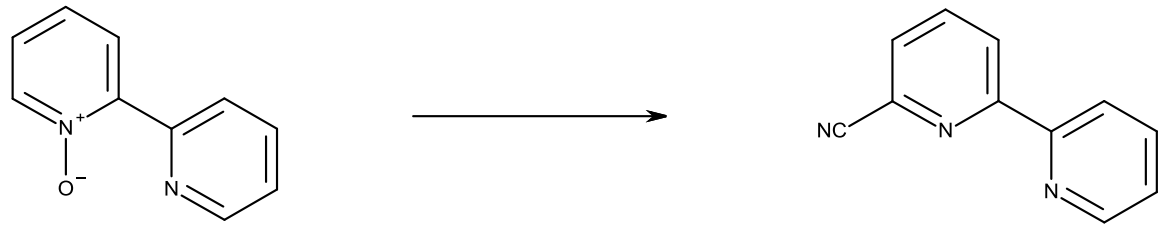
^{1}H NMR (400 MHz, $CDCl_3$): δ7.22-7.29 (4H, m, Ar**H**); δ7.54-7.59 (2H, m, Ar**H**); δ8.22-8.25 (2H, m, Ar**H**).

micrOTOF-Q MS m/z $C_{10}H_8N_2O_2$+Na, calculated 211.0478, observed 211.0482.

IR (cm^{-1}): 722, 763, 836, 958, 1020, 1145, 1251, 1425, 1495.

This data is consistent with that reported in the literature[92,167,168].

2.1.1.4 Synthesis of 6-(2-pyridyl)pyridine-2-carbonitrile



(46)

(48)
$C_{11}H_7N_3$
MW = 181.19 g/mol

To 1-oxido-2-(2-pyridyl)pyridin-1-ium **(46)** (870 mg, 5.05 mmol) in dichloromethane (40 ml) was added benzoyl chloride (0.88 ml, 7.58 mmol) and trimethylsilyl cyanide (1.01 ml, 7.58 mmol) and the mixture set to stir at reflux for 24 hours. After this time, further additions of benzoyl chloride (0.29ml, 2.53 mmol) and trimethylsilyl cyanide (0.34 ml, 2.53 mmol) were made and the reaction mixture stirred at reflux for a further 4 hours. The reaction mixture was then concentrated by rotary evaporation. The crude product was purified by gravity column chromatography with a 100:1 dichloromethane:methanol solvent system to yield the pure product as a white solid (505 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.29 (1H, ddd, J=7.6Hz, 4.7Hz, 1.1Hz, Ar**H**); δ7.62 (1H, dd, J=7.7Hz, 1.0Hz, Ar**H**); δ7.76 (1H, *appt.* td, J=7.8Hz, 1.8Hz, Ar**H**); δ7.86 (1H, t, J=8.0Hz, Ar**H**); δ8.38-8.42 (1H, m, Ar**H**); δ8.57-8.64 (2H, m, Ar**H**).

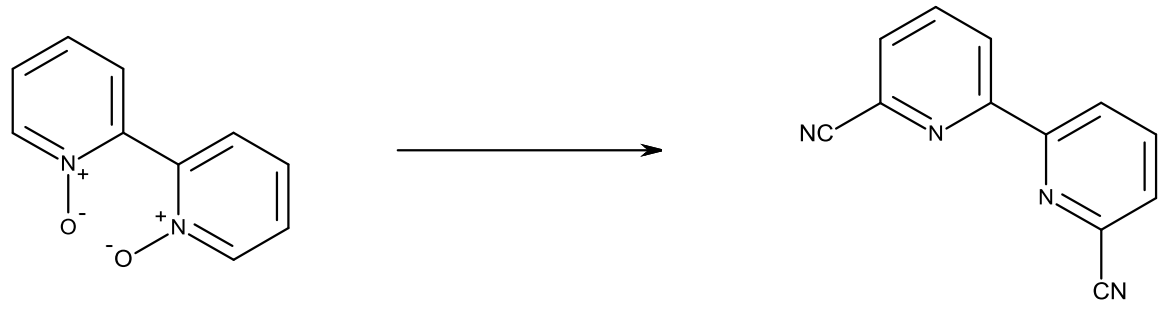
^{13}C NMR (100 MHz, $CDCl_3$): δ120.90 (Ar**C**N), 123.55 (Ar), 124.13 (Ar), 127.48 (Ar), 127.69 (Ar), 128.89 (Ar), 132.26 (Ar), 132.49 (Ar), 136.57 (Ar), 137.25 (Ar), 148.64 (Ar).

micrOTOF-Q MS m/z $C_{11}H_7N_3$+Na, calculated 204.0532, observed 204.0537.

IR (cm^{-1}): 738, 772, 987, 1277, 1424, 1451, 1555, 1582, 2250.

This data is consistent with that reported in the literature[92,167,168].

2.1.1.5 Synthesis of 6-(6-cyano-2-pyridyl)pyridine-2-carbonitrile



(47)

(49)
$C_{12}H_6N_4$
MW = 206.20g/mol

To 1-oxido-2-(1-oxidopyridin-1-ium-2-yl)pyridin-1-ium **(47)** (1.00 g, 5.31 mmol) in dichloromethane (40 ml) was added benzoyl chloride (1.54 ml, 13.28 mmol) and trimethylsilyl cyanide (1.77 ml, 13.28 mmol) and the mixture set to stir at reflux for 24 hours. After this time, further additions of benzoyl chloride (0.31 ml, 2.67 mmol) and trimethylsilyl cyanide (0.36 ml, 2.67 mmol) were made and the reaction mixture stirred at reflux for a further 4 hours. The reaction mixture was then allowed to cool to room temperature, the precipitates filtered and washed with water and then with ethanol and dried under vacuum at RT with no further purification to yield the product as a white crystalline solid (820 mg, 74%).

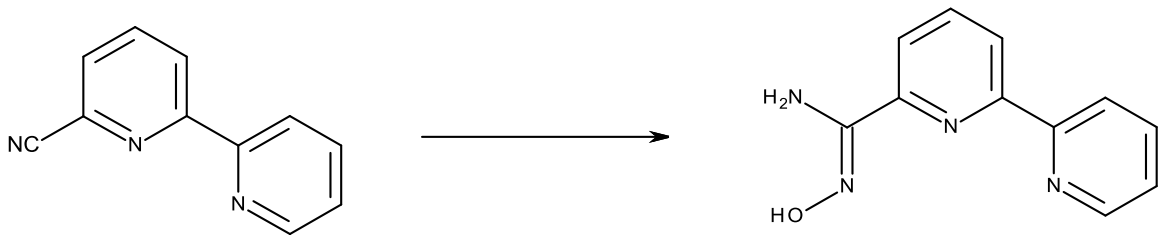
^{1}H NMR (400 MHz, $CDCl_3$): δ7.72 (2H, dd, J=7.8Hz, 0.9Hz, Ar**H**); δ8.03 (2H, t, J=7.8Hz, Ar**H**); δ8.73 (2H, dd, J=8.2Hz, 0.9Hz, Ar**H**).

micrOTOF-Q MS m/z $C_{12}H_6N_4$+Na, calculated 229.0485, observed 229.0488.

IR (cm^{-1}): 734, 800, 988, 1079, 1422, 1433, 1575, 2248.

This data is consistent with that reported in the literature[92,167,168].

2.1.1.6 Synthesis of N'-hydroxy-6-(2-pyridyl)pyridine-2-carboxamidine



(48)

(50)
$C_{11}H_{10}N_4O$
MW = 214.22g/mol

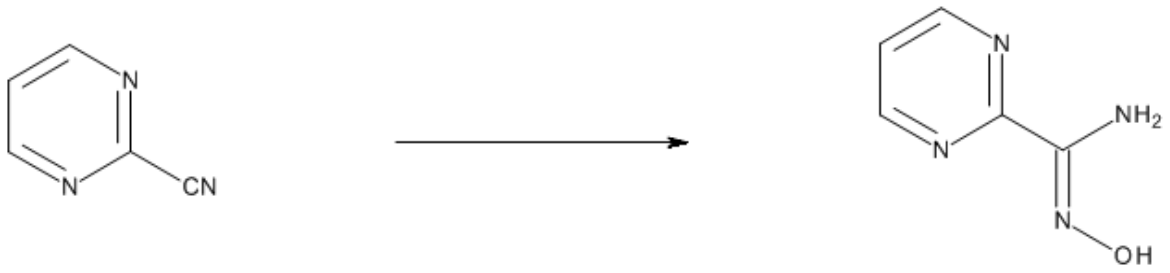
To hydroxylamine hydrochloride (117 mg, 1.69mmol) in water (10 ml) sodium carbonate (179 mg, 1.69mmol) was added in small portions. To this, 6-(2-pyridyl)pyridine-2-carbonitrile **(48)** (280 mg, 1.54 mmol) in ethanol (10 ml) was added and reaction mixture set to stir at reflux for 24 hours. After this time, the reaction mixture was extracted with dichloromethane. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated by rotary evaporation to yield the product as a white solid (297 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ5.69 (2H, broad, N**H$_2$**); δ7.19 (1H, broad, O**H**); δ7.28 (1H, ddd, J=7.6Hz, 4.8Hz, 1.2Hz, Ar**H**); δ7.78 (1H, *appt.* td, J=7.8Hz, 1.2Hz, Ar**H**); δ7.79 (1H, dd, J=7.8Hz, Ar**H**); δ7.89 (1H, dd, J=7.9Hz, 1.0Hz, Ar**H**); δ8.35-8.40 (2H, m, Ar**H**); δ8.62-8.65 (1H, m, Ar**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ119.35 (NH_2**C**=NOH), 120.34 (Ar), 121.12 (Ar), 123.31 (Ar), 136.27 (Ar), 136.92 (Ar), 147.69 (Ar), 148.60 (Ar), 150.40 (Ar), 154.04 (Ar), 154.81 (Ar).

IR (cm^{-1}): 748, 778, 959, 1379, 1429, 1546, 1566, 1580, 1651, 2750-3100, 3400.

2.1.1.7 Synthesis of N'-hydroxypyrimidine-2-carboxamidine



(52)

(53)
$C_5H_6N_4O$
MW = 138.13g/mol

To hydroxylamine hydrochloride (727 mg, 10.46 mmol) in water (15 ml) sodium carbonate (1.11 g, 10.46 mmol) was added in small portions. To this, 2-cyanopyrimidine **(52)** (1.00 g, 9.51 mmol) in ethanol (15 ml) was added and reaction mixture set to stir at reflux for 24 hours. After this time, the reaction mixture was cooled to 0 ^{0}C. The precipitates were filtered, washed with water and dried under vacuum at RT to yield the product as a yellow crystalline solid (897 mg, 68%).

^{1}H NMR (400 MHz, d-DMSO): δ5.85 (2H, s, N**H$_2$**); δ7.51 (1H, t, J=1.2Hz, Ar**H**); δ8.84 (2H, d, J=4.8Hz Ar**H**); δ10.21 (1H, s, O**H**).

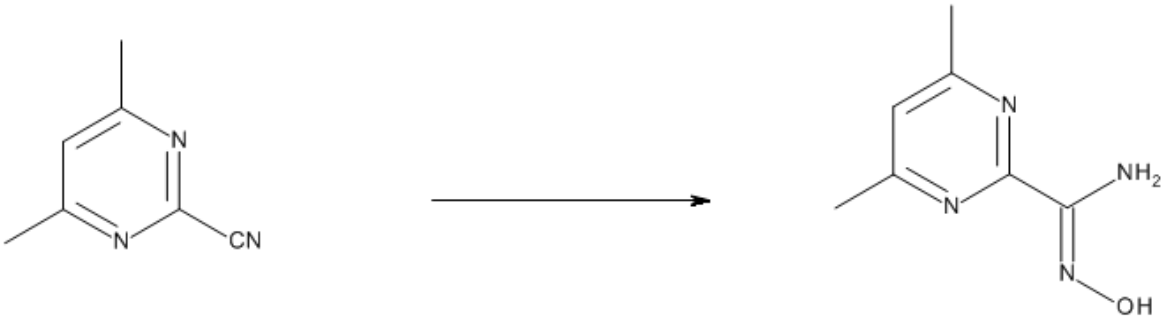
^{13}C NMR (100 MHz, d-DMSO): δ121.69 (NH$_2$**C**=NOH), 149.42 (Ar), 157.73 (Ar), 158.70 (Ar).

IR (cm^{-1}): 789, 808, 841, 939, 1375, 1471, 1563.

micrOTOF-Q MS m/z $C_5H_6N_4O$+Na, calculated 161.0434, observed 161.0438.

M.p.: 258-260 ^{o}C. (Literature value 262 ^{0}C)[130].

2.1.1.8 Synthesis of N'-hydroxy-4,6-dimethyl-pyrimidine-2-carboxamidine



(54)

(55)
$C_7H_{10}N_4O$
MW = 166.18g/mol

To hydroxylamine hydrochloride (574 mg, 8.26 mmol) in water (30 ml) sodium carbonate (875 mg, 8.26 mmol) was added in small portions. To this, 4,6-dimethylpyrimidine-2-carbonitrile **(54)** (1.00 g, 7.51 mmol) in ethanol (30 ml) was added and reaction mixture set to stir at reflux for 24 hours. After this time, the reaction mixture was extracted with dichloromethane. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated by rotary evaporation to yield the product as a light yellow solid (872 mg, 70%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.55 (6H, s, C**H$_3$**); δ5.63 (2H, s, N**H$_2$**); δ6.87 (1H, s, O**H**); δ7.06 (1H, s, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ24.04 (C**H$_3$**), 120.21 (NH_2**C**=NOH), 149.96 (Ar), 157.13 (Ar), 167.03 (Ar).

IR (cm^{-1}): 910, 943, 1257, 1347, 1458, 1533, 1575, 1594, 1673, 3207.

micrOTOF-Q MS m/z $C_7H_{10}N_4O$+Na, calculated 189.0747, observed 189.0752.

2.1.1.9 Synthesis 1,4-dibromobutane-2,3-dione

(56)

(57)
$C_4H_4Br_2O_2$
MW = 243.88g/mol

2,3-Butanedione **(56)** (1.00ml, 11.39mmol) was set to stir at reflux under an atmosphere of nitrogen, in chloroform (10ml). Bromine (0.59ml, 22.79mmol) in chloroform (10ml) was added dropwise and the reaction mixture set to stir at reflux for 24 hours. The solvents were removed by rotary evaporation.

The crude product was purified by recrystallisation from chloroform to yield the pure product as a yellow crystalline solid (2.52g, 91%).

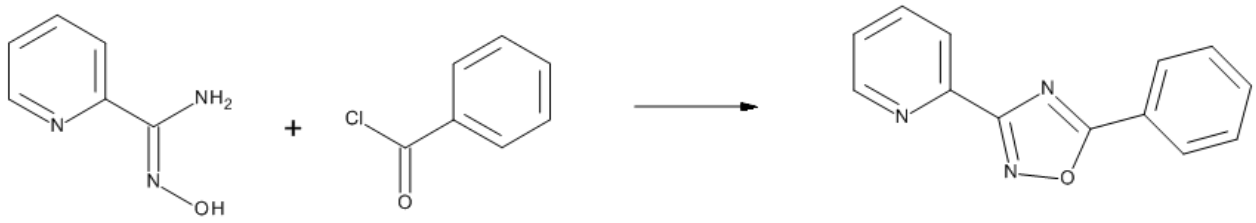
^{1}H NMR (400MHz, $CDCl_3$): δ4.34 (4H, s, C**H_2**).

^{13}C NMR (100MHz, $CDCl_3$):δ28.45 (**C**H_2); 187.98 (**C**=O).

This data is consistent with that reported in the literature[92,167,168].

2.1.2 Experimental Procedures for the Synthesis of 1,2,4-Oxadiazole Ligands

2.1.2.1 Synthesis of 5-phenyl-3-(2-pyridyl)-1,2,4-oxadiazole



(44)

(58)
$C_{13}H_9N_3O$
MW = 223.23g/mol

To benzoyl chloride (0.47 ml, 4.07 mmol) in xylene (25 ml), N'-hydroxypyridine-2-carboxamidine **(44)** (507 mg, 3.70 mmol) and pyridine (0.33 ml, 4.07 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a light brown solid (268 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.49 (1H, ddd, J=6.1Hz, 4.1Hz, 0.8Hz, Ar**H**); δ7.59 (2H, t, J=6.0Hz, Ar**H**); δ7.63-7.68 (1H, m, Ar**H**); δ7.91 (1H, *appt.* td, J=6.2Hz, 1.4Hz, Ar**H**); δ8.24-8.27 (1H, m, Ar**H**); δ8.31-8.34 (2H, m, Ar**H**); δ8.87-8.89 (1H, m, Ar**H**).

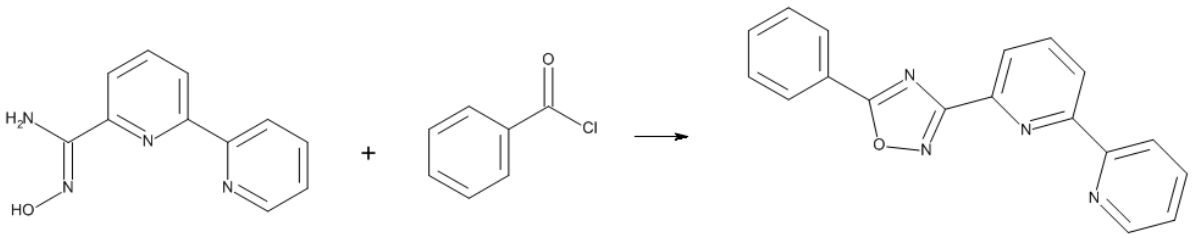
^{13}C NMR (100 MHz, $CDCl_3$): δ123.26 (Ar), 124.04 (Ar), 125.51 (Ar), 128.37 (Ar), 129.10 (Ar), 132.95 (Ar), 137.04 (Ar), 146.51 (Ar), 150.47 (Ar), 168.81 (Ar), 176.51 (Ar).

IR (cm^{-1}): 724, 744, 900, 1361, 1448, 1559.

M.p.: 133-135 ^{o}C (Literature value 128-130 ^{0}C)[131].

This data is consistent with that reported in the literature[80,131].

2.1.2.2 Synthesis of 5-phenyl-3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazole



(50)

(59)
$C_{18}H_{12}N_4O$
MW = 300.31g/mol

To benzoyl chloride (0.30 ml, 2.57 mmol) in xylene (25 ml), (N'-hydroxy-6-(2-pyridyl)-pyridine-2-carboxamidine **(50)** (500 mg, 2.34 mmol) and pyridine (0.21 ml, 2.57 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a white crystalline solid (650 mg, 98%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.32-7.38 (1H, m, Ar**H**); δ7.54-7.64 (3H, m, Ar**H**); δ7.83-7.90 (1H, m, Ar**H**); δ8.01 (1H, *appt.* td, J=7.8Hz, 1.2Hz, Ar**H**); δ8.24 (1H, dd, J=7.6Hz, 1.0Hz, Ar**H**); δ8.26-8.31 (2H, m, Ar**H**); δ8.60 (1H, dd, J=8.2Hz, 0.9Hz, Ar**H**); δ8.67 (1H, t, J=8.2H, Ar**H**); δ8.70-8.73 (1H, m, Ar**H**).

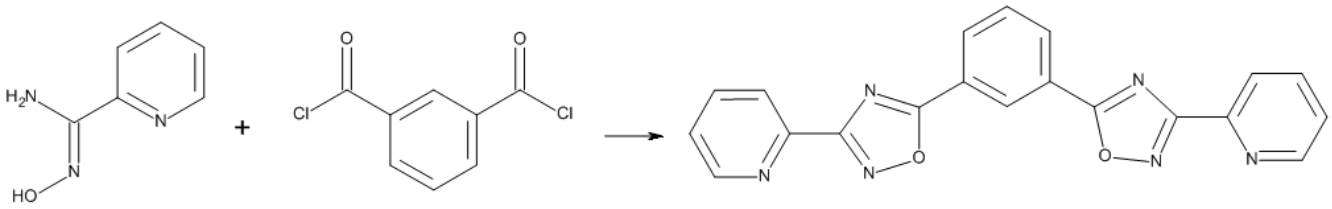
^{13}C NMR (100MHz, $CDCl_3$): 121.95 (Ar), 122.94 (Ar), 123.44 (Ar), 124.10 (Ar), 124.25 (Ar), 128.34 (Ar), 129.15 (Ar), 132.97 (Ar), 137.12 (Ar), 138.05 (Ar), 146.04 (Ar), 149.09 (Ar), 155.30 (Ar), 156.75 (Ar), 168.87 (Ar), 176.38 (Ar).

micrOTOF-Q MS m/z $C_{18}H_{12}N_4O$+H calculated 301.1070, observed 301.1085.

IR (cm^{-1}): 677, 681, 731, 782, 793, 1017, 1261, 1344, 1426, 1562.

M.p.: 142-145 ^oC.

2.1.2.3 Synthesis of 3-(2-pyridyl)-5-[3-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(44)

(60)
$C_{20}H_{12}N_6O_2$
MW = 368.35g/mol

To isophthaloyl chloride (372 mg, 1.83 mmol) in xylene (25 ml), N'-hydroxypyridine-2-carboxamidine **(44)** (500 mg, 3.65 mmol) and pyridine (0.65 ml, 8.03 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a pale yellow crystalline solid (182 mg, 27%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.50 (2H, dd, J=7.4Hz, 5.4Hz, Ar**H**); δ7.80 (1H, t, J=7.8Hz, Ar**H**); δ7.93 (2H, t, J=7.7Hz, Ar**H**); δ8.28 (2H, d, J=7.8Hz, Ar**H**); δ8.55 (2H, d, J=7.8Hz, Ar**H**); δ8.88 (2H, d, J=4.8Hz, Ar**H**); δ9.23 (1H, s, Ph**H**).

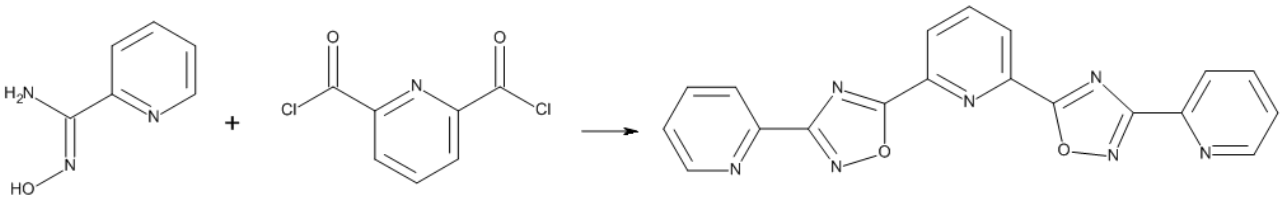
^{13}C NMR (100MHz, $CDCl_3$): δ123.42 (Ar), 125.25 (Ar), 125.76 (Ar), 128.10 (Ar), 130.19 (Ar), 132.28 (Ar), 137.22 (Ar), 146.22 (Ar), 150.57 (Ar), 169.03 (Ar), 175.26 (Ar).

micrOTOF-Q MS m/z $C_{20}H_{12}N_6O_2$+Na, calculated 391.0901, observed 391.0915.

IR (cm^{-1}): 676, 716, 734, 766, 995, 1286, 1353, 1552, 1610.

M.p.: 226-229 ^{o}C.

2.1.2.4 Synthesis of 3-(2-pyridyl)-5-[6-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(44)

(61)
$C_{19}H_{11}N_7O_2$
MW = 369.34g/mol

To 2,6-pyridine dicarbonyl chloride (373 mg, 1.83 mmol) in xylene (25 ml), N'-hydroxypyridine-2-carboxamidine **(44)** (500 mg, 3.65 mmol) and pyridine (0.74 ml, 9.13 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol dried yielding the product a brown crystalline solid (203 mg, 15%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.51 (2H, dd, J=7.8Hz, 4.8Hz, Ar**H**); δ7.94 (2H, t, J=7.8Hz, Ar**H**); δ8.24 (1H, t, J=7.8Hz, Ar**H**); δ8.33 (2H, d, J=7.8Hz, Ar**H**); δ8.68 (2H, d, J=7.8Hz, Ar**H**); δ8.86-8.90 (2H, m, Ar**H**).

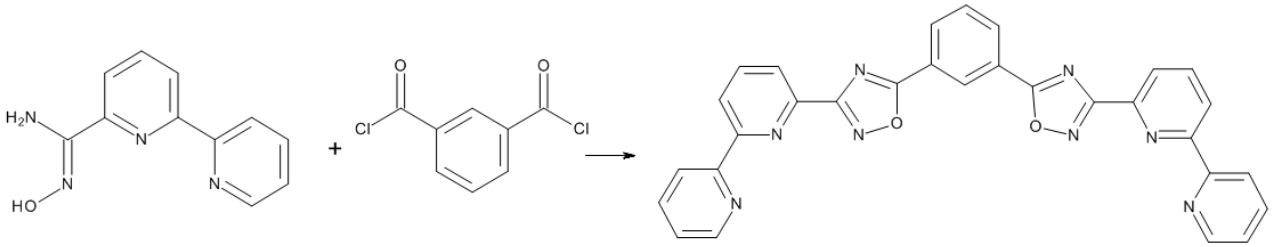
^{13}C NMR (100MHz, $CDCl_3$): δ123.60 (Ar), 125.89 (Ar), 127.29 (Ar), 137.33 (Ar), 139.14 (Ar), 144.38 (Ar), 145.87 (Ar), 150.48 (Ar), 169.02 (Ar), 174.06 (Ar).

micrOTOF-Q MS m/z $C_{19}H_{11}N_7O_2$+Na, calculated 392.0864, observed 392.0866.

IR (cm^{-1}): 619, 650, 684, 710, 728, 739, 992, 1149, 1360, 1551.

M.p.: 241-243 ^oC.

2.1.2.5 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[3-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(50)

(62)
$C_{30}H_{18}N_8O_2$
MW = 522.52g/mol

To isophthaloyl chloride (237 mg, 1.17 mmol) in xylene (25 ml), (N'-hydroxy-6-(2-pyridyl)-pyridine-2-carboxamidine **(50)** (500 mg, 2.34 mmol) and pyridine (0.42 ml, 5.15 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a pale yellow crystalline solid (213 mg, 35%).

^{1}H NMR (400MHz, pyridine-d): δ7.27 (2H, t, J=7.2Hz, Ar**H**); δ7.73 (3H, t, J=7.7Hz, Ar**H**); δ8.01 (2H, dd, J=7.8Hz, Ar**H**); δ8.31 (2H, d, J=7.6Hz, Ar**H**); δ8.47 (2H, d, J=7.8Hz, Ar**H**); δ8.74-8.78 (2H, m, Ar**H**); δ8.84 (4H, t, J=7.8Hz, Ar**H**); δ9.17 (1H, s, Ar**H**).

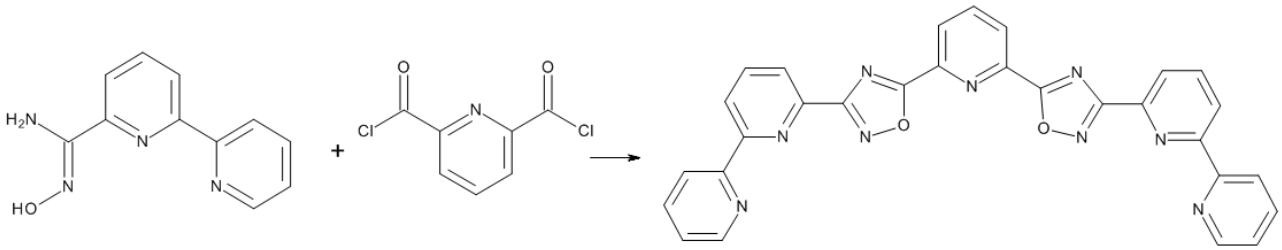
^{13}C NMR (100MHz, pyridine-d): δ121.57 (Ar), 122.74 (Ar), 123.79 (Ar), 123.95 (Ar), 124.49 (Ar), 125.32 (Ar), 127.58 (Ar), 130.52 (Ar), 132.16 (Ar), 137.03 (Ar), 138.34 (Ar), 146.18 (Ar), 155.28 (Ar), 159.87 (Ar), 169.33 (Ar), 175.11 (Ar).

micrOTOF-Q MS m/z $C_{30}H_{18}N_8O_2$+H calculated 523.1626, observed 523.1648.

IR (cm^{-1}): 634, 679, 734, 751, 786, 817, 1343, 1411, 1424, 1550.

M.p.: 255-260 ^oC.

2.1.2.6 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[6-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(50)

(63)
$C_{29}H_{17}N_9O_2$
MW = 523.50g/mol

To 2,6-pyridine dicarbonyl chloride (339 mg, 1.17 mmol) in xylene (25 ml), (N'-hydroxy-6-(2-pyridyl)-pyridine-2-carboxamidine **(50)** (500 mg, 2.34 mmol) and pyridine (0.47 ml, 5.85 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol dried yielding the product as a fine tan powder (66 mg, 11%).

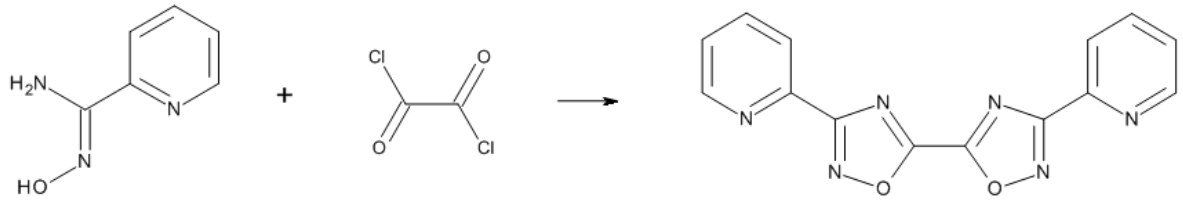
^{1}H NMR (400MHz, d-DMSO): δ7.56 (2H, ddd, J=7.5Hz, 4.8Hz, 1.1Hz, Ar**H**); δ8.07 (2H, *appt.* td, J=7.6Hz, 1.7Hz, Ar**H**); δ8.27 (2H, t, J=7.7Hz, Ar**H**); δ8.33 (2H, dd, J=7.6Hz, 1.1Hz, Ar**H**); δ8.52 (1H, t, J=7.7Hz, Ar**H**); δ8.56 (2H, t, J=7.9Hz, Ar**H**); δ8.65 (2H, dd, J=7.9Hz, 1.1Hz, Ar**H**); δ8.72 (2H, d, J=7.8Hz, Ar**H**); δ8.76-8.79 (2H, m, Ar**H**).

micrOTOF-Q MS m/z $C_{29}H_{17}N_9O_2$+Na, calculated 546.1397, observed 546.1396.

IR (cm^{-1}): 991, 1082, 1173, 1264, 1347, 1360, 1426, 1513, 1553, 1586.

M.p.: 250-252 ^oC.

2.1.2.7 Synthesis of 3-(2-pyridyl)-5-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(44)

(64)
$C_{14}H_8N_6O_2$
MW = 292.25g/mol

To oxalyl chloride (0.15 ml, 1.83 mmol) in xylene (25 ml), N'-hydroxypyridine-2-carboxamidine **(44)** (500 mg, 3.65 mmol) and pyridine (0.74 ml, 9.13 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a yellow crystalline solid (102 mg, 10%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.54 (2H, ddd, J=7.6Hz, 4.7Hz, 0.9Hz, Ar**H**); δ7.95 (2H, *appt.* td, J=7.9Hz, 1.6Hz, Ar**H**); δ8.29 (2H, t, J=7.8Hz, Ar**H**); δ8.87-8.90 (2H, m, Ar**H**).

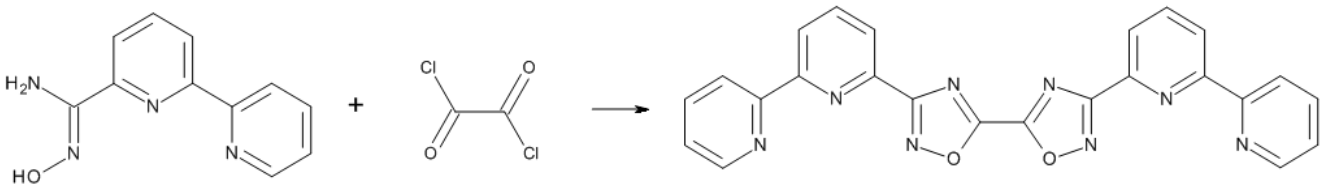
^{13}C NMR (100MHz, $CDCl_3$): δ123.79 (Ar), 126.42 (Ar), 137.41 (Ar), 144.99 (Ar), 150.80 (Ar), 163.34 (Ar), 169.56 (Ar).

micrOTOF-Q MS m/z $C_{14}H_8N_6O_2$+Na, calculated 315.0612, observed 315.0601.

IR (cm^{-1}): 618, 714, 721, 742, 801, 1172, 1343, 1355, 1417, 1521.

M.p.: 260-263 ^{o}C.

2.1.2.8 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(50) **(65)**
$C_{24}H_{14}N_8O_2$
MW = 446.42g/mol

To oxalyl chloride (0.10 ml, 1.17 mmol) in xylene (25 ml), (N'-hydroxy-6-(2-pyridyl)-pyridine-2-carboxamidine **(50)** (500 mg, 2.34 mmol) and pyridine (0.47 ml, 5.85 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a fine tan powder (116 mg, 8%).

^{1}H NMR (400MHz, pyridine-d): δ7.07 (2H, dd, J=7.6Hz, 5.0Hz, Ar**H**); δ7.55 (2H, *appt.* td, J=7.8Hz, 1.4Hz, Ar**H**); δ7.77 (2H, t, J=7.8Hz, Ar**H**); δ8.10 (2H, t, J=7.6Hz, Ar**H**); δ8.53-8.56 (2H, m, Ar**H**); δ8.60 (4H, t, J=8.1Hz, Ar**H**).

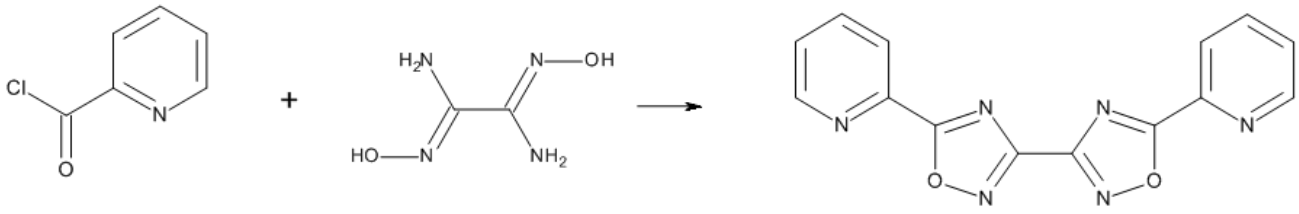
^{13}C NMR (100MHz, pyridine-d): δ122.69 (Ar), 123.87 (Ar), 125.16 (Ar), 125.74 (Ar), 136.92 (Ar), 138.25 (Ar), 139.67 (Ar), 146.08 (Ar), 156.17 (Ar), 158.17 (Ar), 165.41 (Ar), 171.00 (Ar).

micrOTOF-Q MS m/z $C_{24}H_{14}N_8O_2$+H calculated 447.1312, observed 447.1320.

IR (cm^{-1}): 633, 688, 730, 751, 789, 1173, 1263, 1424, 1523, 1581.

M.p.: 281-283 ^{o}C.

2.1.2.9 Synthesis of 5-(2-pyridyl)-3-[5-(2-pyridyl)-1,2,4-oxadiazol-3-yl]-1,2,4-oxadiazole



(66) **(67)**

(68)
$C_{14}H_8N_6O_2$
MW = 292.25g/mol

To pyridine-2-carbonyl chloride hydrochloride **(66)** (1.51 g, 8.47 mmol) in toluene (50 ml), pyridine (0.75 ml, 9.32 mmol) was added and the reaction mixture allowed to stir for 5 minutes. After this time, diaminoglyoxime **(67)** (1.00g mg, 8.47 mmol) and a second aliquot of pyridine (0.75 ml, 9.32 mmol) were added and the reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water, washed with ethanol and dried under vacuum yielding the product as a light yellow solid (189 mg, 8%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.62 (2H, ddd, J=7.6Hz, 4.8Hz, 1.2Hz, Ar**H**); δ8.01 (2H, *appt.* td, J=7.8Hz, 1.2Hz, Ar**H**); δ8.48 (2H, *appt.* dt, J=7.9Hz, 1.1Hz, Ar**H**); δ8.90-8.94 (2H, m, Ar**H**).

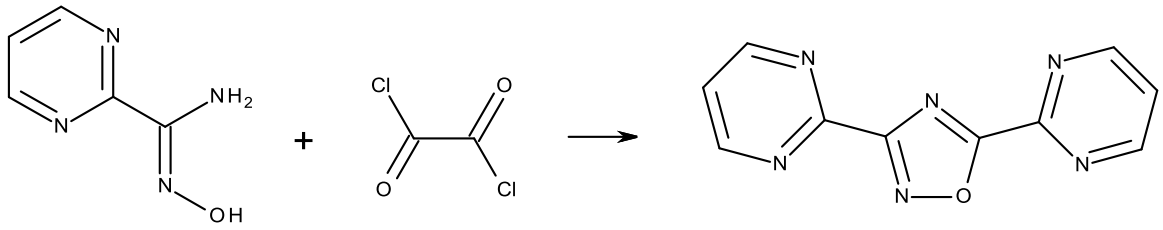
^{13}C NMR (100MHz, $CDCl_3$): δ124.88 (Ar), 125.31 (Ar), 127.35 (Ar), 128.24 (Ar), 129.03 (Ar), 137.54 (Ar), 150.82 (Ar).

IR (cm^{-1}): 723, 738, 799, 910, 1236, 1412, 1439, 1456, 1563, 1573.

micrOTOF-Q MS m/z $C_{14}H_8N_6O_2$+Na, calculated 315.0601, observed 315.0605.

M.p.: 282-284 ^{o}C.

2.1.2.10 Synthesis of 3,5-di(pyrimidin-2-yl)-1,2,4-oxadiazole



(53)

(70)
$C_{10}H_6N_6O$
MW = 226.19g/mol

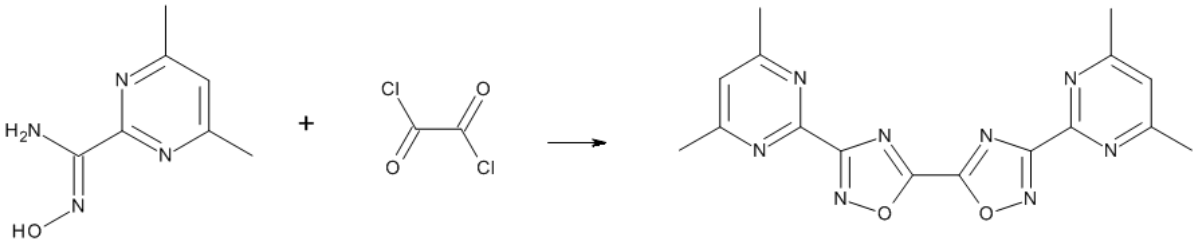
To oxalyl chloride (0.20 ml, 2.33 mmol) in xylene (20 ml), N'-hydroxypyrimidine-2-carboxamidine **(53)** (643 mg, 4.66 mmol) and pyridine (0.90 ml, 11.64 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a pale yellow solid (45 mg, 3%).

^{1}H NMR (400MHz, d-DMSO): δ7.78 (1H, t, J=4.9Hz, Ar**H**); δ7.85 (1H, t, J=4.9Hz, Ar**H**); δ9.10 (2H, d, J=4.9Hz, Ar**H**); δ9.16 (2H, d, J=4.9Hz, Ar**H**).

micrOTOF-Q MS m/z $C_{10}H_6N_6O$+Na, calculated 249.0495, observed 249.0485.

M.p.: 294-296 ^{o}C.

2.1.2.11 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(55)

(71)
$C_{16}H_{14}N_8O_2$
MW = 350.33g/mol

To oxalyl chloride (0.28 ml, 3.31 mmol) in xylene (50 ml), N'-hydroxy-4,6-dimethyl-pyrimidine-2-carboxamidine **(55)** (1.10 g, 6.62 mmol) and pyridine (1.07 ml, 13.24 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water and ethanol and dried yielding the product as a light yellow solid (80 mg, 3%).

^{1}H NMR (400MHz, $CDCl_3$): δ12.67 (12H, s, C**H$_3$**); δ7.24 (2H, s, Ar**H**).

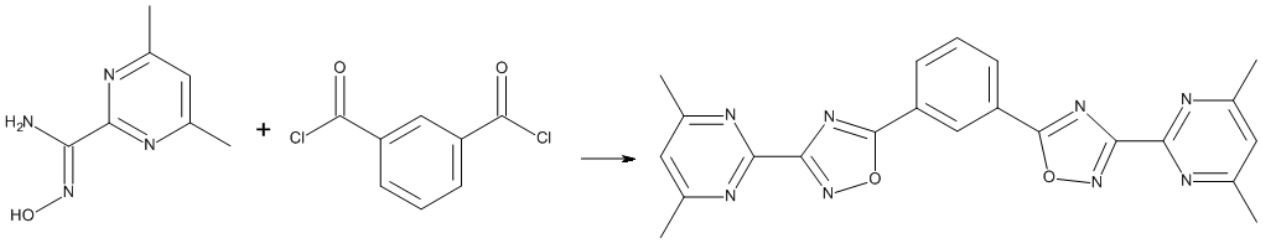
^{13}C NMR (100MHz, $CDCl_3$): δ24.14 (**C**H$_3$), 122.02 (Ar), 154.42 (Ar), 163.67 (Ar), 168.42 (Ar), 169.25 (Ar).

IR (cm^{-1}): 733, 850, 956, 994, 1152, 1239, 1344, 1433, 1523, 1594.

micrOTOF-Q MS m/z $C_{16}H_{14}N_8O_2$+Na, calculated 373.1132, observed 373.1133.

M.p.: >300 ^{o}C.

2.1.2.12 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[3-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(55)

(72)
$C_{22}H_{18}N_8O_2$
MW = 426.43g/mol

To isophthaloyl chloride (611 mg, 3.01 mmol) in toluene (50 ml), N'-hydroxy-4,6-dimethyl-pyrimidine-2-carboxamidine **(55)** (1.00 g, 6.02 mmol) and pyridine (0.97 ml, 12.04 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water, washed with ethanol dried with no fupurification to yield the product a pale grey solid (183 mg, 7%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.69 (12H, s, C**H$_3$**); δ7.23 (2H, s, Ar**H**); δ7.80 (1H, t, J=7.7Hz, Ar**H**); δ8.60 (2H, dd, J=8.0Hz, 1.4Hz, Ar**H**); δ9.26-9.28 (1H, m, Ar**H**).

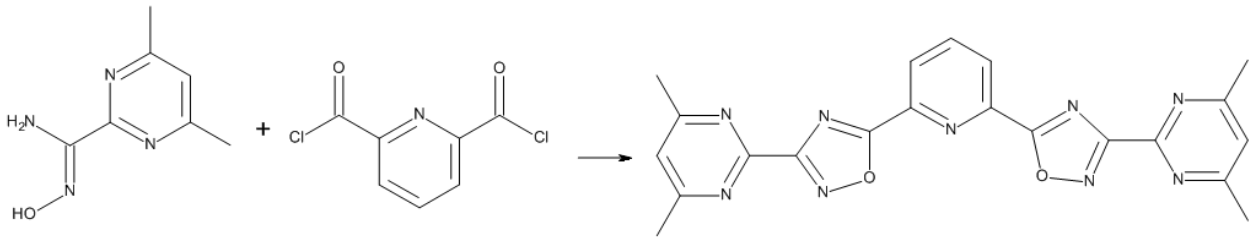
^{13}C NMR (100MHz, $CDCl_3$): δ24.25 (**C**H$_3$), 121.55 (Ar), 124.98 (Ar), 128.36 (Ar), 130.04 (Ar), 132.64 (Ar), 155.47 (Ar), 168.22 (Ar), 168.70 (Ar), 175.75 (Ar).

IR (cm^{-1}): 740, 858, 1241, 1259, 1342, 1368, 1387, 1428, 1559, 1590.

micrOTOF-Q MS m/z $C_{22}H_{18}N_8O_2$+Na, calculated 449.1445, observed 449.1452.

M.p.: 264-266 ^{o}C.

2.1.2.13 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[6-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(55)

(73)
$C_{21}H_{17}N_9O_2$
MW = 427.42g/mol

To pyridine-2-dicarbonyl dichloride (614 mg, 3.01 mmol) in toluene (50 ml), N'-hydroxy-4,6-dimethyl-pyrimidine-2-carboxamidine **(55)** (1.00 g, 6.02 mmol) and pyridine (0.97 ml, 12.04 mmol) were added. The reaction mixture was set to stir at reflux for 24 hours. After this time the precipitates were collected by vacuum filtration, washed with water, washed with ethanol and dried yielding the product a pale orange crystalline solid (98 mg, 4%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.70 (12H, s, C**H$_3$**); δ7.25 (2H, s, Ar**H**); δ8.22 (1H, t, J=7.7Hz, Ar**H**); δ8.72 (2H, d, J=7.8Hz, Ar**H**).

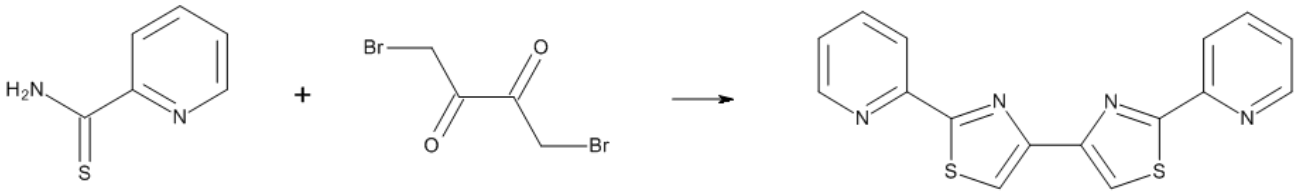
^{13}C NMR (100MHz, $CDCl_3$): δ24.25 (**C**H$_3$), 121.64 (Ar), 127.54 (Ar), 138.56 (Ar), 144.21 (Ar), 155.29 (Ar), 168.32 (Ar), 168.78 (Ar), 174.60 (Ar).

IR (cm^{-1}): 742, 857, 992, 1079, 1124, 1240, 1345, 1386, 1417, 1589.

micrOTOF-Q MS m/z $C_{21}H_{17}N_9O_2$+Na, calculated 450.1397, observed 450.1407.

M.p.: 262-264 ^{o}C.

2.1.2.14 Synthesis of 2-(2-pyridyl)-4-[2-(2-pyridyl)thiazol-4-yl]thiazole



(74) **(57)**

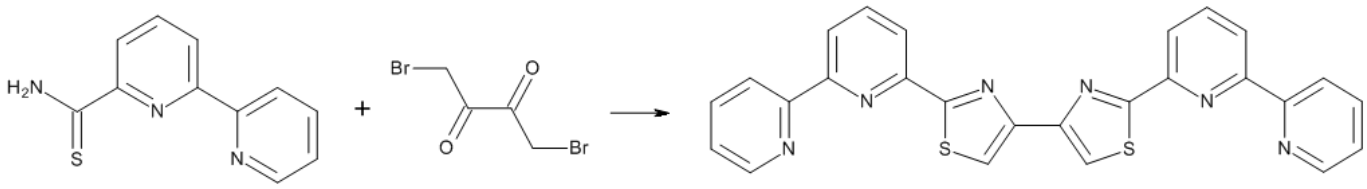
(75)
$C_{16}H_{10}N_4S_2$
MW = 322.41g/mol

Pyridine-2-carbothioamide **(74)** and 1,4-dibromobutane-2,3-dione **(57)** were set to stir in methanol at reflux for 1 hour. The reaction mixture was filtered and the precipitates washed with water, ethanol and ether and air-dried for 1 hour, yielding the product as a pale tan solid (67 mg, 29%).

^{1}H NMR (400MHz, d-DMSO): δ7.56 (2H, ddd, J=7.4Hz, 4.8Hz, 1.1Hz, Ar**H**); δ8.05 (2H, *appt.* td, J=8.2Hz, 1.8Hz, Ar**H**); δ8.25 (2H, s, Ar**H**); δ8.27 (2H, *appt.* dt, J=7.9Hz, 1.0Hz, Ar**H**); δ8.68-8.71 (2H, m, Ar**H**).

This data is consistent with that reported in the literature[94].

2.1.2.15 Synthesis of 2-[6-(2-pyridyl)-2-pyridyl]-4-[2-[6-(2-pyridyl)-2-pyridyl]thiazol-4-yl]thiazole



(76) **(57)**

(77)
$C_{26}H_{16}N_6S_2$
MW = 476.57g/mol

6-(2-Pyridyl)pyridine-2-carbothioamide **(76)** and 1,4-dibromobutane-2,3-dione **(57)** were set to stir in methanol at reflux for 1 hour. The reaction mixture was filtered and the precipitates washed with water, ethanol, and ether and air-dried for 1 hour, yielding the product as a pale tan solid (120 mg, 19%).

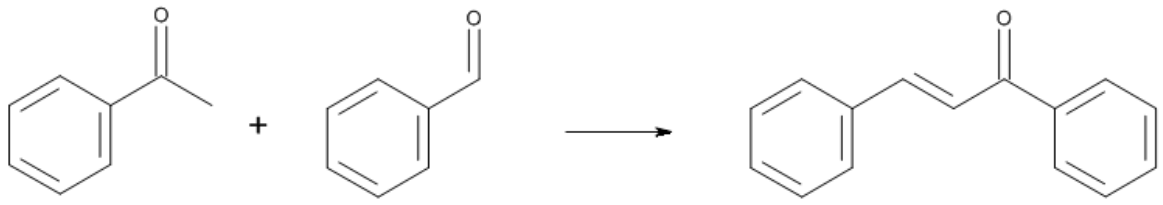
^{1}H NMR (400MHz, d-DMSO): δ7.46-7.60 (2H, m, Ar**H**); δ7.89-8.90 (14H, m, Ar**H**).

This data is consistent with that reported in the literature[94].

2.2 Experimental Procedures for the Synthesis of Extended Isothiazole Dioxides

2.2.1 Experimental Procedures for the Synthesis of 3-Phenyl-α,β-unsaturated Arylketones

2.2.1.1 Synthesis of 1,3-diphenylprop-2-en-1-one



(78) **(79)** **(80)**
$C_{15}H_{12}O$
MW = 208.25g/mol

To benzaldehyde **(79)** (6.31 ml, 62.00 mmol) and acetophenone **(78)** (7.25 ml, 62.00 mmol) in ethanol (25 ml) was added sodium hydroxide (744 mg, 18.60 mmol) in water (2 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes. After this time, the reaction mixture was cooled in an ice bath and precipitates collected by vacuum filtration. The crude product was purified by recrystallisation from ethanol to yield the pure product as a yellow crystalline solid (7.82 g, 61%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.39-7.62 (3H, m, Ph**H**); δ7.48-7.62 (4H, m, Ph**H**, Ph**H**C); δ7.63-7.68 (2H, m, Ph**H**); δ7.82 (1H, d, J=15.7Hz, C**H**CO); δ8.03 (2H, d, J=7.6Hz, Ph**H**).

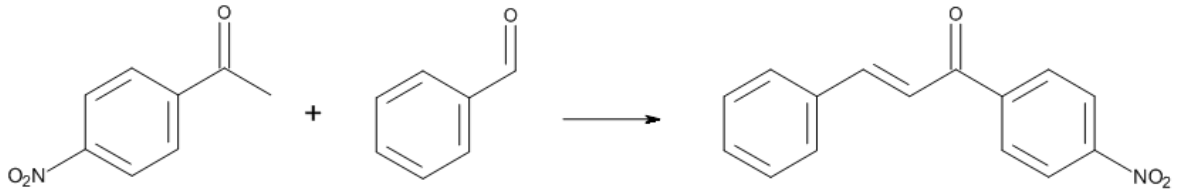
^{13}C NMR (100MHz, $CDCl_3$): δ122.09 (PhH**C**), 128.48 (Ph**C**), 128.54 (Ph**C**), 128.66 (Ph**C**), 128.99 (Ph**C**), 130.59 (**C**HCO), 132.83 (Ph**C**), 134.89 (Ph**C**), 138.22 (Ph**C**), 144.90 (Ph**C**), 190.62 (**C**=O).

micrOTOF-Q MS m/z $C_{15}H_{12}O$+Na, calculated 231.0780, observed 231.0789.

IR (cm^{-1}): 666, 686, 743, 976, 1014, 1215, 1337, 1573, 1602, 1660.

M.p.: 57-59 ^{o}C. (Literature value 57 ^{0}C)[132].
This data is consistent with that reported in the literature[132,169].

2.2.1.2 Synthesis of 1-(4-nitrophenyl)-3-phenyl-prop-2-en-1-one



(81) **(79)** **(82)**
$C_{15}H_{11}NO_2$
MW = 237.25g/mol

To benzaldehyde **(79)** (15.43 ml, 151.38 mmol) and 4-nitroacetophenone **(81)** (25.00 g, 151.38 mmol) in ethanol (75 ml) was added sodium hydroxide (1.82 g, 45.41 mmol) in water (10 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes. After this time, the reaction mixture was cooled in an ice bath for 15 minutes and precipitates collected by vacuum filtration with no further purification required to yield the product as a yellow crystalline solid (6.04 g, 16%).

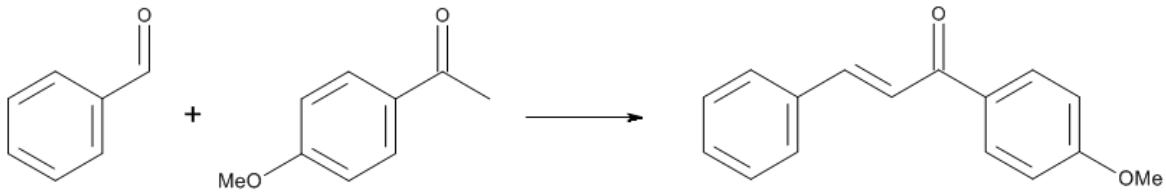
^{1}H NMR (400MHz, $CDCl_3$): δ7.44-7.52 (4H, m, Ph**H**, Ph**H**C); δ7.64-7.70 (2H, m, Ph**H**); δ7.86 (1H, d, J=15.7Hz, C**H**CO); δ8.15 (2H, d, J=8.6Hz, Ar**H**); δ8.37 (2H, d, J=8.6Hz, Ar**H**).

IR (cm^{-1}): 843, 999, 1024, 1205, 1307, 1319, 1332, 1512, 1588.

M.p.: 150-152 ^{o}C. (Literature value 146-147 ^{0}C)[133].

This data is consistent with that reported in the literature[133,169].

2.2.1.3 Synthesis of 1-(4-methoxyphenyl)-3-phenyl-prop-2-en-1-one



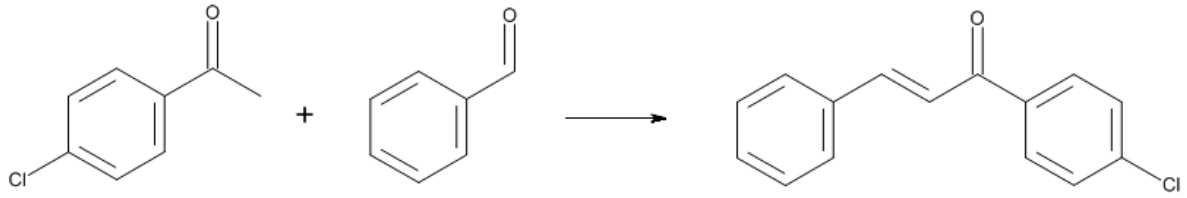
(79) **(83)** **(84)**
$C_{16}H_{14}O_2$
MW = 238.28g/mol

To benzaldehyde **(79)** (16.95 ml, 166.47 mmol) and 4-methoxycetophenone **(83)** (25.00 g, 166.47 mmol) in ethanol (75 ml) was added sodium hydroxide (2.00 g, 49.94 mmol) in water (10 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes. After this time, the reaction mixture was cooled in an ice bath for 15 minutes and precipitates collected by vacuum filtration. The product was purified by recrystallisation from ethanol yielding a pale yellow crystalline solid (28.34g, 71%).

^{1}H NMR (400MHz, $CDCl_3$): δ3.90 (3H, s, ArOC**H**$_3$); δ6.99 (2H, d, J=8.8Hz, Ar**H**); δ7.39-7.45 (3H, m Ar**H**); δ7.55 (1H, d, J=15.6Hz, Ph**H**C); δ7.63-7.68 (2H, m, Ar**H**); δ7.81 (1H, d, J=15.6Hz, C**H**CO); δ8.05 (2H, d, J=8.7Hz, Ar**H**).

This data is consistent with that reported in the literature[169].

2.2.1.4 Synthesis of 1-(4-chlorophenyl)-3-phenyl-prop-2-en-1-one



(85) **(79)** **(86)**
$C_{15}H_{11}ClO$
MW = 242.70g/mol

To benzaldehyde **(79)** (20.00 ml, 196.38 mmol) and 4-chloroacetophenone **(85)** (25.47 ml, 196.38 mmol) in ethanol (200 ml) was added sodium hydroxide (2.36 g, 58.91 mmol) in water (10 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes. After this time, the reaction mixture was cooled in an ice bath for 15 minutes and precipitates collected by vacuum filtration. The crude product was purified by recrystallisation from methylated spirits to yield the pure product as a yellow crystalline solid (42.89 g, 91%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.41-7.46 (3H, m, Ph**H**); δ7.47-7.52 (3H, m, Ph**H**, Ph**H**C); δ7.62-7.67 (2H, m, Ar**H**); δ7.82 (1H, d, J=15.7Hz, C**H**CO); δ7.97 (2H, d, J=8.4Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ121.48 (PhH**C**), 128.52 (Ar), 128.96 (Ar), 129.01 (Ar), 129.92 (Ar), 130.77 (Ar), 134.68 (Ar), 136.48 (Ar), 139.23 (Ar), 145.39 (**C**HCO), 189.23 (**C**=O).

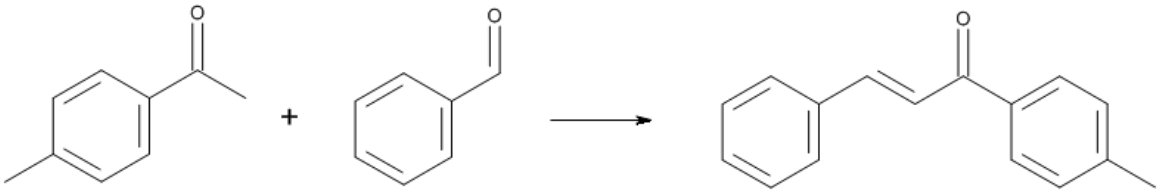
micrOTOF-Q MS m/z $C_{15}H_{11}ClO$+Na, calculated 265.0390, observed 265.0394.

IR (cm^{-1}): 761, 826, 981, 1087, 1215, 1331, 1567, 1585, 1598, 1658.

M.p.: 101-103 ^{o}C. (Literature value 101 ^{0}C)[134].

This data is consistent with that reported in the literature[134,169].

2.2.1.5 Synthesis of 3-phenyl-1-(p-tolyl)prop-2-en-1-one



(87) **(79)** **(88)**
$C_{16}H_{14}O$
MW = 222.28g/mol

To benzaldehyde **(79)** (15.18 ml, 149.05 mmol) and 4-methylacetophenone **(87)** (20.00 ml, 149.05 mmol) in ethanol (150 ml) was added sodium hydroxide (1.79 g, 44.72 mmol) in water (10 ml). The reaction mixture was allowed to stir at room temperature for 30 minutes. After this time, the reaction mixture was cooled in an ice bath for 15 minutes and precipitates collected by vacuum filtration with no further purification required to yield the product as an off-white solid (20.64 g, 62%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.33 (3H, s, ArC**H**$_3$); δ7.20 (2H, d, J=8.0Hz, Ar**H**); δ7.29-7.34 (3H, m, Ar**H**); δ7.44 (1H, d, J=15.7Hz, Ph**H**C); δ7.52-7.56 (2H, m, Ar**H**); δ7.71 (1H, d, J=15.7Hz, C**H**CO); δ7.85 (2H, d, J=8.2Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ21.68 (Ar**C**H$_3$), 122.14 (PhH**C**), 128.42 (Ar), 128.68 (Ar), 128.95 (Ar), 129.35 (Ar), 130.43 (Ar), 135.04 (Ar), 135.68 (Ar), 143.64 (Ar), 144.37 (**C**HCO), 189.98 (**C**=O).

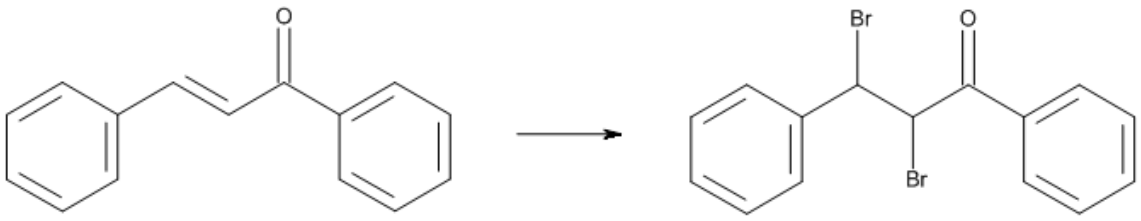
micrOTOF-Q MS m/z $C_{16}H_{14}O$+Na, calculated 245.0937, observed 245.0940.

IR (cm^{-1}): 977, 1180, 1206, 1220, 1286, 1305, 1333, 1567, 1592, 1652.

This data is consistent with that reported in the literature[169].

2.2.2 Experimental Procedures for the Dibromination of 3-Phenyl-α,β-dibrominated arylketones

2.2.2.1 Synthesis of 2,3-dibromo-1,3-diphenyl-propan-1-one



(80) **(89)**
$C_{15}H_{12}Br_2O$
MW = 368.06g/mol

To 1,3-diphenylprop-2-en-1-one **(80)** (7.82 g, 37.55 mmol) in dry chloroform (25 ml) at room temperature under an atmosphere of nitrogen was added a 1M solution of bromine in chloroform (45.06 ml, 45.06 mmol) and the reaction mixture allowed to stir for one hour. After this time petroleum ether (60 ml) was added and the reaction mixture was allowed to stand for one hour at room temperature and for a further hour at 0^0C. The precipitates were collected by vacuum filtration yielding a pure white crystalline solid (4.71 g, 34%).

^{1}H NMR (400MHz, $CDCl_3$): δ5.65 (1H, d, J=11.5Hz, Ph**H**BrC); δ5.84 (1H, d, J=11.3Hz, C**H**BrCO); δ7.36-7.47 (3H, m, Ph**H**); δ7.51-7.59 (4H, m, Ph**H**); δ7.67 (1H, m, Ph**H**); δ8.11 (2H, d, J=7.7Hz, Ph**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ46.84 (PhHBr**C**), 49.78 (**C**HBrCO), 128.37 (Ph**C**), 128.90 (Ph**C**), 128.94 (Ph**C**), 129.04 (Ph), 129.34 (Ph**C**), 134.23 (Ph**C**), 134.42 (Ph**C**), 138.25 (Ph**C**), 191.21 (**C**=O).

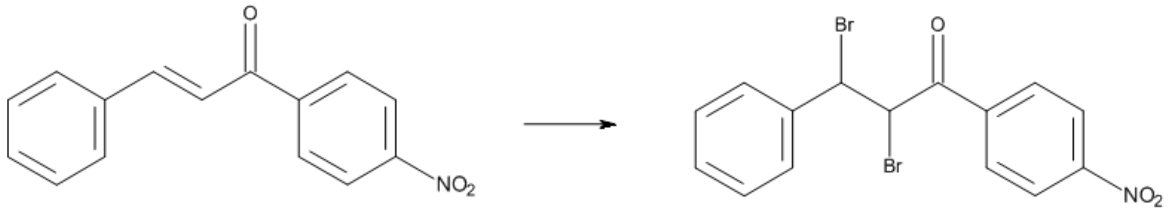
micrOTOF-Q MS m/z $C_{15}H_{12}{}^{79}Br_2O$+Na, calculated 388.9147, observed 388.9148.

IR (cm^{-1}): 682, 696, 721, 981, 1148, 1227, 1272, 1448, 1596, 1678.

M.p.: 160-162 ^{o}C. (Literature value 159-160 ^{0}C)[135].

This data is consistent with that reported in the literature[135,170].

2.2.2.2 Synthesis of 2,3-dibromo-1-(4-nitrophenyl)-3-phenyl-propan-1-one



(82)

(90)
$C_{15}H_{11}Br_2NO_2$
MW = 397.06g/mol

To 1-(4-nitrophenyl)-3-phenyl-prop-2-en-1-one **(82)** (6.04 g, 23.66 mmol) in dry chloroform (20 ml) at room temperature under an atmosphere of nitrogen was added a 1M solution of bromine in chloroform (28.39 ml, 28.39 mmol) and the reaction mixture allowed to stir for one hour. After this time petroleum ether (60 ml) was added and the reaction mixture was allowed to stand for one hour at room temperature and for a further hour at 0^0C. The precipitates were collected by vacuum filtration yielding the product as a yellow crystalline solid (6.08 g, 62%).

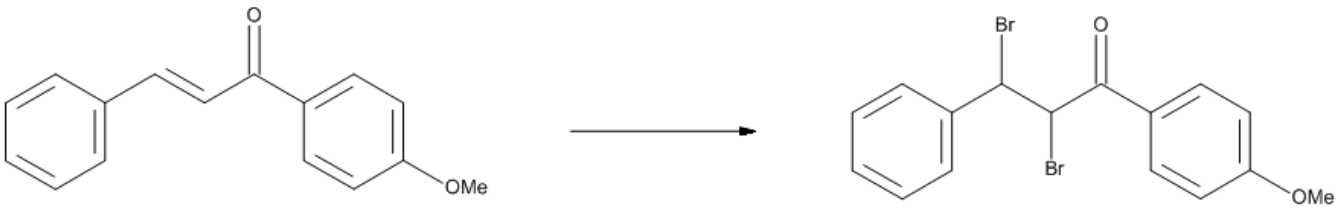
^{1}H NMR (400MHz, d-DMSO): δ5.82 (1H, d, J=11.2Hz, Ph**H**BrC); δ6.84 (1H, d, J=11.2Hz, C**H**BrCO); δ7.36-7.50 (3H, m, Ar**H**); δ7.54 (2H, d, 7.4Hz, Ar**H**); δ8.45 (2H, d, J=8.6Hz, Ar**H**); δ8.55 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, d-DMSO): δ46.99 (PhBr**C**), 50.82 (**C**HBrCO), 124.71 (Ar), 129.11 (Ar), 129.31 (Ar), 129.65 (Ar), 131.03 (Ar), 138.66 (Ar), 138.71 (Ar), 151.20 (Ar), 191.00 (**C**=O).

IR (cm^{-1}): 848, 863, 778, 979, 1026, 1216, 1317, 1352, 1517, 1693.

M.p.: 201-203 ^{o}C. (Literature value 198 ^{0}C)[136].
This data is consistent with that reported in the literature[136,170].

2.2.2.3 Synthesis of 2,3-dibromo-1-(4-methoxyphenyl)-3-phenyl-propan-1-one



(84)

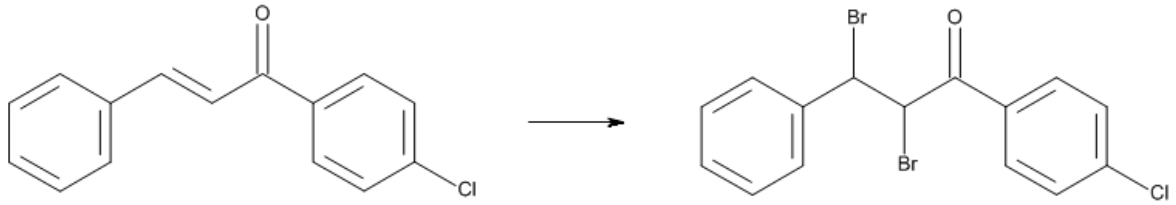
(91)
$C_{16}H_{14}Br_2O_2$
MW = 398.09g/mol

To 1-(4-methoxyphenyl)-3-phenyl-prop-2-en-1-one **(84)** (28.34 g, 118.94 mmol) in dry chloroform (100 ml) at room temperature under an atmosphere of nitrogen was added a 1M solution of bromine in chloroform (118.94 ml, 118.94 mmol) and the reaction mixture allowed to stir for one hour. After this time petroleum ether (120 ml) was added and the reaction mixture was allowed to stand for one hour at room temperature and for a further hour at 0^0C. The precipitates were collected by vacuum filtration yielding the product as a pure white crystalline solid (36.08 g, 30%).

^{1}H NMR (400MHz, $CDCl_3$): δ3.92 (3H, s, ArOC**H**$_3$); δ5.65 (1H, d, J=11.3Hz, Ph**H**BrC); δ5.81 (1H, d, J=11.3Hz, C**H**BrCO); δ7.02 (2H, d, J=8.6Hz, Ar**H**); δ7.35-7.47 (3H, m, Ar**H**); δ7.53 (2H, d, J=7.5Hz, Ar**H**); δ8.10 (2H, d, J=8.6Hz, Ar**H**).

This data is consistent with that reported in the literature[170].

2.2.2.4 Synthesis of 2,3-dibromo-1-(4-chlorophenyl)-3-phenyl-propan-1-one



(86)

(92)
$C_{15}H_{11}Br_2ClO$
MW = 402.51g/mol

To 1-(4-chlorophenyl)-3-phenyl-prop-2-en-1-one **(86)** (42.50 g, 175.11 mmol) in dry chloroform (50 ml) at room temperature under an atmosphere of nitrogen was added a 1M solution of bromine in chloroform (210.13 ml, 210.13 mmol) and the reaction mixture allowed to stir for one hour. After this time petroleum ether (100 ml) was added and the reaction mixture was allowed to stand for one hour at room temperature and for a further hour at 0^0C. The precipitates were collected by vacuum filtration yielding a yellow crystalline solid (14.53 g, 21%).

^{1}H NMR (400MHz, $CDCl_3$): δ5.63 (1H, d, J=11.3Hz, Ph**H**BrC); δ5.77 (1H, d, J=11.3Hz, (C**H**BrCO); δ7.36-7.47 (3H, m, Ar**H**); δ7.50-7.56 (4H, m, Ar**H**); δ8.05 (2H, d, J=8.1Hz, Ar**H**).

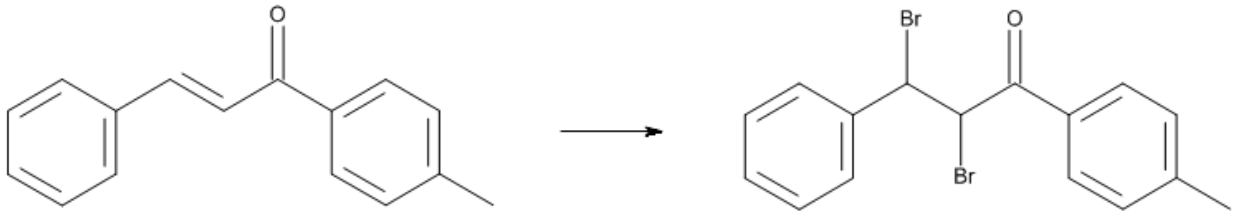
^{13}C NMR (100MHz, $CDCl_3$): δ46.73 (PhHBr**C**), 49.63 (**C**HBrCO), 128.33 (Ar), 128.91 (Ar), 129.40 (Ar), 130.30 (Ar), 132.68 (Ar), 138.02 (Ar), 140.84 (Ar), 190.05 (**C**=O).

IR (cm^{-1}): 755, 785, 824, 976, 1087, 1218, 1269, 1400, 1587, 1685.

M.p.: 191-192 ^{o}C. (Literature value 193 ^{0}C)[136].

This data is consistent with that reported in the literature[136,170].

2.2.2.5 Synthesis of 2,3-dibromo-3-phenyl-1-(p-tolyl)propan-1-one



(88)

(93)
$C_{16}H_{14}Br_2O$
MW = 382.09g/mol

To 3-phenyl-1-(p-tolyl)prop-2-en-1-one **(88)** (23.98 g, 107.88 mmol) in dry chloroform (100 ml) at room temperature under an atmosphere of nitrogen was added a 1M solution of bromine in chloroform (129.46 ml, 129.46 mmol) and the reaction mixture allowed to stir for one hour. After this time petroleum ether (150 ml) was added and the reaction mixture was allowed to stand for one hour at room temperature and for a further hour at 0^0C. The precipitates were collected by vacuum filtration yielding the product as a yellow crystalline solid (19.41 g, 47%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.46 (3H, s, ArC**H**$_3$); δ5.65 (1H, d, J=11.3Hz, Ph**H**BrC); δ5.82 (1H, d, J=11.3Hz, C**H**BrCO); δ7.33-7.46 (5H, m, Ar**H**); δ7.51-7.55 (2H, m, Ar**H**); δ8.01 (2H, d, J=8.2Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ21.83 (Ar**C**H$_3$), 46.80 (PhHBr**C**), 49.85 (**C**HBrCO), 128.36 (Ar), 128.85 (Ar), 129.06 (Ar), 129.27 (Ar), 129.73 (Ar), 131.84 (Ar), 138.34 (Ar), 145.40 (Ar), 190.76 (**C**=O).

micrOTOF-Q MS m/z $C_{16}H_{14}{}^{79}Br_2O$+Na, calculated 402.9304, observed 402.9304.

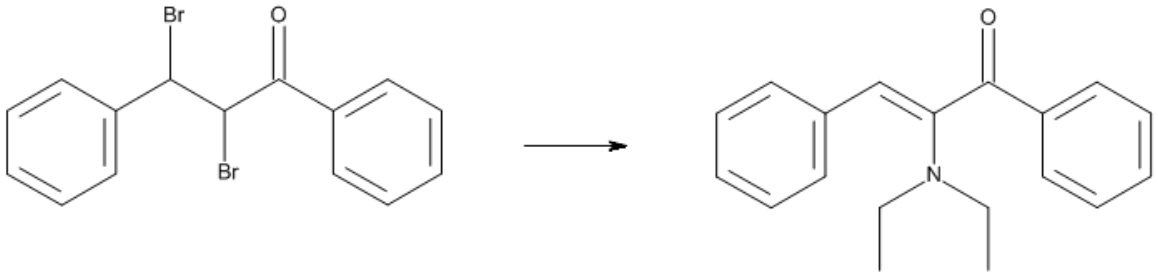
IR (cm^{-1}): 834, 967, 1142, 1208, 1225, 1272, 1324, 1372, 1606, 1683.

M.p.: 180-182 ^{o}C.

This data is consistent with that reported in the literature[170].

2.2.3 Experimental Procedures for the synthesis of α,β-unsaturated-3-phenyl-2-dialkylamino arylketones

2.2.3.1 Synthesis of 2-(diethylamino)-1,3-diphenyl-prop-2-en-1-one

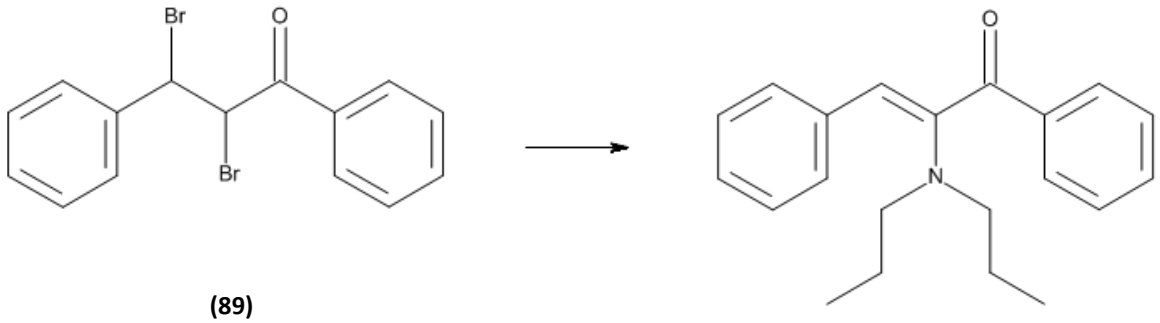


(89)

(94)
$C_{19}H_{21}NO$
MW = 279.38g/mol

To 2,3-dibromo-1,3-diphenyl-propan-1-one **(89)** (4.71 g, 12.80 mmol) stirring in ethanol (5 ml) at room temperature under an atmosphere of nitrogen was added diethylamine (2.65 ml, 25.60 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (871 mg, 12.80 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane (50 ml). The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.2 Synthesis of 2-(dipropylamino)-1,3-diphenyl-prop-2-en-1-one

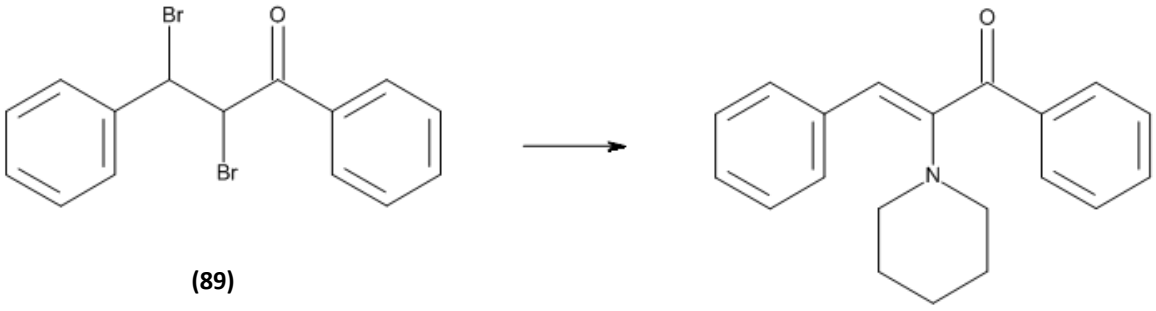


(89)

(95)
$C_{21}H_{25}NO$
MW = 307.43g/mol

To 2,3-dibromo-1,3-diphenyl-propan-1-one **(89)** (5.90 g, 16.03 mmol) stirring in ethanol (6 ml) at room temperature under an atmosphere of nitrogen was added dipropylamine (4.40 ml, 32.06 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (369 mg, 16.03 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.3 Synthesis of 1,3-diphenyl-2-(1-piperidyl)prop-2-en-1-one

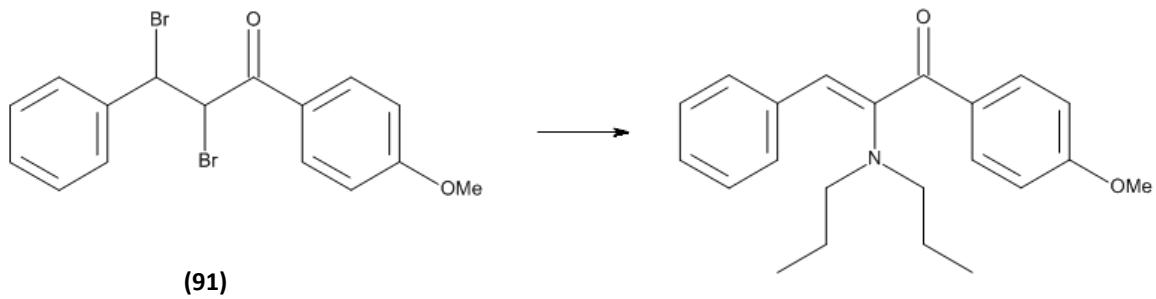


(89)

(96)
$C_{20}H_{21}NO$
MW = 291.39g/mol

To 2,3-dibromo-1,3-diphenyl-propan-1-one **(89)** (6.00 g, 16.30 mmol) stirring in ethanol (6 ml) at room temperature under an atmosphere of nitrogen was added piperidine (3.22 ml, 32.60 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (375 mg, 16.30 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.4 Synthesis of 2-(dipropylamino)-1-(4-methoxyphenyl)-3-phenyl-prop-2-en-1-one

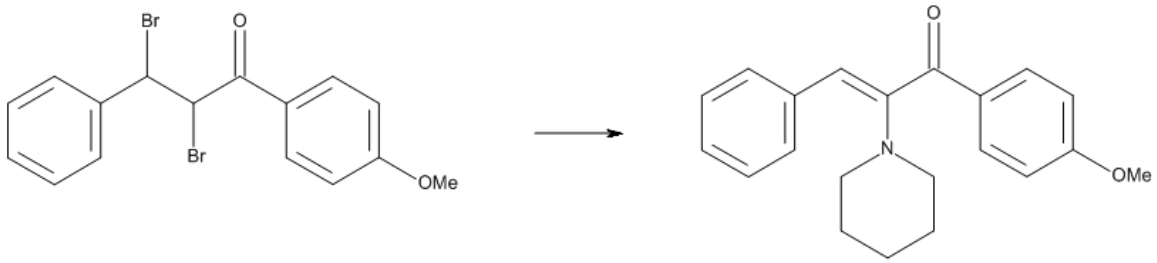


(91)

(98)
$C_{22}H_{27}NO_2$
MW = 337.45g/mol

To 2,3-dibromo-1-(4-methoxyphenyl)-3-phenyl-propan-1-one **(91)** (5.00 g, 12.56 mmol) stirring in ethanol (6 ml) at room temperature under an atmosphere of nitrogen was added dipropylamine (3.40 ml, 25.12 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (289 mg, 12.56 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.5 Synthesis of 1-(4-methoxyphenyl)-3-phenyl-2-(1-piperidyl)prop-2-en-1-one

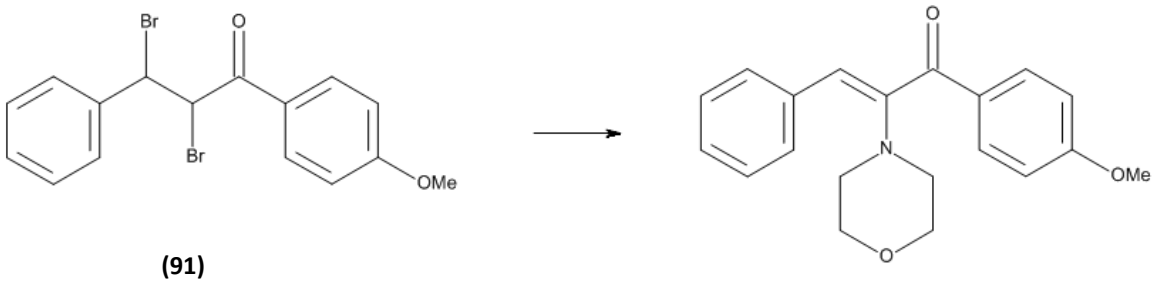


(91)

(99)
$C_{21}H_{23}NO_2$
MW = 321.41g/mol

To 2,3-dibromo-1-(4-methoxyphenyl)-3-phenyl-propan-1-one **(91)** (6.00 g, 15.07 mmol) stirring in ethanol (50 ml) at room temperature under an atmosphere of nitrogen was added piperidine (2.98 ml, 30.14 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (347 mg, 15.07 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.6 Synthesis of 1-(4-methoxyphenyl)-2-morpholino-3-phenyl-prop-2-en-1-one

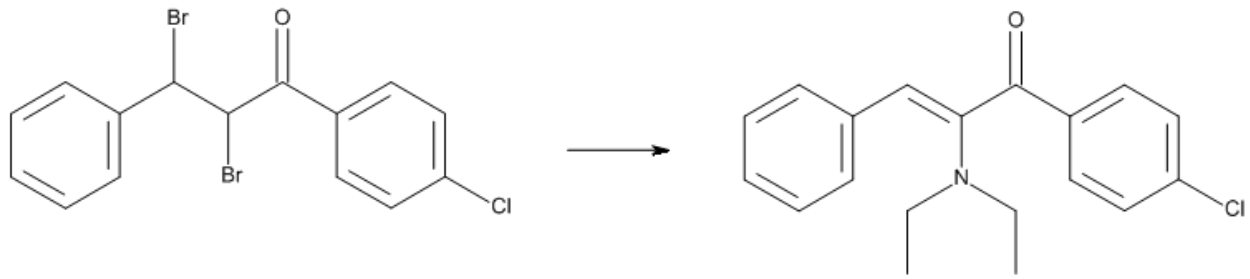


(91)

(100)
$C_{20}H_{21}NO_3$
MW = 323.38g/mol

To 2,3-dibromo-1-(4-methoxyphenyl)-3-phenyl-propan-1-one **(91)** (6.00 g, 15.07 mmol) stirring in ethanol (80 ml) at room temperature under an atmosphere of nitrogen was added morpholine (2.63 ml, 30.14 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (347 mg, 15.07 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.7 Synthesis of 1-(4-chlorophenyl)-2-(diethylamino)-3-phenyl-prop-2-en-1-one

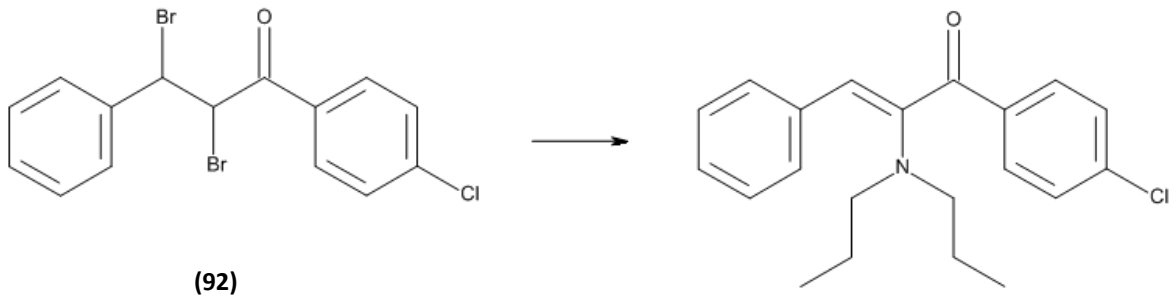


(92)

(101)
$C_{19}H_{20}ClNO$
MW = 313.82g/mol

To 2,3-dibromo-1-(4-chlorophenyl)-3-phenyl-propan-1-one **(92)** (4.60 g, 11.43 mmol) stirring in ethanol (10 ml) at room temperature under an atmosphere of nitrogen was added diethylamine (2.36 ml, 22.86 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (263 mg, 11.43 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.8 Synthesis of 1-(4-chlorophenyl)-2-(dipropylamino)-3-phenyl-prop-2-en-1-one

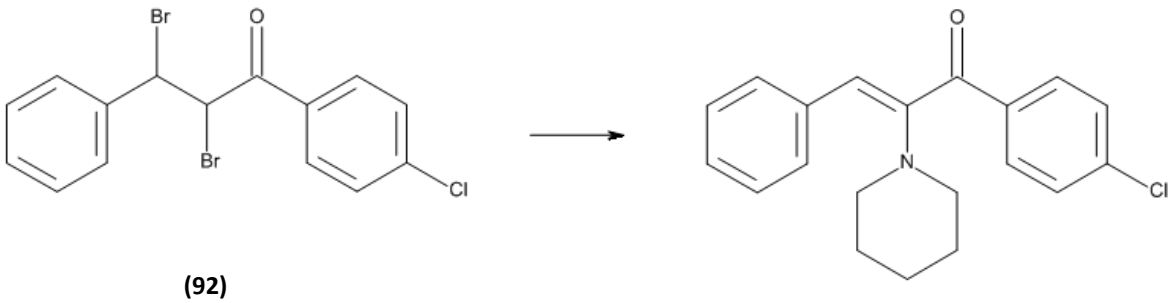


(92)

(102)
$C_{21}H_{24}ClNO$
MW = 341.87g/mol

To 2,3-dibromo-1-(4-chlorophenyl)-3-phenyl-propan-1-one **(92)** (5.00 g, 12.42 mmol) stirring in ethanol (10 ml) at room temperature under an atmosphere of nitrogen was added dipropylamine (3.40 ml, 24.84 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (290 mg, 12.42 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.9 Synthesis of 1-(4-chlorophenyl)-3-phenyl-2-(1-piperidyl)prop-2-en-1-one

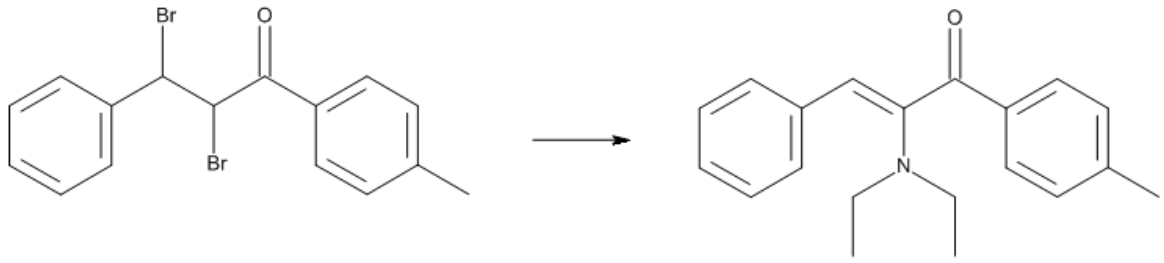


(92)

(103)
$C_{20}H_{20}ClNO$
MW = 325.83g/mol

To 2,3-dibromo-1-(4-chlorophenyl)-3-phenyl-propan-1-one **(92)** (4.80 g, 11.93 mmol) stirring in ethanol (30 ml) at room temperature under an atmosphere of nitrogen was added piperidine (2.36 ml, 23.86 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (274 mg, 11.93 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.10 Synthesis of 2-(diethylamino)-3-phenyl-1-(p-tolyl)prop-2-en-1-one

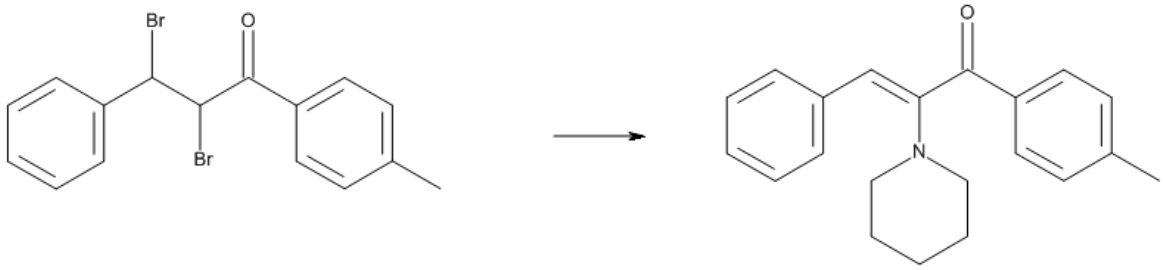


(93)

(104)
$C_{20}H_{23}NO$
MW = 293.40g/mol

To 2,3-dibromo-3-phenyl-1-(p-tolyl)propan-1-one **(93)** (4.52 g, 11.83 mmol) stirring in ethanol (40 ml) at room temperature under an atmosphere of nitrogen was added diethylamine (2.45 ml, 23.66 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (272 mg, 11.83 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.3.11 Synthesis of 3-phenyl-2-(1-piperidyl)-1-(p-tolyl)prop-2-en-1-one



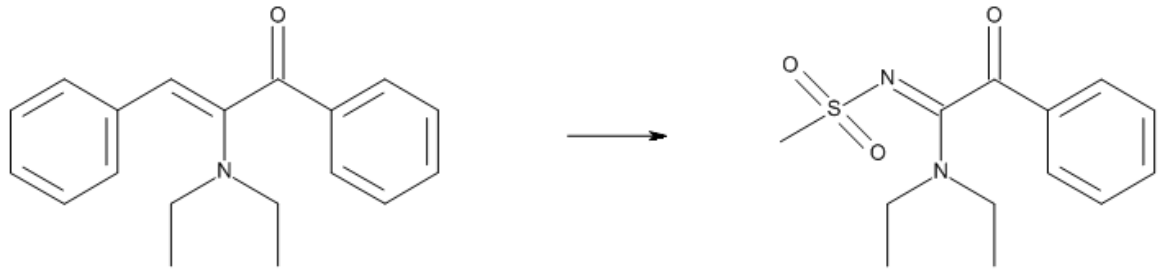
(93)

(105)
$C_{21}H_{23}NO$
MW = 305.41g/mol

To 2,3-dibromo-3-phenyl-1-(p-tolyl)propan-1-one **(93)** (4.78 g, 12.51 mmol) stirring in ethanol (40 ml) at room temperature under an atmosphere of nitrogen was added piperidine (2.50 ml, 25.02 mmol) and the mixture allowed to stir for 24 hours. After this time sodium ethoxide (288 mg, 12.51 mmol) was added and the reaction mixture was stirred for a further 24 hours. Solvents were then removed under reduced pressure and the residues dissolved in dichloromethane. The solution was then filtered to remove sodium bromide and the filtrate was concentrated under reduced pressure. The crude product was taken to the next stage without further purification or analysis.

2.2.4 Experimental Procedures for the Synthesis of 2-Dialkylamino-N-methanesulfonyl arylketoamidines

2.2.4.1 Synthesis of N,N-diethyl-N'-methylsulfonyl-2-oxo-2-phenyl-acetamidine



(94) **(106)**
$C_{13}H_{18}N_2O_3S$
MW = 282.36g/mol

Under an atmosphere of nitrogen, a solution of 2-(diethylamino)-1,3-diphenyl-prop-2-en-1-one **(94)** (920 mg, 3.29 mmol) in ethanol (5 ml) was added to a solution of methanesulfonyl azide (398 mg, 3.29 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a pink solid (533 mg, 57%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.09 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ1.34 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.97 (3H, s, $SO_2C\mathbf{H}_3$); δ3.15 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.46-3.59 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.67-3.83 (1H, m $NC\mathbf{H}_2CH_3$); δ7.53 (2H, t, J=8.0Hz, Ph**H**); δ7.65 (1H, tt, J=7.4Hz, 1.2Hz, Ph**H**); δ7.90 (2H, d, J=7.3Hz, Ph**H**).

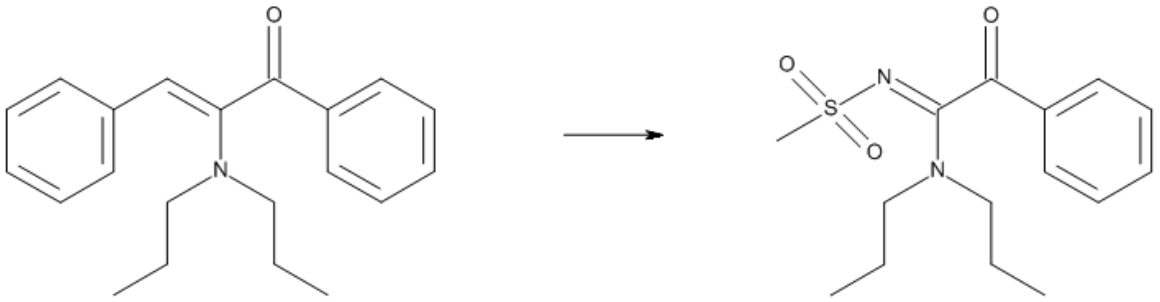
^{13}C NMR (100MHz, $CDCl_3$): δ11.92 ($NCH_2\mathbf{C}H_3$), 13.69 ($NCH_2\mathbf{C}H_3$), 42.58 ($SO_2\mathbf{C}H_3$), 42.67 ($N\mathbf{C}H_2CH_3$), 44.24 ($N\mathbf{C}H_2CH_3$), 128.84 (Ph**C**), 129.23 (Ph**C**), 134.38 (Ph**C**), 134.83 (Ph**C**), 161.94 (N=**C**-N), 192.57 (**C**=O).

micrOTOF-Q MS m/z $C_{13}H_{18}N_2O_3S$+Na, calculated 305.0928, observed 305.0930.

IR (cm^{-1}): 776, 843, 962, 1131, 1233, 1290, 1449, 1550, 1686.

M.p.: 181-183 ^{o}C.

2.2.4.2 Synthesis of N'-methylsulfonyl-2-oxo-2-phenyl-N,N-dipropyl-acetamidine



(95)

(107)
$C_{15}H_{22}N_2O_3S$
MW = 310.41g/mol

Under an atmosphere of nitrogen, a solution of 2-(dipropylamino)-1,3-diphenyl-prop-2-en-1-one **(95)** (4.69 g, 15.26 mmol) in ethanol (35 ml) was added to a solution of methanesulfonyl azide (1.85 g, 15.26 mmol) in ethanol (20 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as an orange solid (2.27 g, 48%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.72 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.02 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.40-1.65 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.72-1.88 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.97 (3H, s, $SO_2C\mathbf{H}_3$); δ3.01 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.33-3.44 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.62-3.76 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.53 (2H, t, J=7.8Hz, Ph**H**); δ7.75 (1H, t, J=7.4Hz, Ph**H**); δ7.90 (2H, d, J=7.5Hz, Ph**H**).

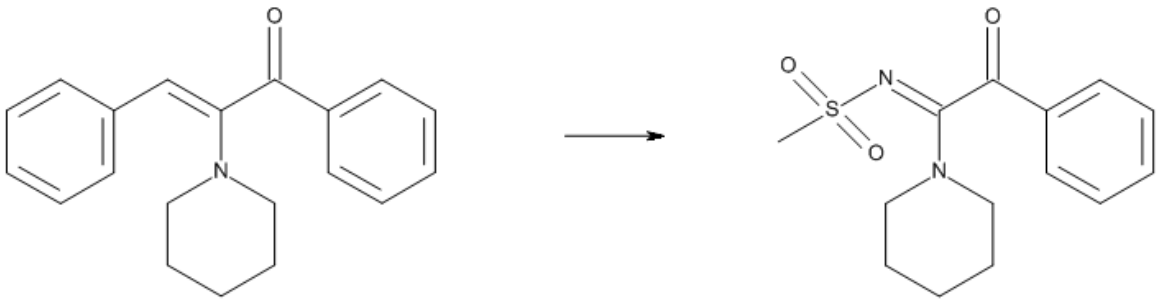
^{13}C NMR (100MHz, $CDCl_3$): δ10.87 ($NCH_2CH_2\mathbf{C}H_3$), 11.45 ($NCH_2CH_2\mathbf{C}H_3$), 19.87 ($NCH_2\mathbf{C}H_2CH_3$), 21.67 ($NCH_2\mathbf{C}H_2CH_3$), 42.57 ($SO_2\mathbf{C}H_3$), 49.64 ($N\mathbf{C}H_2CH_2CH_3$), 51.38 ($N\mathbf{C}H_2CH_2CH_3$), 128.83 (Ph**C**), 129.20 (Ph**C**), 134.46 (Ph**C**), 134.76 (Ph**C**), 162.40 (N=**C**-N), 192.67 (**C**=O).

micrOTOF-Q MS m/z $C_{15}H_{22}N_2O_3S$+Na calculated 333.1243, observed 333.1241.

IR (cm^{-1}): 695, 710, 797, 843, 900, 958, 1127, 1272, 1286, 1545.

M.p.: 117-118 ^oC.

2.2.4.3 Synthesis of N-[2-oxo-2-phenyl-1-(1-piperidyl)ethylidene] methanesulfonamide



(96)

(108)
$C_{14}H_{18}N_2O_3S$
MW = 294.37g/mol

Under an atmosphere of nitrogen, a solution of 1,3-diphenyl-2-(1-piperidyl)prop-2-en-1-one **(96)** (5.17 g, 17.74 mmol) in ethanol (50 ml) was added to a solution of methanesulfonyl azide (2.15 g, 17.74 mmol) in ethanol (20 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as an off-white solid (896 mg, 17%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.35-1.56 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.65-1.80 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.98 (3H, s, $SO_2C\mathbf{H}_3$); δ3.11-3.29 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.78-3.92 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ7.54 (2H, t, J=7.9Hz, Ph**H**); δ7.65 (1H, tt, J=7.4Hz, 1.2Hz, Ph**H**); δ7.92 (2H, d, J=7.3Hz, Ph**H**).

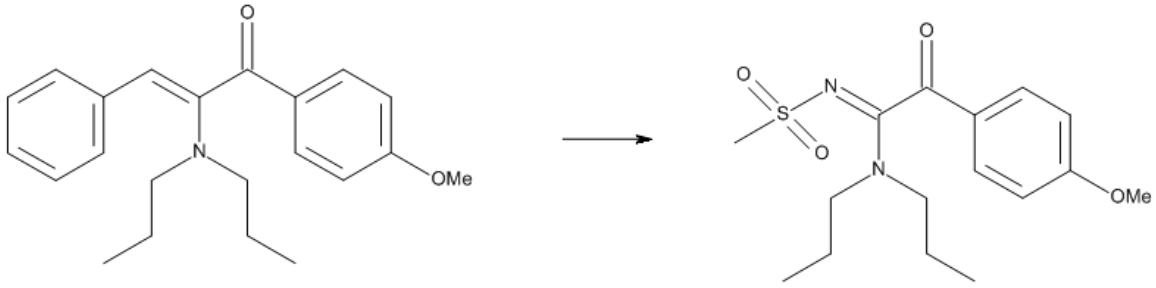
^{13}C NMR (100MHz, $CDCl_3$): δ23.87 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.27 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 26.03 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 42.61 ($SO_2C\mathbf{H}_3$), 45.90 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 48.84 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 128.85 (Ph**C**), 129.24 (Ph**C**), 134.39 (Ph**C**), 134.87 (Ph**C**), 161.34 (N=**C**-N), 193.16 (**C**=O).

micrOTOF-Q MS m/z $C_{14}H_{18}N_2O_3S$+Na calculated 317.0930, observed 317.0922.

IR (cm^{-1}): 758, 779, 821, 856, 963, 1130, 1226, 1295, 1444, 1549.

M.p.: 164-166 ^{o}C.

2.2.4.4 Synthesis of 2-(4-methoxyphenyl)-N'-methylsulfonyl-2-oxo-N,N-dipropyl-acetamidine



(98)

(109)
$C_{16}H_{24}N_2O_4S$
MW = 340.44g/mol

Under an atmosphere of nitrogen, a solution of 2-(dipropylamino)-1-(4-methoxyphenyl)-3-phenyl-prop-2-en-1-one **(98)** (4.58 g, 14.80 mmol) in ethanol (45 ml) was added to a solution of methanesulfonyl azide (1.79 g, 14.80 mmol) in ethanol (15 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as an orange oil (3.40 g, 55%).

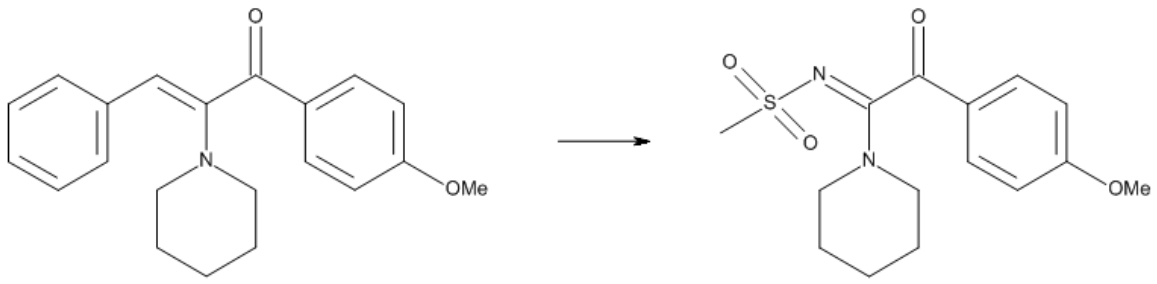
^{1}H NMR (400MHz, $CDCl_3$): δ0.73 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.01 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.41-1.69 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.72-1.87 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.96 (3H, s, $SO_2C\mathbf{H}_3$); δ2.98-3.10 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.35-3.44 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.61-3.71 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.89 (3H, s, $ArOC\mathbf{H}_3$); δ7.00 (2H, d, J=7.8Hz, Ar**H**); δ7.86 (2H, d, J=7.8Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.94 ($NCH_2CH_2\mathbf{C}H_3$), 11.47 ($NCH_2CH_2\mathbf{C}H_3$), 19.90 ($NCH_2\mathbf{C}H_2CH_3$), 21.72 ($NCH_2\mathbf{C}H_2CH_3$), 42.60 ($SO_2\mathbf{C}H_3$), 49.53 ($N\mathbf{C}H_2CH_2CH_3$), 51.36 ($N\mathbf{C}H_2CH_2CH_3$), 55.70 ($ArO\mathbf{C}H_3$), 114.57 (Ar), 127.69 (Ar), 131.36 (Ar), 162.68 (Ar), 164.88 (N=**C**-N), 171.15 (**C**=O).

micrOTOF-Q MS m/z $C_{16}H_{24}N_2O_4S$+Na, calculated 363.1349, observed 363.1348.

IR (cm^{-1}): 833, 959, 1015, 1128, 1168, 1234, 1258, 1291, 1541, 1596.

2.2.4.5 Synthesis of N-[2-(4-methoxyphenyl)-2-oxo-1-(1-piperidyl)ethylidene] methanesulfonamide



(99)

(110)
$C_{15}H_{20}N_2O_4S$
MW = 324.39g/mol

Under an atmosphere of nitrogen, a solution of 1-(4-methoxyphenyl)-3-phenyl-2-(1-piperidyl)prop-2-en-1-one **(99)** (4.75 g, 14.78 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (1.79 g, 14.78 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:2 petroleum ether:ethyl acetate solvent system to yield the pure product as an orange solid (1.14 g, 24%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.36-1.49 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.50-1.61 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.64-1.78 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.98 (3H, s, $SO_2C\mathbf{H}_3$); δ3.13-3.31 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.72-3.82 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.84-3.91 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.89 (3H, s, $ArOC\mathbf{H}_3$); δ7.00 (2H, d, J=8.4Hz, Ar**H**); δ7.89 (2H, d, J=8.4Hz, Ar**H**).

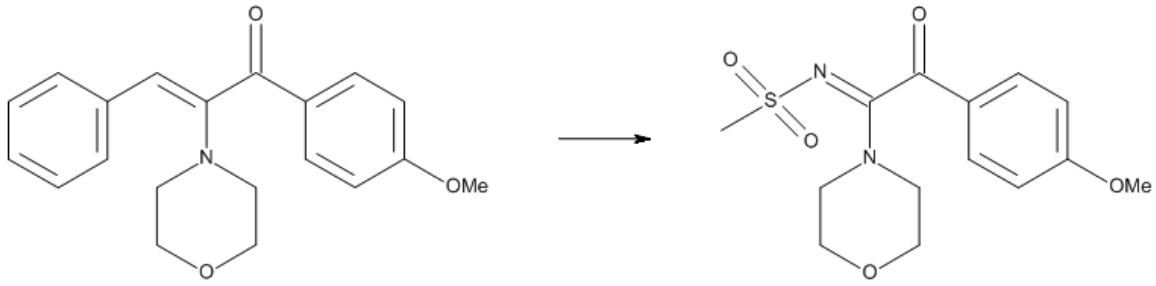
^{13}C NMR (100MHz, $CDCl_3$): δ23.89 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.29 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 26.11 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 42.61 ($SO_2C\mathbf{H}_3$), 43.37 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 45.76 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 55.69 ($ArO\mathbf{C}H_3$), 114.60 (Ar), 127.63 (Ar), 131.40 (Ar), 161.56 (Ar), 164.95 (N=**C**-N), 191.14 (**C=**O).

micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_4S$+Na, calculated 347.1036, observed 347.1037.

IR (cm^{-1}): 809, 972, 1115, 1132, 1157, 1240, 1259, 1281, 1243, 1549.

M.p.: 165-167 ^oC.

2.2.4.6 Synthesis of (NZ)-N-[2-(4-methoxyphenyl)-1-morpholino-2-oxo-ethylidene] methanesulfonamide



(100)

(111)
$C_{14}H_{18}N_2O_5S$
MW = 326.37g/mol

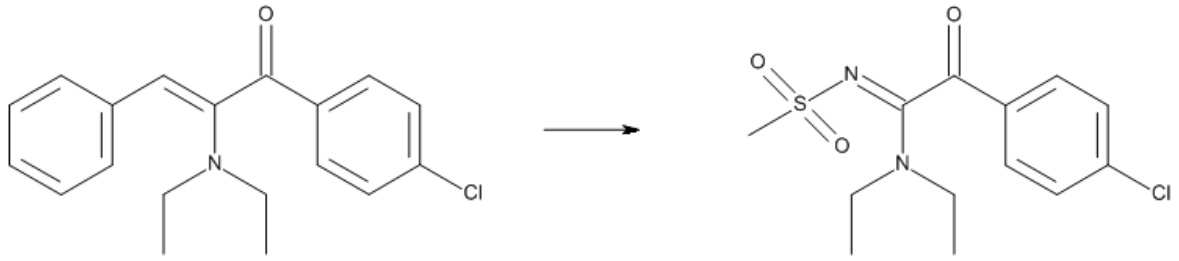
Under an atmosphere of nitrogen, a solution of 1-(4-methoxyphenyl)-2-morpholino-3-phenyl-prop-2-en-1-one **(100)** (5.82 g, 18.00 mmol) in ethanol (50 ml) was added to a solution of methanesulfonyl azide (2.18 g, 18.00 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:2 petroleum ether:ethyl acetate solvent system to yield the pure product as a pale yellow solid (170 mg, 3%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.61 (4H, t, J=4.4Hz, $N(CH_2)_2(\mathbf{CH_2})_2O$); δ3.77 (3H, s, $SO_2\mathbf{CH_3}$); δ3.78 (4H, t, J=4.6Hz, $N(\mathbf{CH_2})_2(CH_2)_2O$); δ3.88 (3H, s, $ArOC\mathbf{H_3}$); δ6.94 (2H, d, J=8.9Hz, Ar**H**); δ8.00 (2H, d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ53.90 ($SO_2\mathbf{C}H_3$), 55.49 ($N(CH_2)_2(\mathbf{C}H_2)_2O$), 64.55 ($N(\mathbf{C}H_2)_2(CH_2)_2O$), 66.83 ($ArO\mathbf{C}H_3$), 113.72 (Ar), 129.03 (Ar), 130.45 (Ar), 163.64 (N=**C**-N), 194.62 (**C**=O).

IR (cm^{-1}): 825, 973, 1022, 1112, 1161, 1226, 1255, 1510, 1597, 1672.

2.2.4.7 Synthesis of 2-(4-chlorophenyl)-N,N-diethyl-N'-methylsulfonyl-2-oxo-acetamidine



(101)

(112)
$C_{13}H_{17}ClN_2O_3S$
MW = 316.80g/mol

Under an atmosphere of nitrogen, a solution of 1-(4-chlorophenyl)-2-(diethylamino)-3-phenyl-prop-2-en-1-one **(101)** (4.50 g, 14.34 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (1.74 g, 14.34 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a red oil (1.92 g, 42%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.09 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ1.33 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.97 (3H, s, $SO_2C\mathbf{H}_3$); δ3.14 (2H, q, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.46-3.60 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.66-3.81 (1H, m, $NC\mathbf{H}_2CH_3$); δ7.51 (2H, d, J=8.8Hz, Ar**H**); δ7.84 (2H, d, J=8.6Hz, Ar**H**).

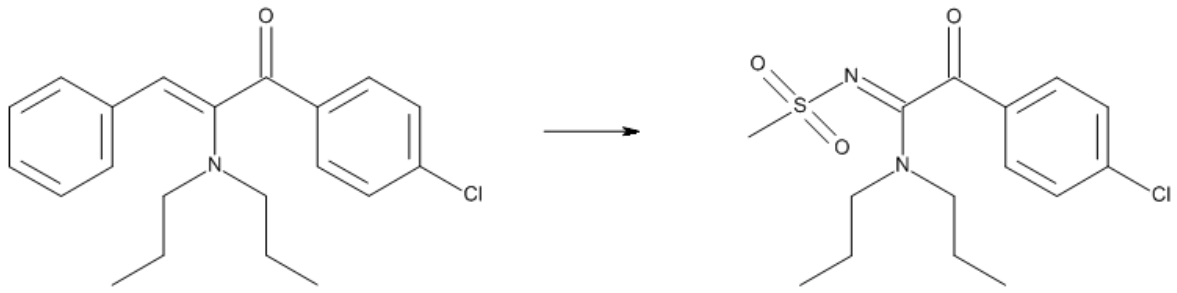
^{13}C NMR (100MHz, $CDCl_3$): δ11.90 ($NCH_2\mathbf{C}H_3$), 13.73 ($NCH_2\mathbf{C}H_3$), 42.59 ($SO_2\mathbf{C}H_3$), 42.75 ($NC\mathbf{H}_2CH_3$), 44.26 ($NC\mathbf{H}_2CH_3$), 124.65 (Ar), 130.11 (Ar), 132.78 (Ar), 141.36 (Ar), 161.32 (N=**C**-N), 191.35 (**C**=O).

micrOTOF-Q MS m/z $C_{13}H_{17}ClN_2O_3S$+Na, calculated 339.0541, observed 339.0535.

IR (cm^{-1}): 781, 823, 950, 1132, 1239, 1291, 1439, 1558, 1681, 2980.

M.p.: 177-179 ^{o}C.

2.2.4.8 Synthesis of 2-(4-chlorophenyl)-N'-methylsulfonyl-2-oxo-N,N-dipropyl-acetamidine



(102)

(113)
$C_{15}H_{21}ClN_2O_3S$
MW = 344.86g/mol

Under an atmosphere of nitrogen, a solution of 1-(4-chlorophenyl)-2-(dipropylamino)-3-phenyl-prop-2-en-1-one **(102)** (5.00 g, 14.63 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (1.77 g, 14.63 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether: ethyl acetate solvent system to yield the pure product as an orange oil (3.21 g, 64%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.73 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.01 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.42-1.66 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.70-11.87 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.97 (3H, s, $SO_2C\mathbf{H}_3$); δ3.00 (2H, t, J=7.8Hz, $NC\mathbf{H}_2CH_2CH_3$); δ3.31-3.46 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.60-3.72 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.51 (2H, d, J=8.8Hz, Ar**H**); δ7.84 (2H, d, J=8.6Hz, Ar**H**).

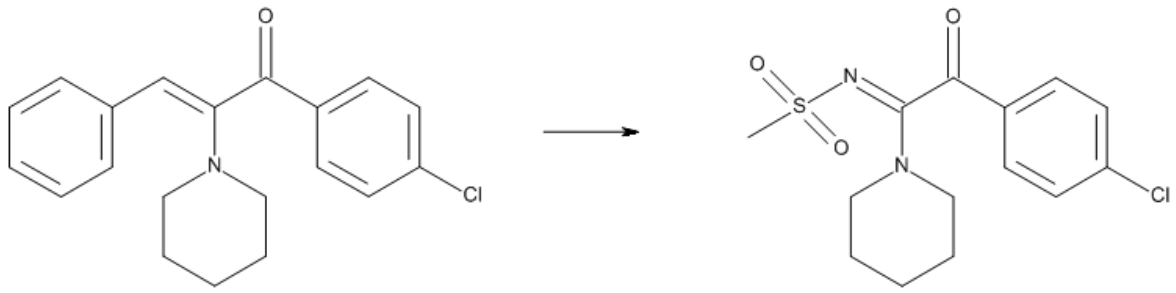
^{13}C NMR (100MHz, $CDCl_3$): δ10.88 ($NCH_2CH_2\mathbf{C}H_3$), 11.43 ($NCH_2CH_2\mathbf{C}H_3$), 19.87 ($NCH_2\mathbf{C}H_2CH_3$), 21.72 ($NCH_2\mathbf{C}H_2CH_3$), 42.59 ($SO_2\mathbf{C}H_3$), 49.71 ($N\mathbf{C}H_2CH_2CH_3$), 51.40 ($N\mathbf{C}H_2CH_2CH_3$), 129.66 (Ar), 130.10 (Ar), 132.87 (Ar), 141.36 (Ar), 161.82 (N=**C**-N), 191.46 (**C**=O).

micrOTOF-Q MS m/z $C_{15}H_{21}ClN_2O_3S$+Na, calculated 367.0854, observed 367.0849.

IR (cm^{-1}): 837, 956, 1008, 1083, 1110, 1126, 1222, 1285, 1551, 1684.

M.p.: 174-176 ^{o}C.

2.2.4.9 Synthesis of N-[2-(4-chlorophenyl)-2-oxo-1-(1-piperidyl)ethylidene] methanesulfonamide



(103)

(114)
$C_{14}H_{17}ClN_2O_3S$
MW = 328.81g/mol

Under an atmosphere of nitrogen, a solution of 1-(4-chlorophenyl)-3-phenyl-2-(1-piperidyl)prop-2-en-1-one **(103)** (4.50 g, 13.81 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (1.67 g, 13.81 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography using a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a dark red oil (2.01 g, 44%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.36-1.61 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.65-1.79 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.98 (3H, s, $SO_2C\mathbf{H}_3$); δ3.12-3.26 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.79-3.88 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ7.52 (2H, d, J=8.7Hz, Ar**H**); δ7.86 (2H, d, J=8.6Hz, Ar**H**).

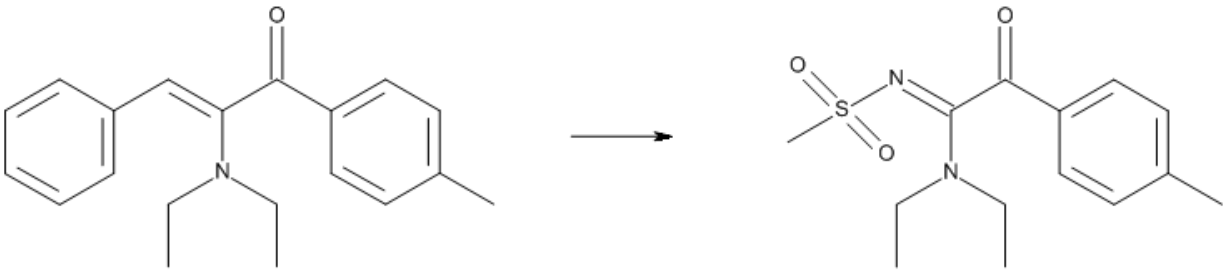
^{13}C NMR (100MHz, $CDCl_3$): δ23.82 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.26 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 26.10 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 42.62 ($SO_2\mathbf{C}H_3$), 45.98 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 48.85 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 129.71 (Ar), 130.11 (Ar), 132.78 (Ar), 141.54 (Ar), 160.78 (N=**C**-N), 191.98 (**C**=O).

micrOTOF-Q MS m/z $C_{14}H_{17}N_2ClO_3S$+Na, calculated 351.0541, observed 351.0531.

IR (cm^{-1}): 762, 807, 966, 1089, 1131, 1221, 1282, 1293, 1549, 1682.

M.p.: 163-165 ^{o}C.

2.2.4.10 Synthesis of N,N-diethyl-N'-methylsulfonyl-2-oxo-2-(p-tolyl)acetamidine



(104)

(115)
$C_{14}H_{20}N_2O_3S$
MW = 296.38g/mol

Under an atmosphere of nitrogen, a solution of 2-(diethylamino)-3-phenyl-1-(p-tolyl)prop-2-en-1-one **(104)** (5.00 g, 17.04 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (2.06 g, 17.04 mmol) in ethanol (40 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a dark yellow oil (1.01 g, 20%).

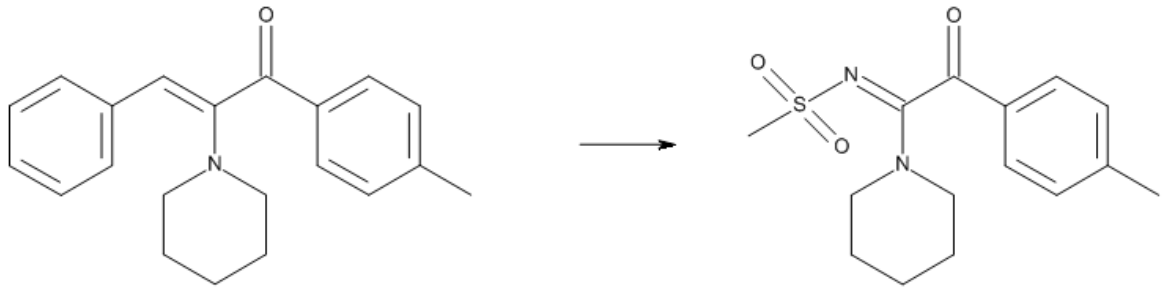
^{1}H NMR (400MHz, $CDCl_3$): δ1.08 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.33 (3H, t, J=7.01Hz, $NCH_2C\mathbf{H}_3$); δ2.43 (3H, s, $ArC\mathbf{H}_3$); δ2.95 (3H, s, $SO_2C\mathbf{H}_3$); δ3.15 (2H, sept, J=6.7Hz, $NC\mathbf{H}_2CH_3$); δ3.45-3.57 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.68-3.79 (1H, m, $NC\mathbf{H}_2CH_3$); δ7.33 (2H, d, J=8.1Hz, Ar**H**); δ7.78 (2H, d, J=8.1Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.90 ($NCH_2\mathbf{C}H_3$), 13.69 ($NCH_2\mathbf{C}H_3$), 21.92 ($Ar\mathbf{C}H_3$), 42.58 ($SO_2\mathbf{C}H_3$), 42.60 ($N\mathbf{C}H_2CH_3$), 44.23 ($N\mathbf{C}H_2CH_3$), 128.94 (Ar), 129.96 (Ar), 131.99 (Ar), 146.17 (Ar), 162.03 (N=**C**-N), 191.94 (**C**=O).

micrOTOF-Q MS m/z $C_{14}H_{20}N_2O_3S$+Na, calculated 319.1087, observed 319.1077.

IR (cm^{-1}): 938, 950, 964, 1131, 1117, 1236, 1290, 1315, 1441, 1553.

2.2.4.11 Synthesis of N-[2-oxo-1-(1-piperidyl)-2-(p-tolyl)ethylidene] methanesulfonamide



(105)

(116)
$C_{15}H_{20}N_2O_3S$
MW = 308.40g/mol

Under an atmosphere of nitrogen, a solution of 3-phenyl-2-(1-piperidyl)-1-(p-tolyl)prop-2-en-1-one **(105)** (5.00 g, 16.37 mmol) in ethanol (40 ml) was added to a solution of methanesulfonyl azide (1.98 g, 16.37 mmol) in ethanol (10 ml). The reaction mixture was set to stir at reflux for 24 hours. After this time, solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a dark red oil (2.09 g, 42%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.36-1.60 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.64-1.79 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.43 (3H, s, $ArC\mathbf{H}_3$); δ2.97 (3H, s, $SO_2C\mathbf{H}_3$); δ3.11-3.29 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.74-3.93 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ7.33 (2H, d, J=7.9Hz, Ar**H**); δ7.81 (2H, d, J=7.8Hz, Ar**H**).

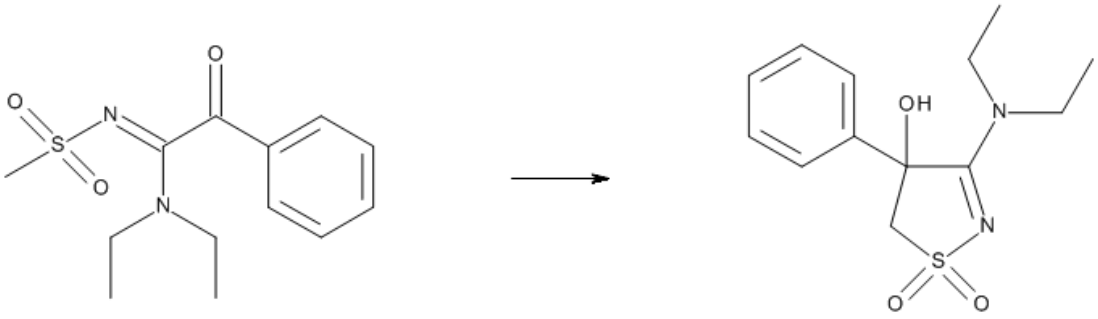
^{13}C NMR (100MHz, $CDCl_3$): δ21.93 ($Ar\mathbf{C}H_3$), 23.85 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.28 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 26.06 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 42.63 ($SO_2C\mathbf{H}_3$), 45.83 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 48.83 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 128.98 (Ar), 130.00 (Ar), 132.04 (Ar), 146.29 (Ar), 161.45 (N=**C**-N), 192.54 (**C**=O).

micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_3S$+Na, calculated 331.1087, observed 331.1083.

IR (cm^{-1}): 804, 860, 968, 1114, 1132, 1227, 1294, 1449, 1546, 1673.

2.2.5 Experimental Procedures for the Synthesis of 3-Dialkylamino-4-hydroxy-4-aryl-isothiazoline-1,1-dioxides

2.2.5.1 Synthesis of 3-(diethylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



(106)

(117)
$C_{13}H_{18}N_2O_3S$
MW = 282.36g/mol

To N,N-diethyl-N'-methylsulfonyl-2-oxo-2-phenyl-acetamidine **(106)** (3.50 g, 12.40 mmol) in dry tetrahydrofuran (28 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (6.96 ml, 12.40 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as an off-white solid (2.85 g, 81%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.74 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.24 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ3.27 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.39-3.58 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.67 (1H, d, J=14.1Hz, $SO_2C\mathbf{H_2}$); δ3.91 (1H, d, J=14.2Hz, $SO_2C\mathbf{H_2}$); δ5.44 (1H, broad, O**H**); δ7.34 (1H, tt, J=7.2Hz, 2.1Hz, Ph**H**); δ7.41 (2H, t, J=7.2Hz, Ph**H**); δ7.53 (2H, *appt.* d, J=7.9Hz, Ph**H**).

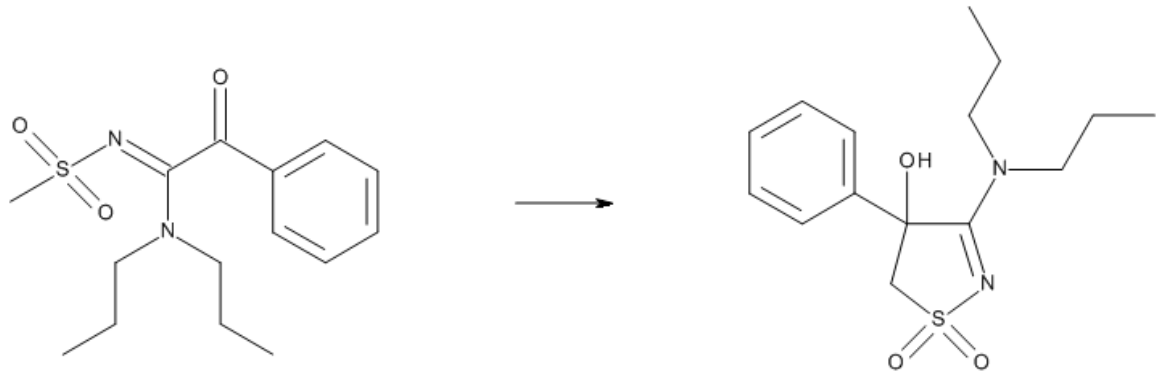
^{13}C NMR (100MHz, $CDCl_3$): δ11.34 ($NCH_2\mathbf{C}H_3$), 12.60 ($NCH_2\mathbf{C}H_3$), 43.43 ($N\mathbf{C}H_2CH_3$), 44.90 ($N\mathbf{C}H_2CH_3$), 64.59 ($SO_2\mathbf{C}H_2$), 83.65 (**C**OH), 123.94 (Ph**C**), 128.46 (Ph**C**), 129.11 (Ph**C**), 141.00 (Ph**C**), 168.49 (N=**C**-N).

micrOTOF-Q MS m/z $C_{13}H_{18}N_2O_3S$+Na, calculated 305.0930, observed 305.0923.

IR (cm^{-1}): 762, 846, 917, 965, 1070, 1121, 1232, 1292, 1578, 3424.

M.p.: 164-166 ^oC.

2.2.5.2 Synthesis of 3-(dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



(107)

(118)
$C_{15}H_{22}N_2O_3S$
MW = 310.41g/mol

To N'-methylsulfonyl-2-oxo-2-phenyl-N,N-dipropyl-acetamidine **(107)** (1.00 g, 3.22 mmol) in dry tetrahydrofuran (8 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (1.81 ml) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure yielding the product as an off-white solid (960 mg, 96%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.56 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.77-0.87 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ0.90 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.38-1.52 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.56-1.69 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.70-1.83 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.16 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.36 (2H, m $NC\mathbf{H}_2CH_2CH_3$); δ3.66 (1H, d, J=14.0Hz, $SO_2C\mathbf{H}_2$); δ3.95 (1H, d, J=14.2Hz, $SO_2C\mathbf{H}_2$); δ5.69 (1H, s, O**H**); δ7.33 (1H, m, Ph**H**); δ7.40 (2H, t, J=7.9Hz, Ph**H**); δ7.55 (2H, d, J=8.0Hz, Ph**H**).

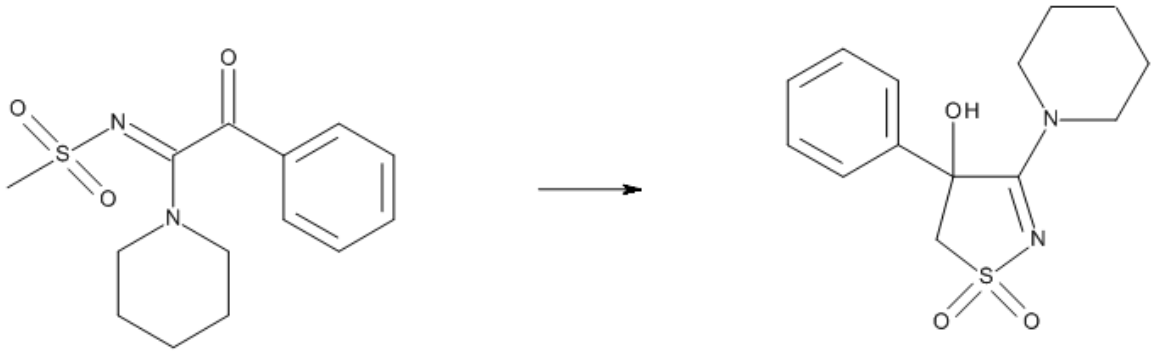
^{13}C NMR (100MHz, $CDCl_3$): δ10.81 ($NCH_2CH_2\mathbf{C}H_3$), 11.30 ($NCH_2CH_2\mathbf{C}H_3$), 19.27 ($NCH_2\mathbf{C}H_2CH_3$), 20.89 ($NCH_2\mathbf{C}H_2CH_3$), 50.65 ($N\mathbf{C}H_2CH_2CH_3$), 52.13 ($N\mathbf{C}H_2CH_2CH_3$), 64.47 ($SO_2\mathbf{C}H_2$), 83.72 (**C**OH), 123.97 (Ph**C**) 128.41 (Ph**C**), 129.02 (Ph**C**), 141.24 (Ph**C**), 169.00 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{22}N_2O_3S$+Na, calculated 333.1243, observed 333.1240.

IR (cm^{-1}): 767, 853, 905, 1070, 1122, 1146, 1223, 1282, 1580.

M.p.: 136-138 ^{o}C.

2.2.5.3 Synthesis of 3-(dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



(108)

(119)
$C_{14}H_{18}N_2O_3S$
MW = 294.37g/mol

To N-[2-oxo-2-phenyl-1-(1-piperidyl)ethylidene] methanesulfonamide **(108)** (896 mg, 3.04 mmol) in dry tetrahydrofuran (7 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (1.71 ml, 3.04 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure yielding the product as an orange solid (780 mg, 87%).

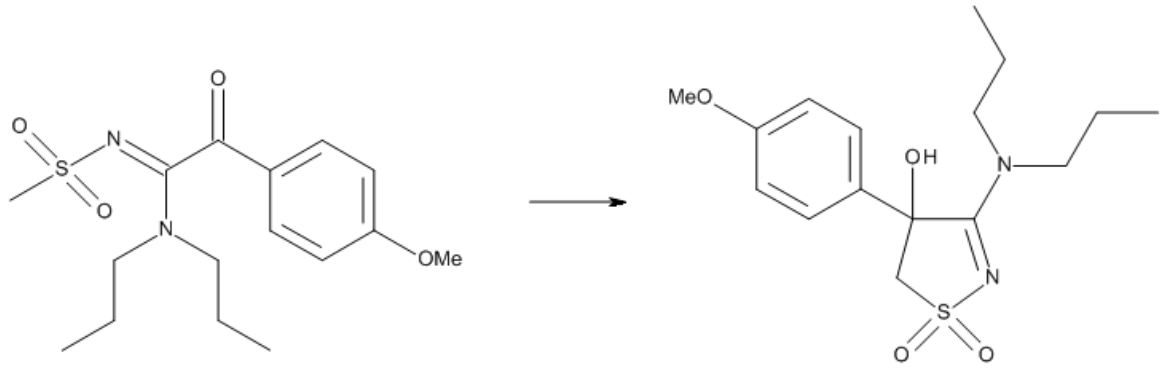
^{1}H NMR (400MHz, $CDCl_3$): δ0.84-0.97 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.29-1.42 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.45-1.72 (5H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.34 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.66 (1H, d, J=14.2, $SO_2C\mathbf{H}_2$); δ3.67-3.72 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.90 (1H, d, J=14.2, $SO_2C\mathbf{H}_2$); δ6.36 (1H, broad, O**H**); δ7.29-7.35 (1H, m, Ph**H**); δ7.40 (2H, t, J=7.3Hz, Ph**H**); δ7.53 (2H, *appt.* d, J=7.5Hz, Ph**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ23.69 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), δ25.24 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), δ25.36 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), δ25.61 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), δ48.37 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), δ65.00 (**C**OH), δ83.49 (SO_2CH_2), δ123.79 (Ph**C**), δ128.52 (Ph**C**), δ129.17 (Ph**C**), δ140.74 (Ph**C**), δ167.64 (N=**C**-N).

IR (cm^{-1}): 766, 859, 943, 1073, 1124, 1141, 1227, 1287, 1586.

M.p.: 172-174 ^oC.

2.2.5.4 Synthesis of 3-(dipropylamino)-4-(4-methoxyphenyl)-1,1-dioxo-5H-isothiazol-4-ol



(109)

(120)
$C_{16}H_{24}N_2O_4S$
MW = 340.44g/mol

To 2-(4-methoxyphenyl)-N'-methylsulfonyl-2-oxo-N,N-dipropyl-acetamidine **(109)** (3.40 g, 9.98 mmol) in dry tetrahydrofuran (12 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (6.00 ml, 9.98 mmol) was added rapidly at room temperature and the reaction mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a yellow oil (3.35 g, 99%).

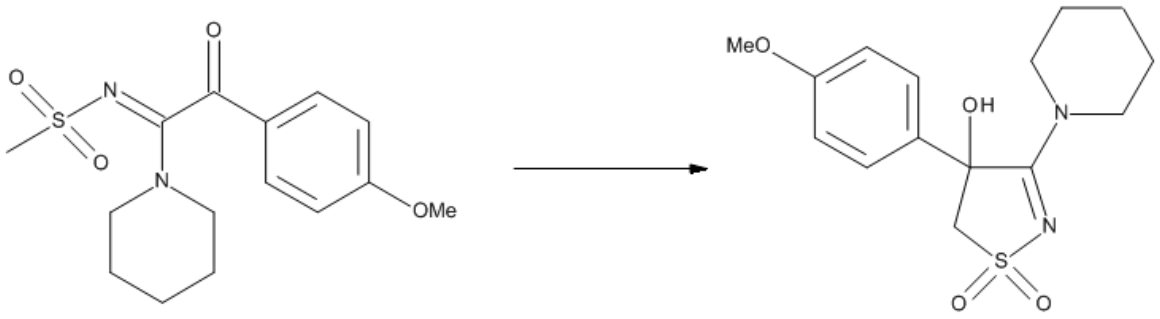
^{1}H NMR (400MHz, $CDCl_3$): δ0.60 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.87-0.96 (4H, m, $NCH_2CH_2C\mathbf{H}_3$, $NCH_2C\mathbf{H}_2CH_3$); δ1.40-1.51 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.57-1.80 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.15 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.35 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.62 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ3.82 (3H, s, $ArOC\mathbf{H}_3$); δ3.89 (1H, d, J=14.0Hz, $SO_2C\mathbf{H}_2$); δ5.52-5.89 (1H, broad, O**H**); δ6.91 (2H, d, J=8.9Hz, Ar**H**); δ7.45 (2H, d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.88 ($NCH_2CH_2\mathbf{C}H_3$), 11.29 ($NCH_2CH_2\mathbf{C}H_3$), 19.29 ($NCH_2\mathbf{C}H_2CH_3$), 21.01 ($NCH_2\mathbf{C}H_2CH_3$), 50.62 ($N\mathbf{C}H_2CH_2CH_3$), 52.15 ($N\mathbf{C}H_2CH_2CH_3$), 55.36 ($ArO\mathbf{C}H_3$), 64.62 ($SO_2\mathbf{C}H_2$), 83.54 (**C**OH), 114.31 (Ar), 125.28 (Ar), 133.03 (Ar), 159.52 (Ar), 169.02 (N=**C**-N).

micrOTOF-Q MS m/z $C_{16}H_{24}N_2O_4S$+Na, calculated 363.1349, observed 363.1340.

IR (cm^{-1}): 834, 857, 913, 1033, 1127, 1147, 1229, 1264, 1513, 1581.

2.2.5.5 Synthesis of 3-(dipropylamino)-4-(4-methoxyphenyl)-1,1-dioxo-5H-isothiazol-4-ol



(110)

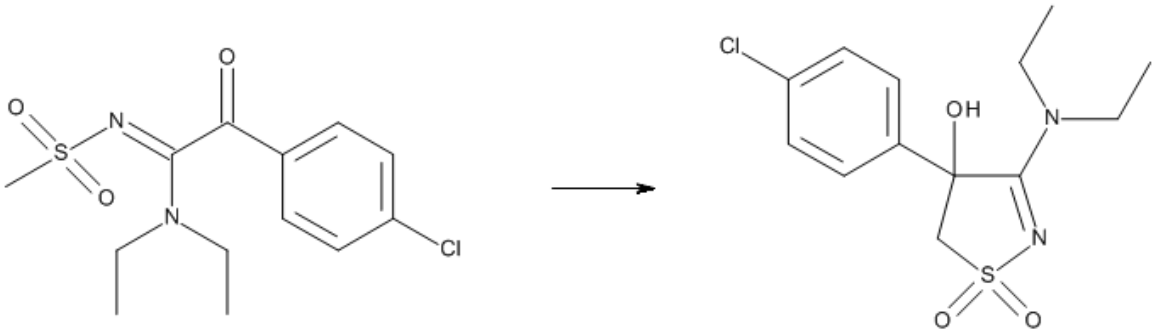
(121)
$C_{15}H_{20}N_2O_4S$
MW = 324.39g/mol

To N-[2-(4-methoxyphenyl)-2-oxo-1-(1-piperidyl)ethylidene] methanesulfonamide **(110)** (1.10 g, 3.39 mmol) in dry tetrahydrofuran (9 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (1.90 ml, 3.39 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as an off-white solid (660 mg, 60%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.93-1.05 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.36-1.73 (6H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.21-3.30 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.44-3.52 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.64 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ3.68-3.73 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.81 (3H, s, $ArOC\mathbf{H}_3$); δ3.94 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ5.39-6.14 (1H, broad, O**H**); δ6.91 (2H, d, J=8.9Hz, Ar**H**); δ7.44 (2H, d, J=8.8Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ23.75 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.33 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 25.39 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 48.28 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 49.26 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 55.30 ($ArO\mathbf{C}H_3$), 64.71 ($SO_2\mathbf{C}H_2$), 83.38 (**C**OH), 114.28 (Ar), 125.26 (Ar), 133.17 (Ar), 159.41 (Ar), 168.20 (N=**C**-N).

2.2.5.6 Synthesis of 4-(4-chlorophenyl)-3-(diethylamino)-1,1-dioxo-5H-isothiazol-4-ol



(112)

(123)
$C_{13}H_{17}ClN_2O_3S$
MW = 316.80g/mol

To 2-(4-chlorophenyl)-N,N-diethyl-N'-methylsulfonyl-2-oxo-acetamidine **(112)** (1.92 g, 6.06 mmol) in dry tetrahydrofuran (10 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (4.08 ml, 7.27 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as an off-white solid (1.60 g, 83%).

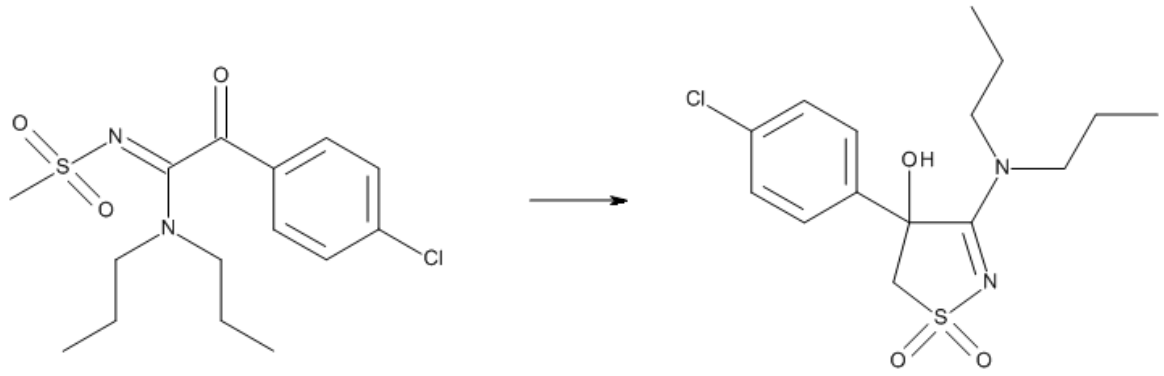
^{1}H NMR (400MHz, $CDCl_3$): δ0.81 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.22 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ3.25 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.48 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.62 (1H, d, J=14.2Hz, $SO_2C\mathbf{H}_2$); δ3.91 (1H, d, J=14.2Hz, $SO_2C\mathbf{H}_2$); δ5.70-5.94 (1H, broad, O**H**); δ7.39 (2H, d, J=8.7Hz, Ar**H**); δ7.48 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.32 ($NCH_2\mathbf{C}H_3$), 12.80 ($NCH_2\mathbf{C}H_3$), 43.43 ($N\mathbf{C}H_2CH_3$), 44.99 ($N\mathbf{C}H_2CH_3$), 64.24 ($SO_2\mathbf{C}H_2$), 83.30 (**C**OH), 125.53 (Ar), 129.30 (Ar), 134.49 (Ar), 139.61 (Ar), 168.27 (N=**C**-N).

micrOTOF-Q MS m/z $C_{13}H_{17}ClN_2O_3S$+Na, calculated 339.0541, observed 339.0533.

IR (cm^{-1}): 838, 916, 967, 1078, 1141, 1124, 1207, 1220, 1286, 1585.

2.2.5.7 Synthesis of 4-(4-chlorophenyl)-3-(dipropylamino)-1,1-dioxo-5H-isothiazol-4-ol



(113)

(124)
$C_{15}H_{21}ClN_2O_3S$
MW = 344.86g/mol

To 2-(4-chlorophenyl)-N'-methylsulfonyl-2-oxo-N,N-dipropyl-acetamidine **(113)** (3.21 g, 9.31 mmol) in dry tetrahydrofuran (15 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (6.27 ml, 11.17 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a red oil (2.45 g, 76%).

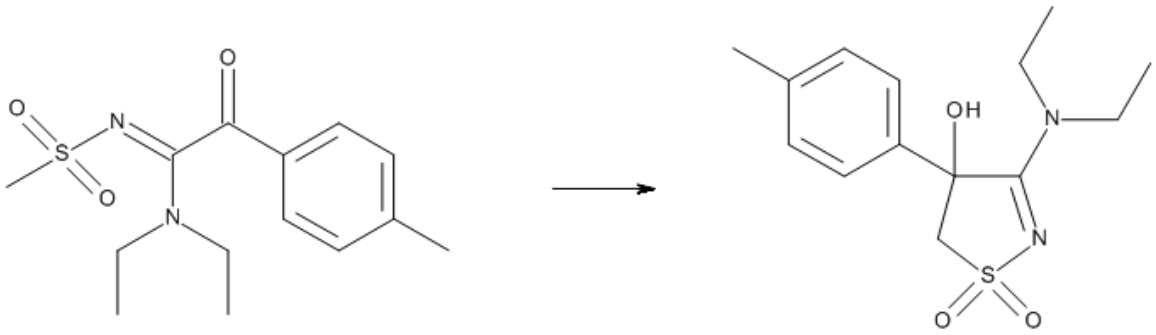
^{1}H NMR (400MHz, $CDCl_3$): δ0.62 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.91 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.94-1.03 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.48-1.53 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.54-1.67 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.68-1.78 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.03-3.20 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.23-3.33 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.39-3.48 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.60 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ3.90 (1H, d, J=14.2Hz, $SO_2C\mathbf{H}_2$); δ5.51-5.81 (1H, broad, O**H**); δ7.39 (2H, d, J=8.7Hz, Ar**H**); δ7.49 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.84 ($NCH_2CH_2\mathbf{C}H_3$), 11.27 ($NCH_2CH_2\mathbf{C}H_3$), 19.27 ($NCH_2\mathbf{C}H_2CH_3$), 21.07 ($NCH_2\mathbf{C}H_2CH_3$), 50.66 ($N\mathbf{C}H_2CH_2CH_3$), 52.18 ($N\mathbf{C}H_2CH_2CH_3$), 64.24 ($SO_2\mathbf{C}H_2$), 83.37 (**C**OH), 125.54 (Ar), 129.25 (Ar), 134.46 (Ar), 139.69 (Ar), 168.56 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{21}ClN_2O_3S$+Na, calculated 367.0854, observed 367.0852.

IR (cm^{-1}): 815, 856, 912, 1081, 1129, 1143, 1226, 1276, 1578.

2.2.5.8 Synthesis of 3-(diethylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol



(115)

(126)
$C_{14}H_{20}N_2O_3S$
MW = 296.38g/mol

To N,N-diethyl-N'-methylsulfonyl-2-oxo-2-(p-tolyl)acetamidine **(115)** (1.07 g, 3.41 mmol) in dry tetrahydrofuran (7 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (2.29 ml, 4.09 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a yellow solid (780 mg, 77%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.78 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.23 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ2.35 (3H, s, $ArC\mathbf{H}_3$); δ3.28 (2H, n, J=8.2Hz, $NC\mathbf{H}_2CH_3$); δ3.47 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.63 (1H, d, J=14.0Hz, $SO_2C\mathbf{H}_2$); δ3.93 (1H, d, J=14.0Hz, $SO_2C\mathbf{H}_2$); δ5.57 (1H, s, O**H**); δ7.20 (2H, d, J=8.0Hz, Ar**H**); δ7.41 (2H, d, J=7.9Hz, Ar**H**).

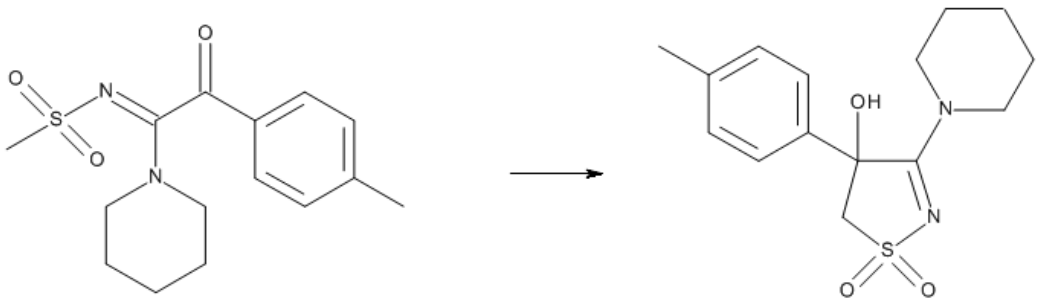
^{13}C NMR (100MHz, $CDCl_3$): δ11.33 ($NCH_2\mathbf{C}H_3$), 12.71 ($NCH_2\mathbf{C}H_3$), 21.09 ($Ar\mathbf{C}H_3$), 43.45 ($N\mathbf{C}H_2CH_3$), 44.87 ($N\mathbf{C}H_2CH_3$), 64.44 ($SO_2\mathbf{C}H_2$), 83.64 (**C**OH), 123.85 (Ar), 129.66 (Ar), 138.13 (Ar), 138.20 (Ar), 168.85 (N=**C**-N).

micrOTOF-Q MS m/z $C_{14}H_{20}N_2O_3S$+Na, calculated 319.1087, observed 319.1086.

IR (cm^{-1}): 820, 854, 916, 964, 1076, 1128, 1144, 1228, 1297, 1585, 3395.

M.p.: 179-180 ^oC.

2.2.5.9 Synthesis of 3-(dipropylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol



(116)

(127)
$C_{15}H_{20}N_2O_3S$
MW = 308.40g/mol

To N-[2-oxo-1-(1-piperidyl)-2-(p-tolyl)ethylidene] methanesulfonamide **(116)** (2.09 g, 6.78 mmol) in dry tetrahydrofuran (10 ml) under an atmosphere of nitrogen, a 20% w/v solution of potassium t-butoxide in tetrahydrofuran (4.57 ml, 8.14 mmol) was added rapidly at room temperature and the mixture set to stir for 24 hours. After this time, the reaction mixture was neutralised with 1M hydrochloric acid. The aqueous mixture was extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a dark brown solid (830 mg, 42%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.95-1.05 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.38-1.53 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ1.54-1.63 (2H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ1.64-1.75 (1H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.35 (3H, s, $ArC\mathbf{H}_3$); δ3.17-3.26 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.45-3.54 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.63-3.70 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.65 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ3.72-3.81 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.96 (1H, d, J=14.1Hz, $SO_2C\mathbf{H}_2$); δ5.56 (1H, s, O**H**); δ7.20 (2H, d, J=7.8Hz, Ar**H**); δ7.40 (2H, d, J=7.6Hz, Ar**H**).

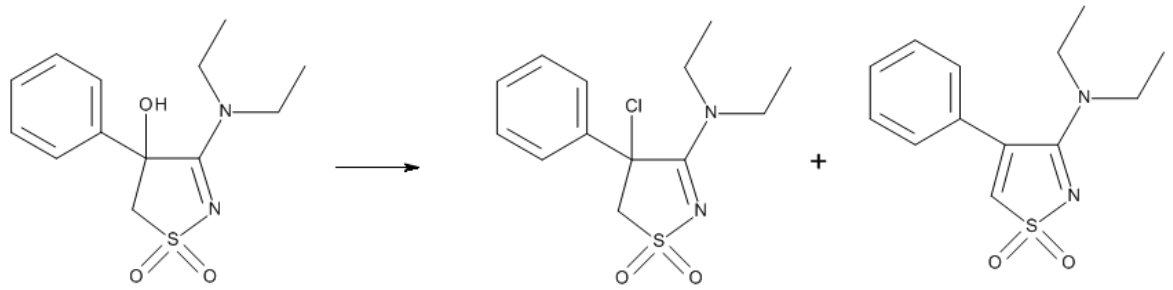
^{13}C NMR (100MHz, $CDCl_3$): δ21.10 ($Ar\mathbf{C}H_3$), 23.76 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.25 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 25.39 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 48.34 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 49.27 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 64.68 ($SO_2C\mathbf{H}_2$), 83.54 (**C**OH), 123.80 (Ar), 129.66 (Ar), 138.09 (Ar), 138.18 (Ar), 168.21 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_3S$+Na, calculated 331.1087, observed 331.1085.

IR (cm^{-1}): 803, 859, 942, 1073, 1138, 1217, 1289, 1442, 1594, 3348.

2.2.6 Experimental Procedures for the Synthesis of 3-Dialkylamino-4-chloro-4-aryl-isothiazoline-1,1-dioxides

2.2.6.1 Synthesis of 4-chloro-N,N-diethyl-1,1-dioxo-4-phenyl-5H-isothiazol-3-amine and N,N-diethyl-1,1-dioxo-4-phenyl-isothiazol-3-amine



(117)

(128)
$C_{13}H_{17}ClN_2O_2S$
MW = 300.80g/mol

(137)
$C_{13}H_{16}N_2O_2S$
MW = 264.34g/mol

Under an atmosphere of nitrogen, thionyl chloride (21.96ml, 302.70mmol) was added to 3-(diethylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol **(117)** (2.85g, 10.09mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude products were purified by gravity column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield a mixture of the chlorinated (1.69g, 56%) and dehydrochlorinated (828mg, 31%) products.

2.2.6.1.1 Data for 4-chloro-N,N-diethyl-1,1-dioxo-4-phenyl-5H-isothiazol-3-amine (128)

^{1}H NMR (400MHz, $CDCl_3$): δ0.82 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.29 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ3.09 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.58 (1H, m, J=7.0Hz, $NC\mathbf{H}_2CH_3$); δ3.61-3.69 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.83 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ4.18 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ7.38-7.53 (5H, m, Ph**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.08 ($NCH_2\mathbf{C}H_3$), 12.17 ($NCH_2\mathbf{C}H_3$), 44.06 ($NC\mathbf{H}_2CH_3$), 45.03 ($NC\mathbf{H}_2CH_3$), 67.86 ($SO_2\mathbf{C}H_2$), 71.20 (**C**Cl), 124.65 (Ph**C**), 129.41 (Ph**C**), 129.64 (Ph**C**), 138.57 (Ph**C**), 164.43 (N=**C**-N).

micrOTOF-Q MS m/z $C_{13}H_{17}ClN_2O_2S$+Na, calculated 323.0591, observed 323.0607.

IR (cm^{-1}): 697, 754, 771, 904, 1119, 1143, 1233, 1312, 1585.

2.2.6.1.2 Data for N,N-diethyl-1,1-dioxo-4-phenyl-isothiazol-3-amine (137)

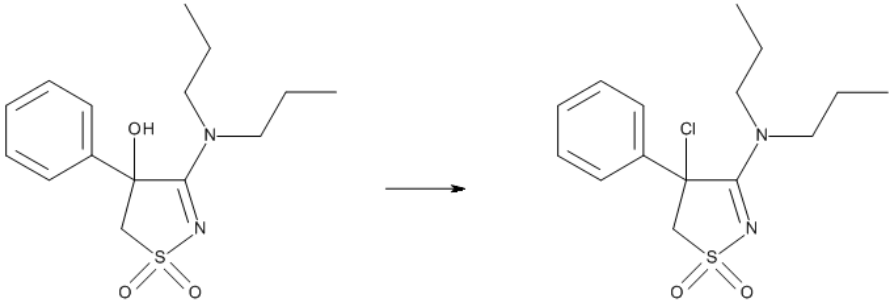
^{1}H NMR (400MHz, $CDCl_3$): δ0.90 (3H, t, J=6.8Hz, $NCH_2C\mathbf{H}_3$); δ1.31 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ3.08 (2H, q, J=7.0Hz, $NC\mathbf{H}_2CH_3$); δ3.64 (2H, q, J=7.0Hz, $NC\mathbf{H}_2CH_3$); δ7.21 (1H, s, $SO_2C\mathbf{H}$); δ7.30-7.34 (2H, m, Ph**H**); δ7.45-7.49 (3H, m, Ph**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.94 ($NCH_2\mathbf{C}H_3$), 14.03 ($NCH_2\mathbf{C}H_3$), 43.84 ($N\mathbf{C}H_2CH_3$), 46.69 ($N\mathbf{C}H_2CH_3$), 127.32 (Ph**C**), 129.15 (Ph**C**), 129.76 (Ph**C**), 132.00 (SO_2C=**C**), 139.62 ($SO_2\mathbf{C}$=C), 143.28 (Ph**C**), 160.71 (N=**C**-N).

micrOTOF-Q MS m/z $C_{13}H_{16}N_2O_2S$+Na, calculated 287.0825, observed 287.0844.

IR (cm^{-1}): 703, 740, 765, 825, 911, 1076, 1121, 1194, 1288, 1555, 3133.

2.2.6.2 Synthesis of 4-chloro-1,1-dioxo-4-phenyl-N,N-dipropyl-5H-isothiazol-3-amine



(118)

(129)
$C_{15}H_{21}ClN_2O_2S$
MW = 328.86g/mol

Under an atmosphere of nitrogen, thionyl chloride (6.72 ml, 92.70 mmol) was added to 3-(dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol **(118)** (960 mg, 3.09 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white solid (1.34 g, 55%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.50 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.85-1.00 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ0.95 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.41-1.57 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.64-1.85 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.89-3.05 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.38-3.53 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.83 (2H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ4.18 (2H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ7.40-7.50 (3H, m, Ph**H**); δ7.51-7.55 (2H, m, Ph**H**).

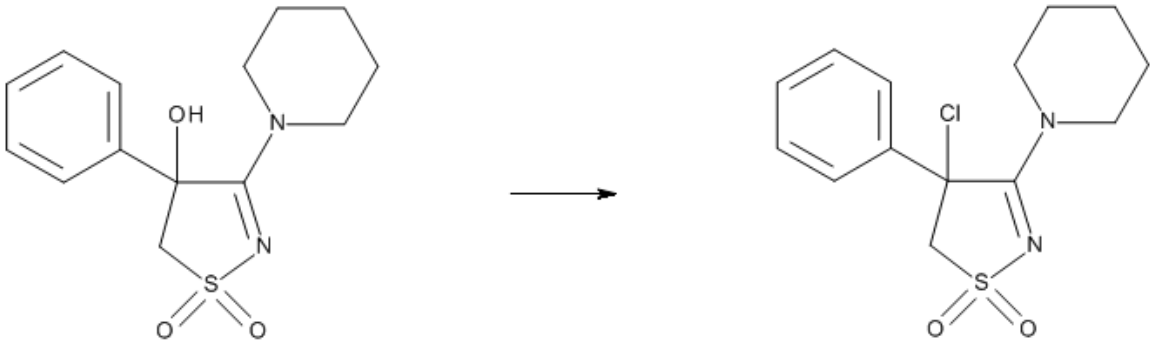
^{13}C NMR (100MHz, $CDCl_3$): δ10.74 ($NCH_2CH_2\mathbf{C}H_3$), 11.20 ($NCH_2CH_2\mathbf{C}H_3$), 19.07 ($NCH_2\mathbf{C}H_2CH_3$), 20.53 ($NCH_2\mathbf{C}H_2CH_3$), 51.22 ($N\mathbf{C}H_2CH_2CH_3$), 52.16 ($N\mathbf{C}H_2CH_2CH_3$), 68.00 ($SO_2\mathbf{C}H_2$), 71.36 (**C**Cl), 124.65 (Ph**C**), 129.42 (Ph**C**), 129.61 (Ph**C**), 138.51 (Ph**C**), 164.69 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{21}ClN_2O_2S$+Na, calculated 351.0904, observed 351.0903.

IR (cm^{-1}): 751, 843, 896, 915, 1142, 1202, 1237, 1316, 1436, 1580.

M.p.: 146-149 ^{o}C.

2.2.6.3 Synthesis of 4-chloro-4-phenyl-3-(1-piperidyl)-5H-isothiazole-1,1-dioxide



(119)

(130)
$C_{14}H_{17}ClN_2O_2S$
MW = 312.81g/mol

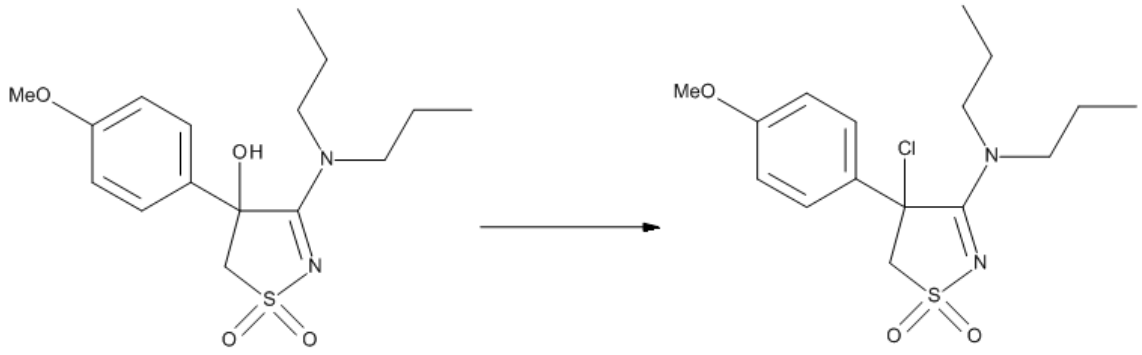
Under an atmosphere of nitrogen, thionyl chloride (5.77 ml, 79.50mmol) was added to 3-(dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol **(119)** (780 mg, 2.65 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 1:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a yellow oil (405 mg, 49%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.31-1.42 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.59-1.68 (2H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ1.70-1.83 (2H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ3.05-3.13 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.75-3.87 (2H, m, $N(\mathbf{CH}_2)_2(CH_2)_2CH_2$); δ7.25 (1H, s, $SO_2C\mathbf{H}$); δ7.30-7.34 (2H, m, Ph**H**); δ7.46-7.49 (3H, m, Ph**H**).

micrOTOF-Q MS m/z $C_{14}H_{17}N_2O_2SCl$+Na, calculated 299.0825, observed 299.0837.

IR (cm^{-1}): 762, 801, 852, 1120, 1169, 1189, 1289, 1444, 1552, 1594.

2.2.6.4 Synthesis of 4-chloro-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine



(120)

(131)
$C_{16}H_{23}ClN_2O_3S$
MW = 358.88g/mol

Under an atmosphere of nitrogen, thionyl chloride (6.38 ml, 87.90 mmol) was added to 3-(dipropylamino)-4-(4-methoxyphenyl)-1,1-dioxo-5H-isothiazol-4-ol **(120)** (1.00 g, 2.93 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a yellow solid (1.06 g, 97%).

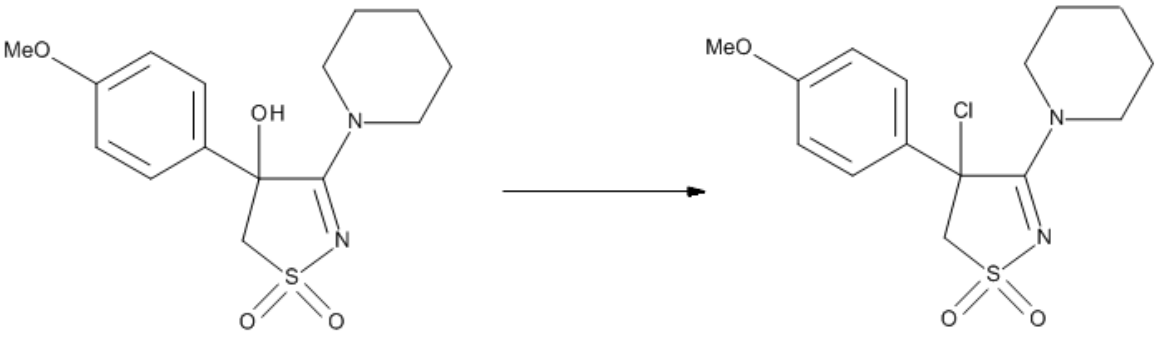
^{1}H NMR (400MHz, $CDCl_3$): δ0.57 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.95 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.00-1.14 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.45-4.60 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.61-1.87 (2H, m, $CH_2C\mathbf{H}_2CH_3$); δ2.89-3.08 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.35-3.44 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.47-3.56 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.81 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ3.84 (3H, s, $ArOC\mathbf{H}_3$); δ4.16 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ6.95 (2H, *appt.* d, J=9.0Hz, Ar**H**); δ7.42 (2H, *appt.* d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.84 ($NCH_2CH_2\mathbf{C}H_3$), 11.24 ($NCH_2CH_2\mathbf{C}H_3$), 19.12 ($NCH_2\mathbf{C}H_2CH_3$), 20.68 ($NCH_2\mathbf{C}H_2CH_3$), 51.21 ($N\mathbf{C}H_2CH_2CH_3$), 52.22 ($N\mathbf{C}H_2CH_2CH_3$), 55.51 ($ArO\mathbf{C}H_3$), 67.98 ($SO_2\mathbf{C}H_2$), 71.22 (**C**OH), 114.75 (Ar), 126.15 (Ar), 130.48 (Ar), 160.15 (Ar), 164.87 (N=**C**-N).

micrOTOF-Q MS m/z $C_{16}H_{23}ClN_2O_3S$+Na, calculated 381.1010, observed 381.1011.

IR (cm^{-1}): 832, 911, 1027, 1139, 1237, 1255, 1313, 1509, 1577, 2964.

2.2.6.5 Synthesis of 4-chloro-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine



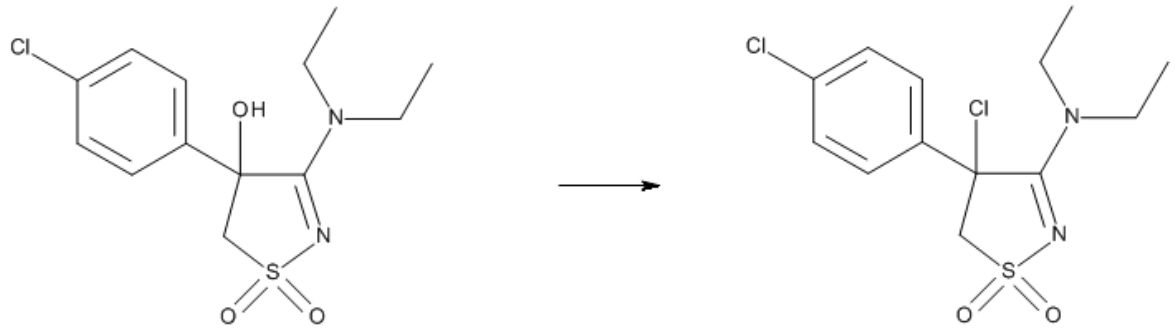
(121)

(132)
$C_{15}H_{19}ClN_2O_3S$
MW = 342.84g/mol

Under an atmosphere of nitrogen, thionyl chloride (4.42 ml, 60.90 mmol) was added to 3-(dipropylamino)-4-(4-methoxyphenyl)-1,1-dioxo-5H-isothiazol-4-ol **(121)** (660 mg, 2.03 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layers was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as an off-white solid (618 mg, 89%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.10-1.21 (1H, m, $N(CH_2)_2(CH_2)_2CH_2$); δ1.38-1.49 (1H, m, $N(CH_2)_2(CH_2)_2CH_2$); δ1.51-1.78 (5H, m, $N(CH_2)_2(CH_2)_2CH_2$, $N(CH_2)_2(CH_2)_2CH_2$); δ3.02-3.11 (1H, m, $N(CH_2)_2(CH_2)_2CH_2$); δ3.24-3.34 (1H, m, $N(CH_2)_2(CH_2)_2CH_2$); δ3.76-3.87 (2H, m, $N(CH_2)_2(CH_2)_2CH_2$); δ3.79 (1H, d, J=14.6Hz, SO_2CH_2); δ3.84 (3H, s, $ArOCH_3$); δ4.17 (1H, d, J=14.5Hz, SO_2CH_2); δ6.96 (2H, d, J=8.8Hz, ArH); δ7.42 (2H, d, J=8.8Hz, ArH).

2.2.6.6 Synthesis of 4-chloro-4-(4-chlorophenyl)-N,N-diethyl-1,1-dioxo-5H-isothiazol-3-amine



(123)

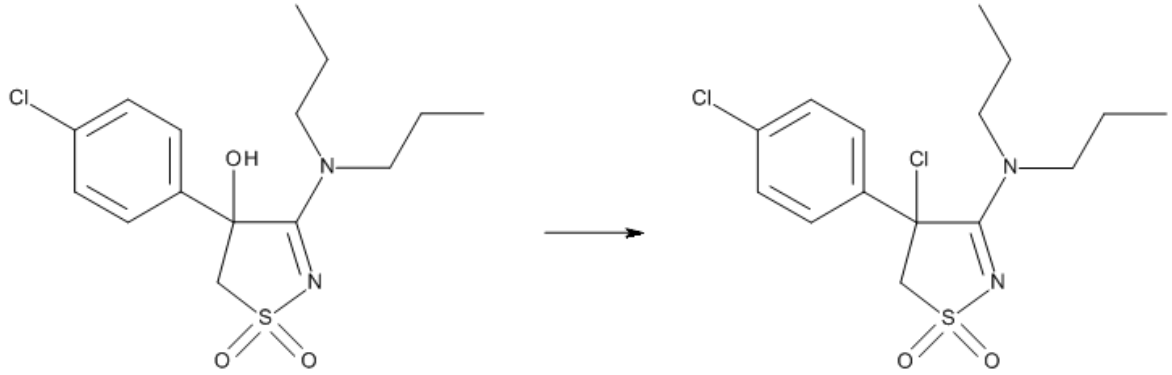
(133)
$C_{13}H_{16}Cl_2N_2O_2S$
MW = 335.25g/mol

Under an atmosphere of nitrogen, thionyl chloride (10.99 ml, 151.50 mmol) was added to 4-(4-chlorophenyl)-3-(diethylamino)-1,1-dioxo-5H-isothiazol-4-ol **(123)** (1.60 g, 5.05 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as an off-white solid (1.39 g, 82%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.91 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.29 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.97-3.22 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.45-3.56 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.61-3.72 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.79 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ4.17 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ7.42-7.48 (4H, m, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.08 ($NCH_2\mathbf{C}H_3$), 12.37 ($NCH_2\mathbf{C}H_3$), 44.07 ($N\mathbf{C}H_2CH_3$), 45.11 ($N\mathbf{C}H_2CH_3$), 67.59 ($SO_2\mathbf{C}H_2$), 70.64 (**C**Cl), 126.21 (Ar), 129.84 (Ar), 135.68 (Ar), 137.17 (Ar), 163.93 (N=**C**-N).

2.2.6.7 Synthesis of 4-chloro-4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine



(124)

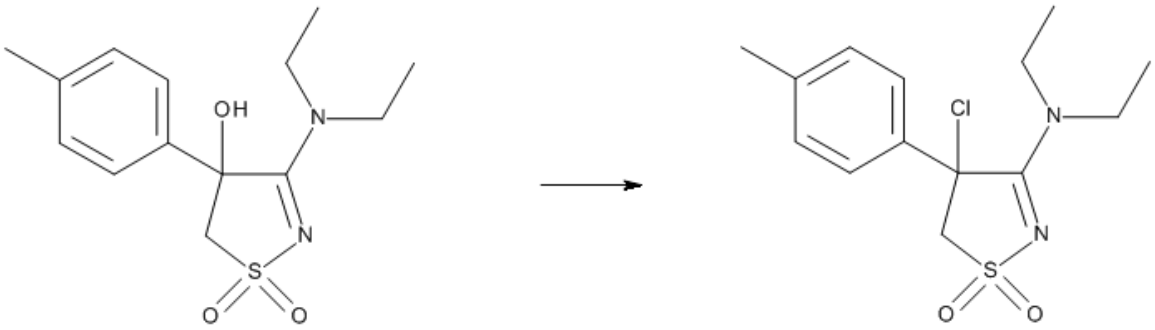
(134)
$C_{15}H_{20}Cl_2N_2O_2S$
MW = 363.30g/mol

Under an atmosphere of nitrogen, thionyl chloride (15.45 ml, 213.00 mmol) was added to 4-(4-chlorophenyl)-3-(dipropylamino)-1,1-dioxo-5H-isothiazol-4-ol **(124)** (2.45 g, 7.10 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a dark red oil (2.18 g, 85%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.58 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.95 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.02-1.16 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.48-1.84 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.84-3.04 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.35-3.45 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.49-3.56 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.79 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ4.17 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ7.42 (7.50, 4H, m, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.80 ($NCH_2CH_2\mathbf{C}H_3$), 11.21 ($NCH_2CH_2\mathbf{C}H_3$), 19.10 ($NCH_2\mathbf{C}H_2CH_3$), 20.72 ($NCH_2\mathbf{C}H_2CH_3$), 51.26 ($N\mathbf{C}H_2CH_2CH_3$), 52.26 ($N\mathbf{C}H_2CH_2CH_3$), 67.72 ($SO_2\mathbf{C}H_2$), 70.78 (**C**Cl), 126.24 (Ar), 129.79 (Ar), 135.66 (Ar), 137.18 (Ar), 164.16 (N=**C**-N).

2.2.6.8 Synthesis of 4-chloro-N,N-diethyl-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-3-amine



(126)

(135)
$C_{14}H_{19}ClN_2O_2S$
MW = 314.83g/mol

Under an atmosphere of nitrogen, thionyl chloride (5.75 ml, 78.90 mmol) was added to 3-(diethylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol **(126)** (780 mg, 2.63 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a yellow oil (545 mg, 66%).

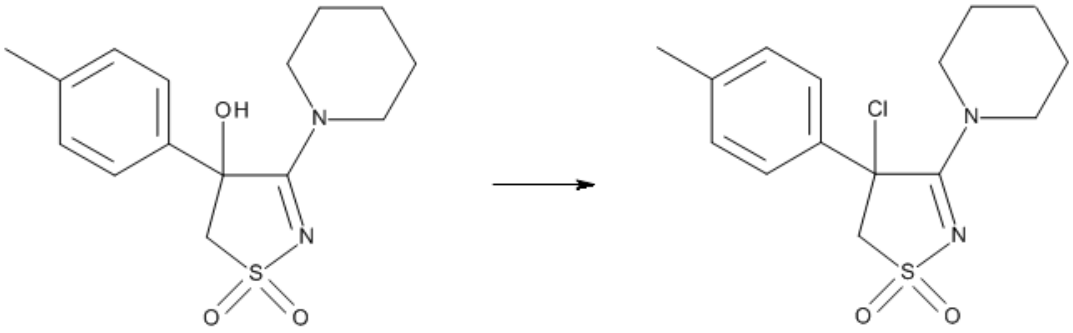
^{1}H NMR (400MHz, $CDCl_3$): δ0.87 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.29 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.38 (3H, s, $ArC\mathbf{H}_3$); δ3.02-3.24 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.45-3.57 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.60-3.71 (1H, m, $NC\mathbf{H}_2CH_3$); δ3.79 (1H, d, J=14.6Hz, $SO_2\mathbf{C}H_2$); δ4.14 (1H, d, J=14.6Hz, $SO_2\mathbf{C}H_2$); δ7.27 (2H, d, J=8.2Hz, Ar**H**); δ7.38 (2H, d, J=8.3Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.05 ($NCH_2\mathbf{C}H_3$), 12.20 ($NCH_2\mathbf{C}H_3$), 20.99 ($Ar\mathbf{C}H_3$), 44.11 ($N\mathbf{C}H_2CH_3$), 44.97 ($N\mathbf{C}H_2CH_3$), 67.86 ($SO_2\mathbf{C}H_2$), 71.18 (**C**Cl), 124.52 (Ar), 130.19 (Ar), 135.53 (Ar), 139.48 (Ar), 164.54 (N=**C**-N).

micrOTOF-Q MS m/z $C_{14}H_{19}N_2ClO_2S$+Na, calculated 337.0745, observed 337.0747.

IR (cm^{-1}): 781, 822, 905, 971, 1141, 1189, 1201, 1235, 1312, 1587.

2.2.6.9 Synthesis of 4-chloro-1,1-dioxo-N,N-dipropyl-4-(p-tolyl)-5H-isothiazol-3-amine



(127)

(136)
$C_{15}H_{19}ClN_2O_2S$
MW = 326.84g/mol

Under an atmosphere of nitrogen, thionyl chloride (5.85 ml, 80.70 mmol) was added to 3-(dipropylamino)-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-4-ol **(127)** (830 mg, 2.69 mmol) and the mixture set to stir at reflux for 24 hours. After this time the excess thionyl chloride was removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 10% w/v aqueous sodium bicarbonate solution. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a brown oil (627 mg, 71%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.01-1.20 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.36-1.48 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.50-1.79 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.38 (3H, s, $ArC\mathbf{H}_3$); δ2.99-3.07 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.22-3.30 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.74-3.82 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.79 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ3.83-3.91 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ4.16 (1H, d, J=14.6Hz, $SO_2C\mathbf{H}_2$); δ7.26 (2H, d, J=8.2Hz, Ar**H**); δ7.39 (2H, d, J=8.3Hz, Ar**H**).

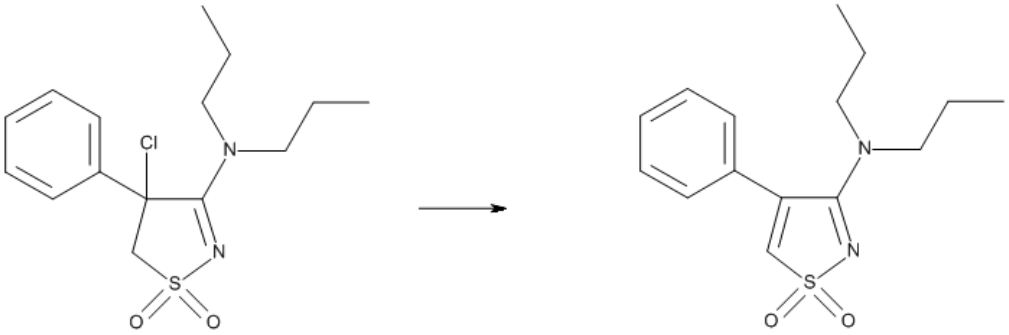
^{13}C NMR (100MHz, $CDCl_3$): δ21.05 ($Ar\mathbf{C}H_3$), 23.45 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 24.99 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 25.27 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 49.08 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 49.62 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 67.90 ($SO_2C\mathbf{H}_2$), 71.07 (**C**Cl), 124.44 (Ar), 130.24 (Ar), 135.64 (Ar), 139.51 (Ar), 164.24 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{19}N_2ClO_2S$+Na, calculated 349.0748, observed 349.0748.

IR (cm^{-1}): 797, 805, 857, 930, 1120, 1143, 1201, 1234, 1310, 1593.

2.2.7 Experimental Procedures Synthesis of 3-Dialkylamino-4-aryl-isothiazole-1,1-dioxides

2.2.7.1 Synthesis of 1,1-dioxo-4-phenyl-N,N-dipropyl-isothiazol-3-amine



(129)

(138)
$C_{15}H_{20}N_2O_2S$
MW = 292.40g/mol

To 4-chloro-1,1-dioxo-4-phenyl-N,N-dipropyl-5H-isothiazol-3-amine **(129)** (1.34 g, 4.07 mmol) in dry acetone (10 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (619 mg, 4.48 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure yielding the product as an orange solid (742 mg, 62%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.36 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.96 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.32-1.44 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.71-1.85 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.91-2.98 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.50-3.56 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.20 (1H, s, $SO_2C\mathbf{H}$); δ7.31-7.36 (2H, m, Ph**H**); δ7.46-7.51 (3H, m, Ph**H**).

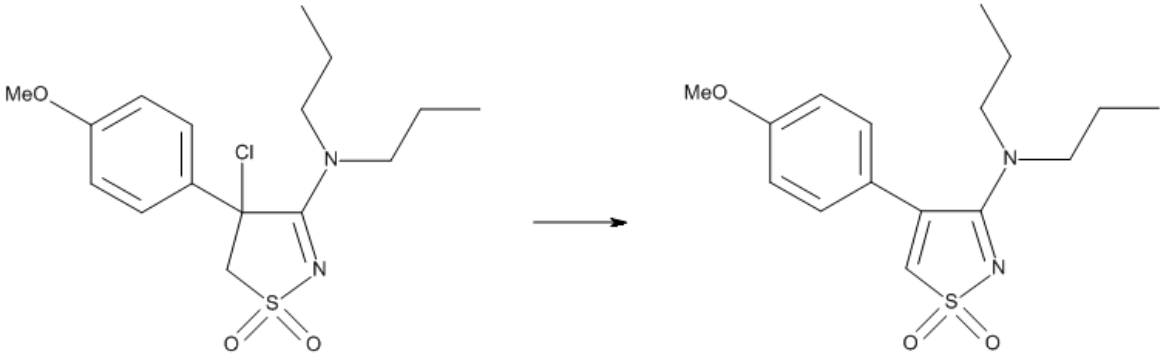
^{13}C NMR (100MHz, $CDCl_3$): δ10.28 ($NCH_2CH_2\mathbf{C}H_3$), 11.32 ($NCH_2CH_2\mathbf{C}H_3$), 19.92 ($NCH_2\mathbf{C}H_2CH_3$), 22.56 ($NCH_2\mathbf{C}H_2CH_3$), 51.44 ($N\mathbf{C}H_2CH_2CH_3$), 54.29 ($N\mathbf{C}H_2CH_2CH_3$), 127.31 (Ph**C**), 129.16 (Ph**C**), 129.64 (Ph**C**), 131.95 (Ph**C**), 139.76 ($SO_2\mathbf{C}H$), 143.22 (C=**C**-Ph), 160.86 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{20}N_2O_2S$+Na, calculated 315.1138, observed 315.1130.

IR (cm^{-1}): 704, 765, 814, 845, 1096, 1119, 1184, 1285, 1299, 1562, 3094.

M.p.: 114-116 ^{o}C.

2.2.7.2 Synthesis of 4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(131)

(140)
$C_{16}H_{22}N_2O_3S$
MW = 322.42g/mol

To 4-chloro-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine **(131)** (3.72 g, 10.34 mmol) in dry acetone (50 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (1.57 g, 11.37 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a brown solid (3.30 g, 76%).

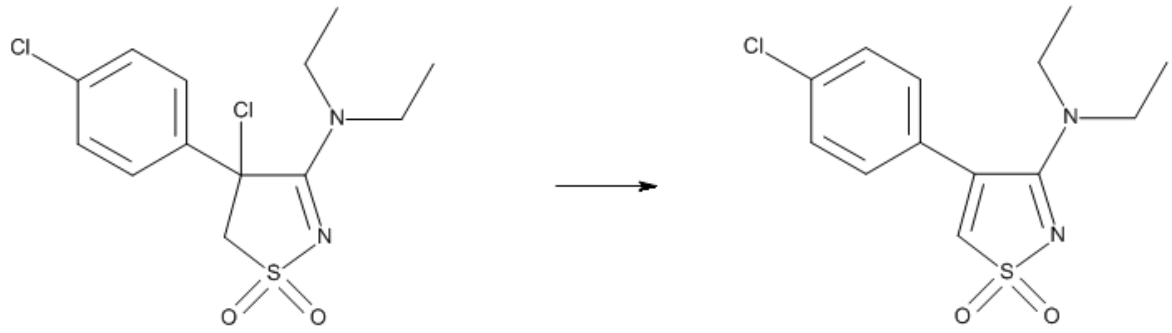
^{1}H NMR (400MHz, $CDCl_3$): δ0.43 (3H, t, J=7.2Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.95 (3H, t, J=7.2Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.32-1.44 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.70-1.83 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.98 (2H, t, J=7.8Hz, $NC\mathbf{H}_2CH_2CH_3$); δ3.52 (2H, t, J=7.6Hz, $NC\mathbf{H}_2CH_2CH_3$); δ3.85 (3H, s, $ArOC\mathbf{H}_3$); δ6.97 (2H, d, J=8.8Hz, Ar**H**); δ7.17 (1H, s, $SO_2C\mathbf{H}$); δ7.23 (2H, d, J=8.8Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.51 ($NCH_2CH_2\mathbf{C}H_3$), 11.36 ($NCH_2CH_2\mathbf{C}H_3$), 19.98 ($NCH_2\mathbf{C}H_2CH_3$), 22.62 ($NCH_2\mathbf{C}H_2CH_3$), 51.45 ($N\mathbf{C}H_2CH_2CH_3$), 54.29 ($N\mathbf{C}H_2CH_2CH_3$), 55.49 ($ArO\mathbf{C}H_3$), 114.59 (Ar), 123.86 (Ar), 128.70 (Ar), 139.69 (Ar), 143.05 ($SO_2\mathbf{C}H$), 160.57 (C=**C**-Ar), 161.31 (N=**C**-N).

micrOTOF-Q MS m/z $C_{16}H_{22}N_2O_3S$+Na, calculated 345.1243, observed 345.1244.

IR (cm^{-1}): 733, 835, 1027, 1123, 1189, 1249, 1290, 1506, 1556, 1603, 3102.

2.2.7.3 Synthesis of 4-(4-chlorophenyl)-N,N-diethyl-1,1-dioxo-isothiazol-3-amine



(133)

(141)
$C_{13}H_{15}ClN_2O_2S$
MW = 298.79g/mol

To 4-chloro-4-(4-chlorophenyl)-N,N-diethyl-1,1-dioxo-5H-isothiazol-3-amine **(133)** (650 mg, 1.93 mmol) in dry acetone (50 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (290mg, 2.28mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a brown, highly viscous semi-solid (500 mg, 79%).

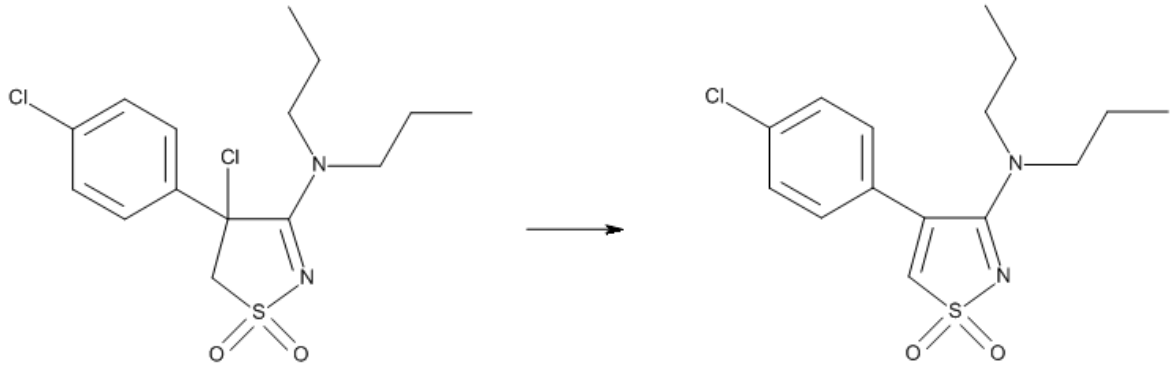
^{1}H NMR (400MHz, $CDCl_3$): δ0.94 (3H, t, J=6.5Hz, $NCH_2C\mathbf{H}_3$); δ1.31 (3H, t, J=6.5Hz, ($NCH_2C\mathbf{H}_3$); δ3.06-3.17 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.59-3.71 (2H, m, $NC\mathbf{H}_2CH_3$); δ7.24 (1H, s, $SO_2C\mathbf{H}$); δ7.30 (2H, *appt.* d, J=8.4Hz, Ar**H**); δ7.46 (2H, *appt.* d, J=8.5Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.85 ($NCH_2\mathbf{C}H_3$), 14.05 ($NCH_2\mathbf{C}H_3$), 43.95 ($N\mathbf{C}H_2CH_3$), 46.77 ($N\mathbf{C}H_2CH_3$), 128.78 (Ar), 129.47 (Ar), 130.39 (Ar), 136.05 (Ar), 138.58 (Ar), 143.87 (Ar), 160.39 (N=**C**-N).

micrOTOF-Q MS m/z $C_{13}H_{15}ClN_2O_2S$+Na, calculated 321.0435, observed 321.0437.

IR (cm^{-1}): 741, 824, 913, 942, 1087, 1122, 1188, 1293, 1557, 1590, 2950.

2.2.7.4 Synthesis of 4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(134)

(142)
$C_{15}H_{19}ClN_2O_2S$
MW = 326.84g/mol

To 4-chloro-4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-5H-isothiazol-3-amine **(134)** (2.18 g, 6.00 mmol) in dry acetone (40 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (995 mg, 7.20 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a brown oil (2.07 g, 97%).

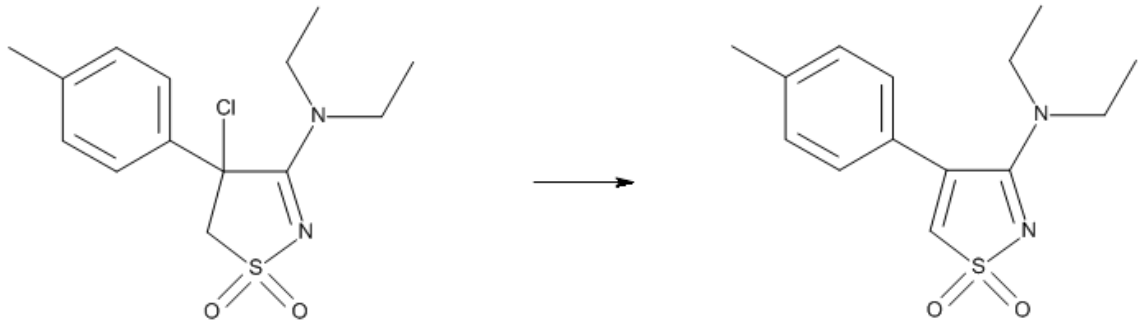
^{1}H NMR (400MHz, $CDCl_3$): δ0.43 (3H, t, J= 7.2Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.96 (3H, t, J=7.2Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.32-1.45 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.70-1.83 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.89-2.98 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.49-3.56 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.23 (1H, s, $SO_2C\mathbf{H}$); δ7.25-7.30 (2H, *appt.* d, Ar**H**); δ7.46 (2H, d, J=8.0Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.42 ($NCH_2CH_2\mathbf{C}H_3$), 11.35 ($NCH_2CH_2\mathbf{C}H_3$), 19.96 ($NCH_2\mathbf{C}H_2CH_3$), 22.63 ($NCH_2\mathbf{C}H_2CH_3$), 51.47 ($N\mathbf{C}H_2CH_2CH_3$), 54.39 ($N\mathbf{C}H_2CH_2CH_3$), 128.75 (Ar), 129.49 (Ar), 130.48 (Ar), 136.03 (Ar), 138.50 (Ar), 144.05 (Ar), 160.58 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{19}N_2ClO_2S$+Na, calculated 349.0748, observed 349.0745.

IR (cm^{-1}): 747, 834, 908, 1088, 1186, 1123, 1295, 1556, 1590, 2964.

2.2.7.5 Synthesis of N,N-diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine



(135)

(143)
$C_{14}H_{18}N_2O_2S$
MW = 278.37g/mol

To 4-chloro-N,N-diethyl-1,1-dioxo-4-(p-tolyl)-5H-isothiazol-3-amine **(135)** (545 mg, 1.73 mmol) in dry acetone (40 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (287 mg, 2.08 mmol) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a pale yellow solid (146 mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.92 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.31 (3H, t, J=6.8Hz, $NCH_2C\mathbf{H}_3$); δ2.41 (3H, s, $ArC\mathbf{H}_3$); δ3.07-3.17 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.58-3.70 (2H, m, $NC\mathbf{H}_2CH_3$); δ7.17 (1H, s, $SO_2C\mathbf{H}$); δ7.18-7.22 (2H, m, Ar**H**); δ7.24-7.29 (2H, m, Ar**H**).

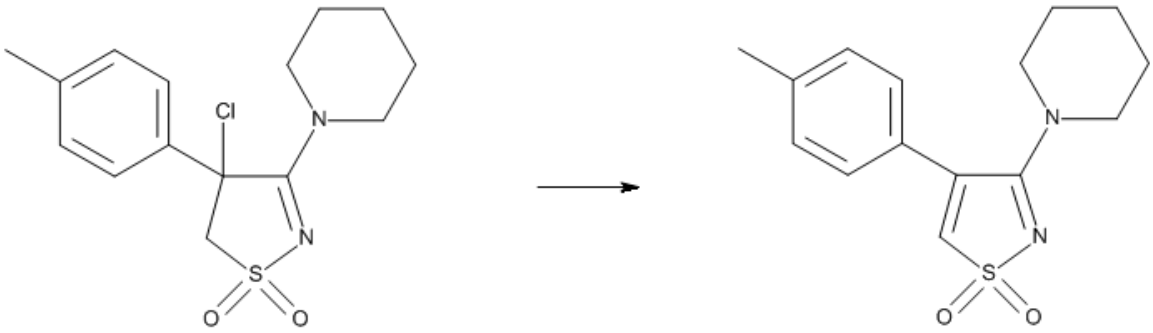
^{13}C NMR (100MHz, $CDCl_3$): δ11.89 ($NCH_2\mathbf{C}H_3$), 14.08 ($NCH_2\mathbf{C}H_3$), 21.35 ($Ar\mathbf{C}H_3$), 43.86 ($N\mathbf{C}H_2CH_3$), 46.66 ($N\mathbf{C}H_2CH_3$), 127.19 (Ar), 128.91 (Ar), 129.78 (Ar), 139.88 (Ar), 139.97 (Ar), 142.96 (Ar), 160.90 (N=**C**-N).

micrOTOF-Q MS m/z $C_{14}H_{18}N_2O_2S$+Na, calculated 301.0981, observed 301.0981.

IR (cm^{-1}): 739, 775, 791, 826, 913, 940, 1122, 1187, 1284, 1572, 3008.

M.p.: 122-124 ^{o}C.

2.2.7.6 Synthesis of 3-(1-piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide



(136)

(144)
$C_{15}H_{18}N_2O_2S$
MW = 290.38g/mol

To 4-chloro-1,1-dioxo-N,N-dipropyl-4-(p-tolyl)-5H-isothiazol-3-amine **(136)** (627 mg, 1.91 mmol) in dry acetone (40 ml) under an atmosphere of nitrogen, anhydrous potassium carbonate (317 mg) was added and the reaction mixture set to stir at reflux for 24 hours. After this time the mixture was filtered to remove excess potassium carbonate and the solvents removed under reduced pressure. The residues were then dissolved in dichloromethane and neutralised with 1M aqueous hydrochloric acid. The aqueous layer was removed and extracted with dichloromethane (3 x 25 ml) and the organic layers combined and washed with water. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a brown solid (112 mg, 20%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.33-1.45 (2H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.59-1.67 (2H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ1.71-1.84 (2H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.41 (3H, s, $ArC\mathbf{H}_3$); δ3.06-3.21 (2H, m $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.74-3.88 (2H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ7.18-7.23 (3H, m, Ar**H**, $SO_2C\mathbf{H}$); δ7.25-7.29 (2H, m, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ21.37 ($Ar\mathbf{C}H_3$), 23.75 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.20 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 26.09 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 49.54 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 50.38 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 127.00 (Ar), 128.82 (Ar), 130.01 (Ar), 139.98 (Ar), 140.21 (Ar), 142.49 (Ar), 161.71 (N=**C**-N).

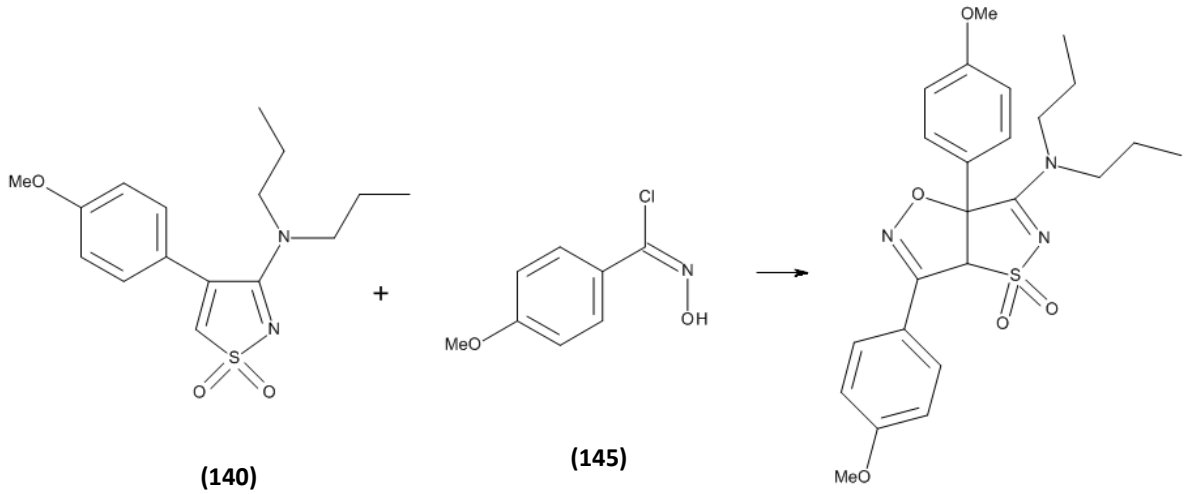
micrOTOF-Q MS m/z $C_{15}H_{18}N_2O_2S$+Na, calculated 313.0981, observed 313.0982.

IR (cm^{-1}): 744, 800, 855, 941, 1114, 1127, 1179, 1191, 1296, 1548, 2986.

M.p.: 178-180 ^{0}C.

2.2.8 Experimental Procedures for the Synthesis of 3,6-diaryl-7-dialkylamino-isothiazolo-isoxazole-1,1-dioxides

2.2.8.1 Synthesis of 3,6a-bis(4-methoxyphenyl)-4,4-dioxo-N,N-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(140) **(145)**

(147)
$C_{24}H_{29}N_3O_5S$
MW = 471.57g/mol

To a mixture of 4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(140)** (100 mg, 0.31 mmol) and 4-methoxy-N-hydroxybenzimidoyl chloride (58 mg, 0.31 mmol) **(145)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (50 µl, 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (43mg, 29%).

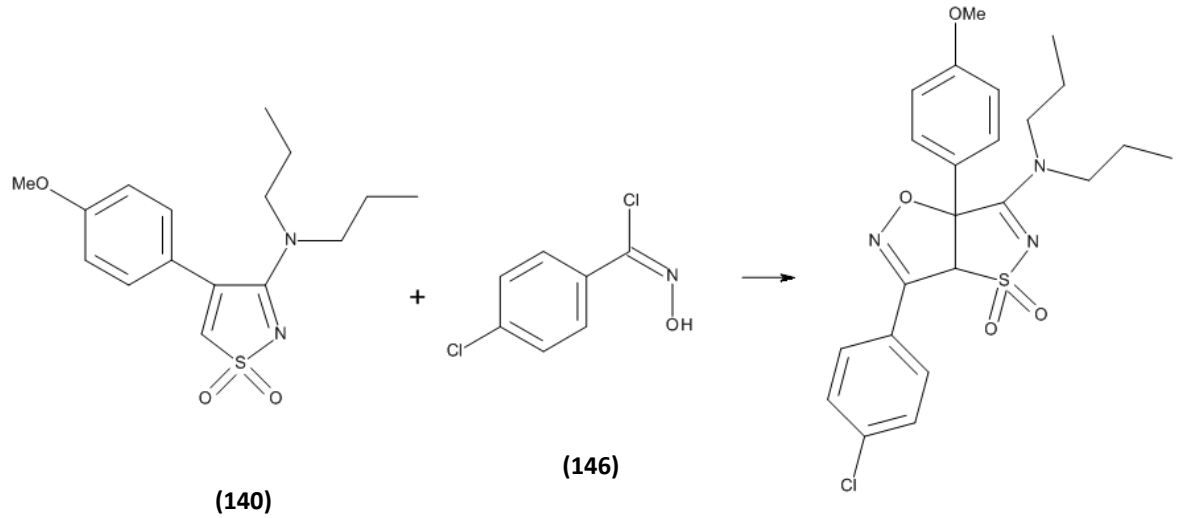
^{1}H NMR (400MHz, $CDCl_3$): δ0.66 (3H, t, J=8.0Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.93 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.98-1.11 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.49-1.86 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.00-3.20 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.21-3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.56-3.65 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.827 (3H, s, $ArOC\mathbf{H}_3$); δ3.831 (3H, s, $ArOC\mathbf{H}_3$); δ5.07 (1H, s, $SO_2C\mathbf{H}$); δ6.92 (2H, d, J=8.9Hz, Ar**H**); δ6.97 (2H, d, J=9.0Hz, Ar**H**); δ7.37 (2H, d, J=8.8Hz, 1.9Hz, Ar**H**); δ7.72 (2H, d, J=8.9Hz, 2.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.87 ($NCH_2CH_2\mathbf{C}H_3$), 11.24 ($NCH_2CH_2\mathbf{C}H_3$), 19.40 ($NCH_2\mathbf{C}H_2CH_3$), 21.10 ($NCH_2\mathbf{C}H_2CH_3$), 51.40 ($N\mathbf{C}H_2CH_2CH_3$), 52.15 ($N\mathbf{C}H_2CH_2CH_3$), 55.40 ($ArO\mathbf{C}H_3$), 55.47 ($ArO\mathbf{C}H_3$), 79.71 ($SO_2\mathbf{C}H$), 98.98 (**C**q), 114.37 (Ar), 115.00 (Ar), 119.28 (Ar), 125.12 (Ar), 129.23 (Ar), 129.25 (Ar), 152.00 (Ar), 160.38 (Ar), 161.79 (**C**=N), 164.05 (**C**=N).

micrOTOF-Q MS m/z $C_{24}H_{29}N_3O_5S$+Na, calculated 494.1720, observed 494.1717.

IR (cm^{-1}): 833, 888, 915, 1026, 1135, 1175, 1251, 1319, 1513, 1589.

2.2.8.2 Synthesis of 3-(4-chlorophenyl)-6a-(4-methoxyphenyl)-4,4-dioxo-N,N-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(140) **(146)** **(148)**

$C_{23}H_{26}ClN_3O_4S$
MW = 475.99g/mol

To a mixture of 4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(140)** (100 mg, 0.31 mmol) and 4-chloro-N-hydroxybenzimidoyl chloride (59 mg, 0.31 mmol) **(146)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (50 µl, 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (44 mg, 30%).

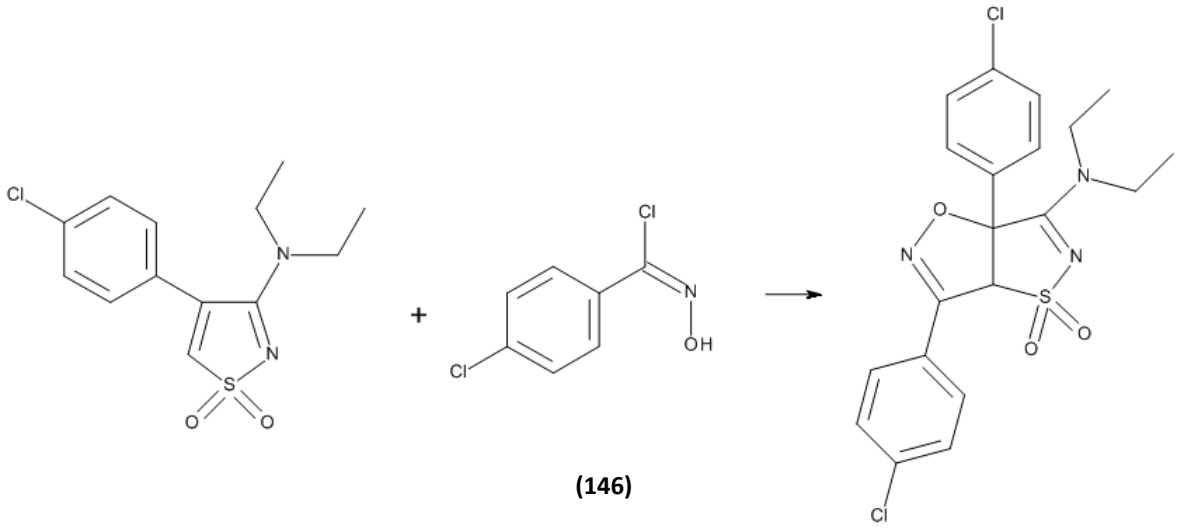
^{1}H NMR (400MHz, $CDCl_3$): δ0.67 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.93 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.99-1.12 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); 1.49-1.86 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); δ3.00-3.30 (3H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.56-3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.83 (3H, s, $ArOC\mathbf{H}_3$); δ5.06 (1H, s, $SO_2C\mathbf{H}$); δ6.98 (2H, d, J=8.9Hz, Ar**H**); δ7.36 (2H, d, J=8.8Hz, Ar**H**); δ7.40 (2H, d, J=8.6Hz, Ar**H**); δ7.72 (2H, d, J=8.6Hz, 2.4Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.86 ($NCH_2CH_2\mathbf{C}H_3$), 11.22 ($NCH_2CH_2\mathbf{C}H_3$), 19.40 ($NCH_2\mathbf{C}H_2CH_3$), 21.11 ($NCH_2\mathbf{C}H_2CH_3$), 51.41 ($N\mathbf{C}H_2CH_2CH_3$), 52.23 ($N\mathbf{C}H_2CH_2CH_3$), 55.49 ($ArO\mathbf{C}H_3$), 79.08 ($SO_2\mathbf{C}H$), 99.54 (**C**q), 115.09 (Ar), 125.08 (Ar), 125.42 (Ar), 128.79 (Ar), 128.81 (Ar), 129.22 (Ar), 137.23 (Ar), 151.76 (Ar), 160.50 (**C**=N), 163.86 (**C**=N).

micrOTOF-Q MS m/z $C_{23}H_{26}ClN_3O_4S$+Na, calculated 498.1225, observed 498.1222.

IR (cm^{-1}): 729, 832, 923, 1091, 1134, 1174, 1250, 1320, 1511, 1589.

2.2.8.3 Synthesis of 3,6a-bis(4-chlorophenyl)-N,N-diethyl-4,4-dioxo-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(141) **(146)** **(149)**
$C_{20}H_{19}Cl_2N_3O_3S$
MW = 452.35g/mol

To a mixture of 4-(4-chlorophenyl)-N,N-diethyl-1,1-dioxo-isothiazol-3-amine **(141)** (100 mg, 0.31 mmol) and 4-chloro-N-hydroxybenzimidoyl chloride (58 mg, 0.31 mmol) **(146)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (47 µl, 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (23 mg, 17%).

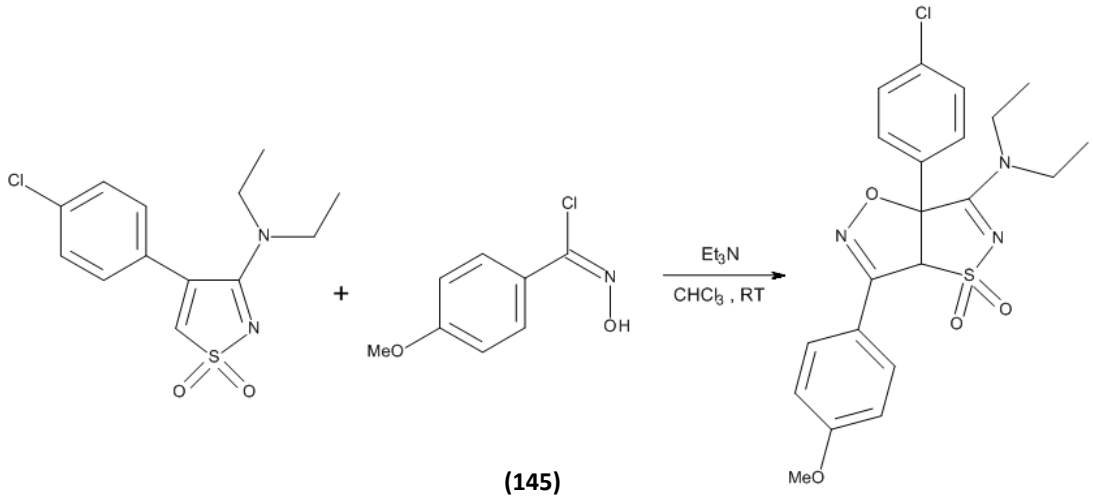
^{1}H NMR (400MHz, $CDCl_3$): δ0.89 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ1.27 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ3.15-3.32 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.42 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.69 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ5.08 (1H, s, $SO_2C\mathbf{H}$); δ7.38-7.44 (4H, m, Ar**H**); δ7.47 (2H, d, J=8.8Hz, Ar**H**); δ7.71 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.36 ($NCH_2\mathbf{C}H_3$), 12.82 ($NCH_2\mathbf{C}H_3$), 44.29 ($N\mathbf{C}H_2CH_3$), 45.23 ($N\mathbf{C}H_2CH_3$), 79.04 ($SO_2\mathbf{C}H$), 98.95 (**C**q), 125.10 (Ar), 125.25 (Ar), 128.88 (Ar), 129.31 (Ar), 130.16 (Ar), 135.37 (Ar), 136.01 (Ar), 137.49 (Ar), 151.91 (**C**=N), 162.94 (**C**=N).

micrOTOF-Q MS m/z $C_{20}H_{19}Cl_2N_3O_3S$+Na, calculated 474.0416, observed 474.0414.

IR (cm^{-1}): 728, 828, 890, 906, 1013, 1091, 1135, 1175, 1321, 1593.

2.2.8.4 Synthesis of 6a-(4-chlorophenyl)-N,N-diethyl-3-(4-methoxyphenyl)-4,4-dioxo-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(141) **(145)** **(150)**

$C_{21}H_{22}ClN_3O_4S$

MW = 447.94g/mol

To a mixture of 4-(4-chlorophenyl)-N,N-diethyl-1,1-dioxo-isothiazol-3-amine **(141)** (100 mg, 0.31 mmol) and 4-methoxy-N-hydroxybenzimidoyl chloride (57 mg, 0.31 mmol) **(145)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (47 µl, 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (57 mg, 42%).

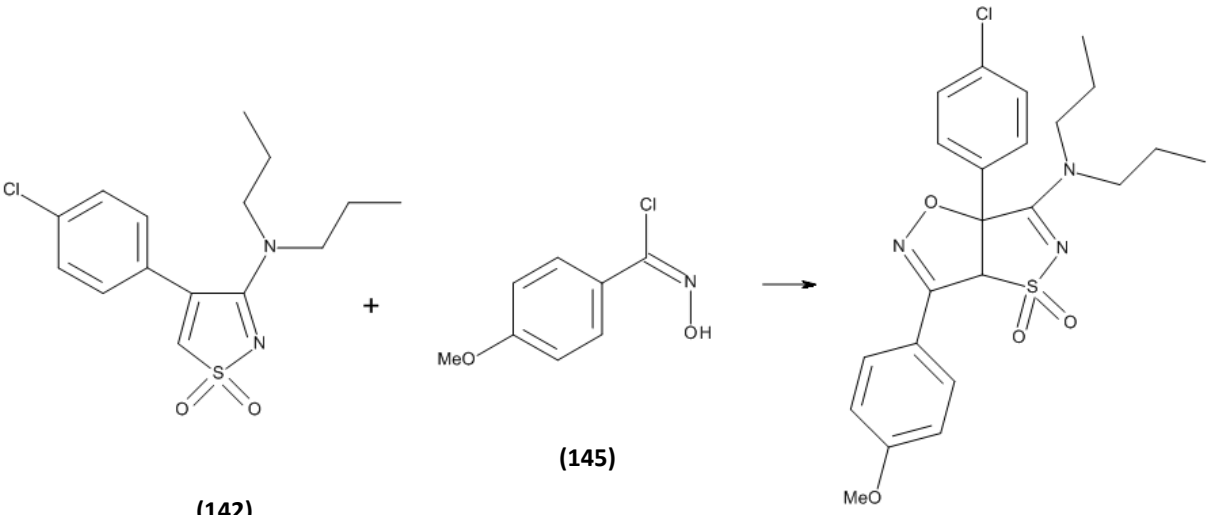
^{1}H NMR (400MHz, $CDCl_3$): δ0.87 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.27 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ3.22 (2H, non, J=7.3Hz, $NC\mathbf{H}_2CH_3$); δ3.42 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.68 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.83 (3H, s, $ArOC\mathbf{H_3}$); δ5.09 (1H, s, $SO_2C\mathbf{H}$); δ6.93 (2H, d, J=8.9Hz, Ar**H**); δ7.41 (2H, d, J=8.7Hz, Ar**H**); δ7.46 (2H, d, J=8.9Hz, Ar**H**); δ7.71 (2H, d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.38 ($NCH_2\mathbf{C}H_3$), 12.81 ($NCH_2\mathbf{C}H_3$), 44.27 ($N\mathbf{C}H_2CH_3$), 45.11 ($N\mathbf{C}H_2CH_3$), 55.44 ($ArO\mathbf{C}H_3$), 79.66 ($SO_2\mathbf{C}H$), 98.41 (**C**q), 114.45 (Ar), 118.94 (Ar), 125.31 (Ar), 129.34 (Ar), 130.06 (Ar), 135.77 (Ar), 135.79 (Ar), 152.15 (Ar), 161.96 (**C**=N), 163.13 (**C**=N).

micrOTOF-Q MS m/z $C_{21}H_{22}ClN_3O_4S$+Na, calculated 470.0912, observed 470.0909.

IR (cm^{-1}): 828, 915, 966, 1092, 1135, 1174, 1254, 1320, 1350, 1591.

2.2.8.5 Synthesis of 6a-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,4-dioxo-N,N-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(142) **(145)** **(151)**

$C_{23}H_{26}ClN_3O_4S$
MW = 475.99g/mol

To a mixture of 4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(142)** (100 mg, 0.31 mmol) and 4-methoxy-N-hydroxybenzimidoyl chloride (58 mg, 0.31 mmol) **(145)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (50 µl), 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (37 mg, 25%).

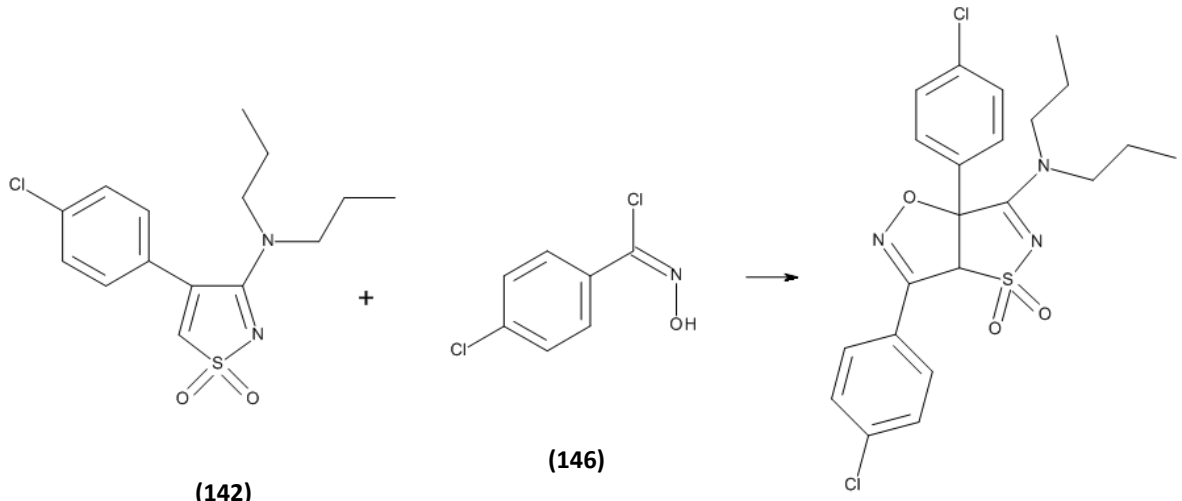
^{1}H NMR (400MHz, $CDCl_3$): δ0.68 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.93 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.99-1.12 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.50-1.83 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.97-3.16 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.22-3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.57-3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.84 (3H, s, $ArOC\mathbf{H}_3$); δ5.09 (1H, s, $SO_2C\mathbf{H}$); δ6.93 (2H, d, J=8.9Hz, Ar**H**); δ7.40-7.48 (4H, m, Ar**H**); δ7.72 (2H, d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.83 ($NCH_2CH_2\mathbf{C}H_3$), 11.21 ($NCH_2CH_2\mathbf{C}H_3$), 19.39 ($NCH_2\mathbf{C}H_2CH_3$), 21.15 ($NCH_2\mathbf{C}H_2CH_3$), 51.43 ($N\mathbf{C}H_2CH_2CH_3$), 52.16 ($N\mathbf{C}H_2CH_2CH_3$), 55.41 ($ArO\mathbf{C}H_3$), 79.73 ($SO_2\mathbf{C}H$), 98.46 (**C**q), 114.43 (Ar), 118.93 (Ar), 125.26 (Ar), 129.32 (Ar), 130.00 (Ar), 135.76 (Ar), 135.93 (Ar), 152.13 (Ar), 161.94 (**C**=N), 163.45 (**C**=N).

micrOTOF-Q MS m/z $C_{23}H_{26}ClN_3O_4S$+Na, calculated 498.1225, observed 498.1241.

IR (cm^{-1}): 729, 832, 887, 917, 1092, 1135, 1175, 1255, 1321, 1589.

2.2.8.6 Synthesis of 3,6a-bis(4-chlorophenyl)-4,4-dioxo-N,N-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(142) **(146)** **(152)**
$C_{22}H_{23}Cl_2N_3O_3S$
MW = 480.41g/mol

To a mixture of 4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(142)** (100 mg, 0.31 mmol) and 4-chloro-N-hydroxybenzimidoyl chloride (59 mg, 0.31 mmol) **(146)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (50 µl, 0.34 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography using a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (43 mg, 29%).

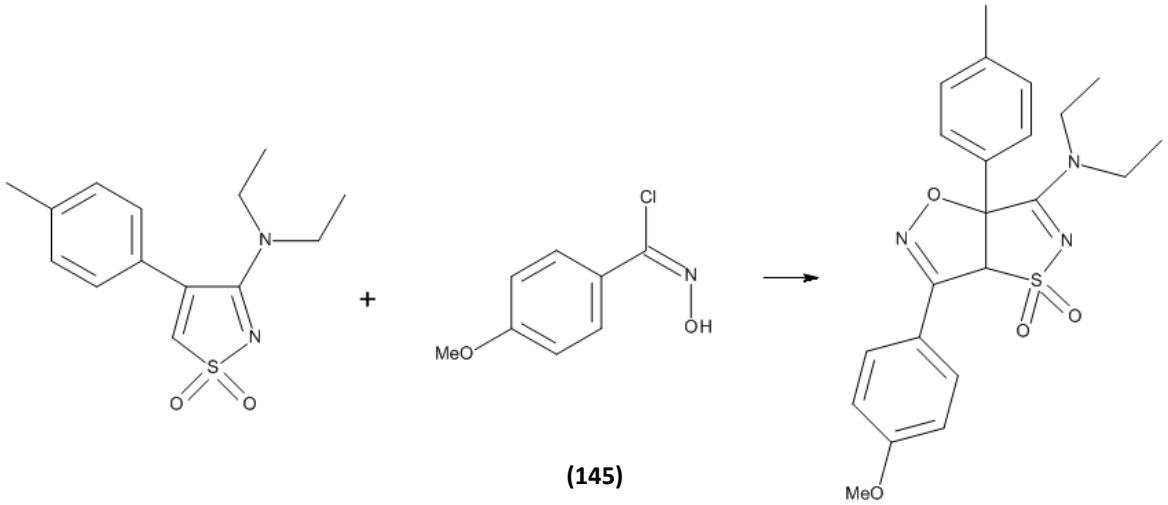
^{1}H NMR (400MHz, $CDCl_3$): δ0.69 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.93 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.99-1.13 (1H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.50-1.83 (3H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.96-3.18 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.22-3.31 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.59-3.66 (1H, m, $NC\mathbf{H}_2CH_2CH_3$); δ5.08 (1H, s, $SO_2C\mathbf{H}$); δ7.38-7.43 (4H, m, Ar**H**); δ7.47 (2H, d, J=8.8Hz, Ar**H**); δ7.71 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.82 ($NCH_2CH_2\mathbf{C}H_3$), 11.20 ($NCH_2CH_2\mathbf{C}H_3$), 19.38 ($NCH_2\mathbf{C}H_2CH_3$), 21.16 ($NCH_2\mathbf{C}H_2CH_3$), 51.45 ($N\mathbf{C}H_2CH_2CH_3$), 52.45 ($N\mathbf{C}H_2CH_2CH_3$), 79.09 ($SO_2\mathbf{C}H$), 99.00 (**C**q), 125.09 (Ar), 125.21 (Ar), 128.86 (Ar), 129.28 (Ar), 130.09 (Ar), 130.35 (Ar), 135.49 (Ar), 135.97 (Ar), 137.46 (Ar), 151.89 (**C**=N), 163.25 (**C**=N).

micrOTOF-Q MS m/z $C_{22}H_{23}N_3Cl_2O_3S$+Na, calculated 502.0729, observed 502.0729.

IR (cm^{-1}): 730, 830, 889, 922, 1013, 1090, 1135, 1174, 1321, 1590.

2.2.8.7 Synthesis of N,N-diethyl-3-(4-methoxyphenyl)-4,4-dioxo-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(143) **(145)** **(153)**

$C_{22}H_{25}N_3O_4S$

MW = 427.52g/mol

To a mixture of N,N-diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine **(143)** (75 mg, 0.27 mmol) and 4-methoxy-N-hydroxybenzimidoyl chloride (50 mg, 0.27 mmol) **(145)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (42 µl, 0.30 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (45 mg, 39%).

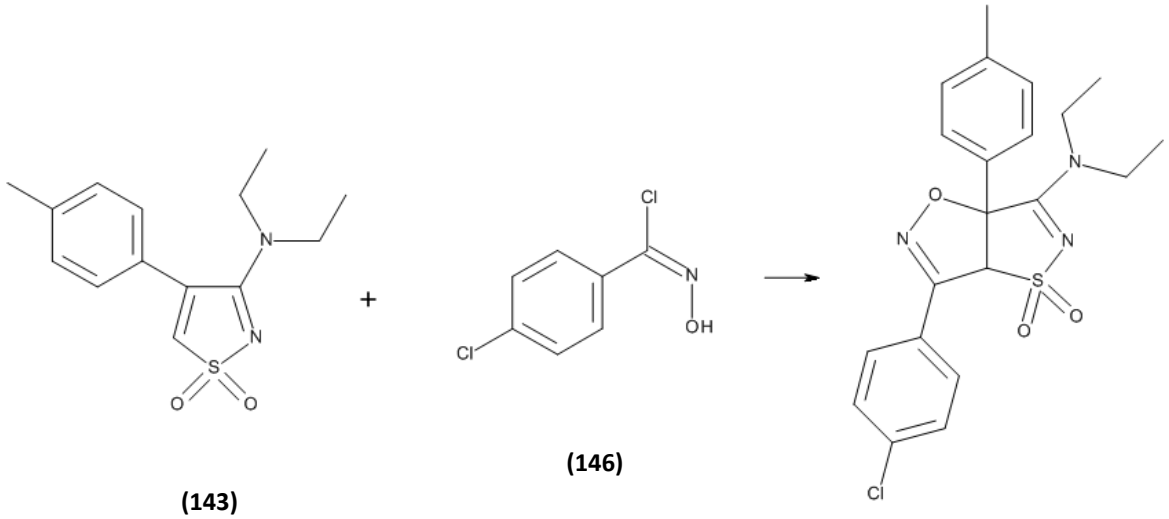
^{1}H NMR (400MHz, $CDCl_3$): δ0.84 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.27 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.38 (3H, s, $ArC\mathbf{H}_3$); δ3.24 (2H, non, J=7.3Hz, $NC\mathbf{H}_2CH_3$); δ3.41 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.69 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.83 (3H, s, $ArOC\mathbf{H}_3$); δ5.08 (1H, s, $SO_2C\mathbf{H}$); δ6.93 (2H, d, J=8.8Hz, Ar**H**); δ7.26 (2H, d, J=8.3Hz, Ar**H**); δ7.33 (2H, d, J=8.2Hz, Ar**H**); δ7.72 (2H, d, J=8.8Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.39 ($NCH_2\mathbf{C}H_3$), 12.71 ($NCH_2\mathbf{C}H_3$), 21.20 ($Ar\mathbf{C}H_3$), 44.26 ($N\mathbf{C}H_2CH_3$), 45.00 ($N\mathbf{C}H_2CH_3$), 55.42 ($ArO\mathbf{C}H_3$), 79.77 ($SO_2\mathbf{C}H$), 99.03 (**C**q), 115.40 (Ar), 119.29 (Ar), 123.63 (Ar), 129.27 (Ar), 130.38 (Ar), 134.35 (Ar), 139.69 (Ar), 152.00 (Ar), 161.82 (**C**=N), 163.66 (**C**=N).

micrOTOF-Q MS m/z $C_{22}H_{25}N_3O_4S$+Na, calculated 450.1458, observed 450.1455.

IR (cm^{-1}): 728, 822, 889, 916, 967, 1135, 1175, 1255, 1320, 1591.

2.2.8.8 Synthesis of 3-(4-chlorophenyl)-N,N-diethyl-4,4-dioxo-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(143) **(146)** **(154)**

$C_{21}H_{22}ClN_3O_3S$

MW = 431.94g/mol

To a mixture of N,N-diethyl-1,1-dioxo-4-(p-tolyl)isothiazol-3-amine **(143)** (75 mg, 0.27 mmol) and 4-chloro-N-hydroxybenzimidoyl chloride (51 mg, 0.27 mmol) **(146)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (42 µl, 0.30 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (16 mg, 14%).

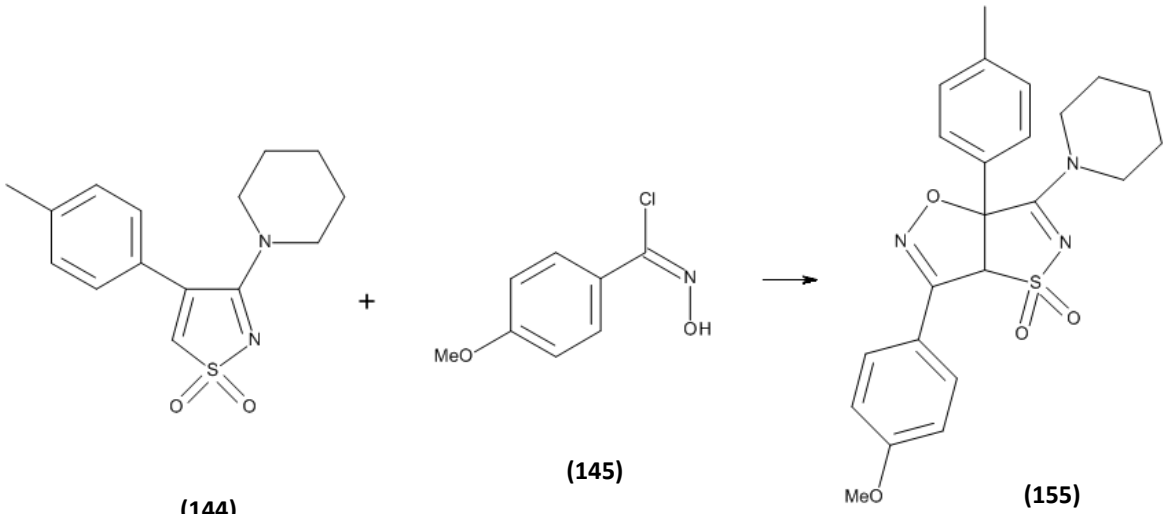
^{1}H NMR (400MHz, $CDCl_3$): δ0.85 (3H, t, J=7.0Hz, $NCH_2C\mathbf{H}_3$); δ1.27 (3H, t, J=7.1Hz, $NCH_2C\mathbf{H}_3$); δ2.38 (3H, s, $ArC\mathbf{H}_3$); δ3.15-3.33 (2H, m, $NC\mathbf{H}_2CH_3$); δ3.42 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ3.69 (1H, *appt.* sxt, J=7.1Hz, $NC\mathbf{H}_2CH_3$); δ5.07 (1H, s, $SO_2C\mathbf{H}$); δ7.26-7.34 (4H, m, Ar**H**); δ7.40 (2H, d, J=8.6Hz, Ar**H**); δ7.72 (2H, d, J=8.6Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ11.37 ($NCH_2\mathbf{C}H_3$), 12.72 ($NCH_2\mathbf{C}H_3$), 21.21 ($Ar\mathbf{C}H_3$), 44.30 ($N\mathbf{C}H_2CH_3$), 45.12 ($N\mathbf{C}H_2CH_3$), 79.15 ($SO_2\mathbf{C}H$), 99.58 (**C**q), 123.58 (Ar), 125.42 (Ar), 128.83 (Ar), 129.25 (Ar), 130.47 (Ar), 133.94 (Ar), 137.26 (Ar), 139.91 (Ar), 151.74 (**C**=N), 163.46 (**C**=N).

micrOTOF-Q MS m/z $C_{21}H_{22}N_3ClO_3S$+Na, calculated 454.0963, observed 454.0976.

IR (cm^{-1}): 729, 822, 906, 967, 1091, 1135, 1175, 1322, 1593, 2922.

2.2.8.9 Synthesis of 3-(4-methoxyphenyl)-6-(1-piperidyl)-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazole 4,4-dioxide



(144) **(145)** **(155)**
$C_{23}H_{25}N_3O_4S$
MW = 439.53g/mol

To a mixture of 3-(1-piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide **(144)** (50 mg, 0.17 mmol) and 4-methoxy-N-hydroxybenzimidoyl chloride (32 mg, 0.17 mmol) **(145)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (27 µl, 0.19 mmol) in dry chloroform (100 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (40 mg, 54%).

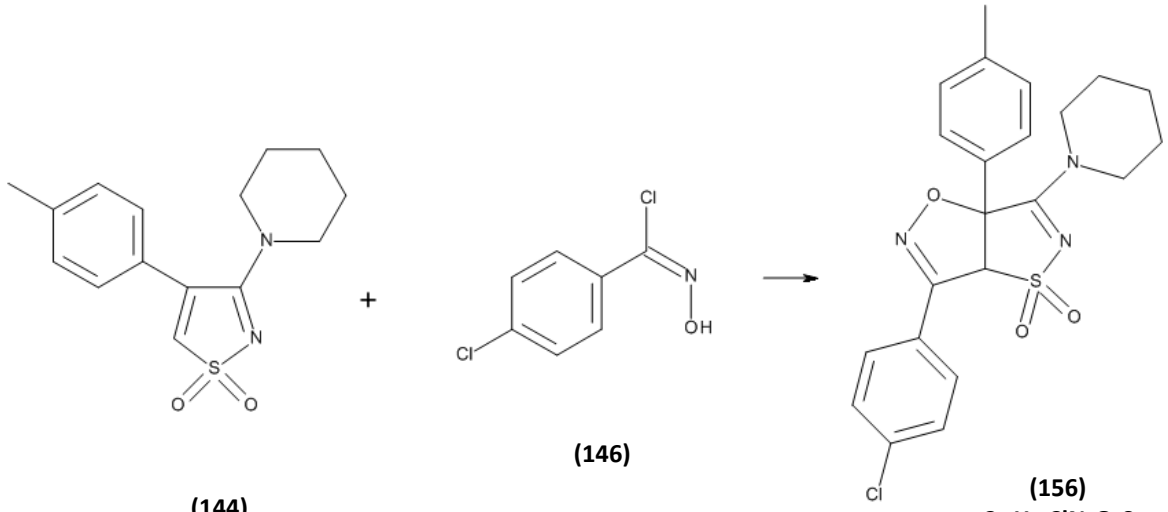
^{1}H NMR (400MHz, $CDCl_3$): δ1.05-1.16 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.39-1.49 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.50-1.79 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.37 (3H, s, $ArC\mathbf{H}_3$); δ3.14-3.23 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.31-3.40 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.78 (2H, t, J=5.2Hz, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.83 (3H, s, $ArOC\mathbf{H}_3$); δ5.08 (1H, s, $SO_2C\mathbf{H}$); δ6.93 (2H, d, 8.9Hz, Ar**H**); δ7.26 (2H, d, J=8.1Hz, Ar**H**); δ7.32 (2H, d, J=8.2Hz, Ar**H**); δ7.72 (2H, d, J=8.9Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ21.21 ($Ar\mathbf{C}H_3$), 23.55 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.23 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 25.36 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 48.99 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 49.41 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 55.43 ($ArO\mathbf{C}H_3$), 79.87 ($SO_2\mathbf{C}H$), 98.92 (**C**q), 114.41 (Ar), 119.35 (Ar), 123.59 (Ar), 129.27 (Ar), 130.36 (Ar), 134.30 (Ar), 139.67 (Ar), 151.94 (Ar), 161.83 (**C**=N), 163.09 (**C**=N).

micrOTOF-Q MS m/z $C_{23}H_{25}N_3O_4S$+Na, calculated 462.1458, observed 462.1458.

IR (cm^{-1}): 880, 910, 936, 1020, 1134, 1175, 1255, 1319, 1514, 1593.

2.2.8.10 Synthesis of 3-(4-chlorophenyl)-6-(1-piperidyl)-6a-(p-tolyl)-3aH-isothiazolo[5,4-d]isoxazole 4,4-dioxide



(144) **(146)** **(156)**
$C_{22}H_{22}ClN_3O_3S$
MW = 443.95g/mol

To a mixture of 3-(1-piperidyl)-4-(p-tolyl)isothiazole-1,1-dioxide **(144)** (50 mg, 0.17 mmol) and 4-chloro-N-hydroxybenzimidoyl chloride (32 mg, 0.17 mmol) **(146)** in dry chloroform (10 ml) under an atmosphere of nitrogen, triethylamine (27 µl, 0.19 mmol) in dry chloroform (10 ml) was added dropwise over a period of 6 hours and the mixture allowed to stir for a further hour. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 7:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a white crystalline solid (21 mg, 28%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.07-1.17 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.39-1.49 (1H, m, $N(CH_2)_2(CH_2)_2C\mathbf{H}_2$); δ1.51-1.80 (4H, m, $N(CH_2)_2(C\mathbf{H}_2)_2CH_2$); δ2.38 (3H, s, $ArC\mathbf{H}_3$); δ3.15-3.24 (1H, m ($N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.32-3.41 (1H, m, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ3.78 (2H, t, J=5.2Hz, $N(C\mathbf{H}_2)_2(CH_2)_2CH_2$); δ5.07 (1H, s, $SO_2C\mathbf{H}$); δ7.25-7.33 (4H, m, Ar**H**); δ7.39 (2H, d, J=8.6Hz, Ar**H**); δ7.72 (2H, d, J=8.6Hz, Ar**H**).

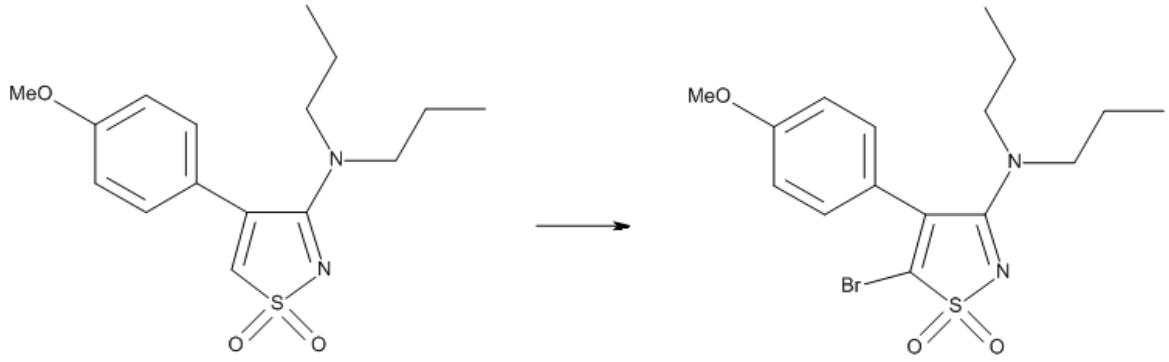
^{13}C NMR (100MHz, $CDCl_3$): δ21.21 ($Ar\mathbf{C}H_3$), 23.53 ($N(CH_2)_2(CH_2)_2\mathbf{C}H_2$), 25.23 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 25.37 ($N(CH_2)_2(\mathbf{C}H_2)_2CH_2$), 49.02 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 49.52 ($N(\mathbf{C}H_2)_2(CH_2)_2CH_2$), 79.25 ($SO_2\mathbf{C}H$), 99.48 (**C**q), 123.54 (Ar), 125.44 (Ar), 128.83 (Ar), 129.26 (Ar), 130.45 (Ar), 133.90 (Ar), 137.27 (Ar), 139.88 (Ar), 151.68 (**C**=N), 162.89 (**C**=N).

micrOTOF-Q MS m/z $C_{22}H_{22}N_3ClO_3S$+Na, calculated 466.0963, observed 466.0960.

IR (cm^{-1}): 814, 889, 936, 1012, 1092, 1135, 1176, 1258, 1321, 1595.

2.2.9 Experimental Procedures The Synthesis of 3-Dialkylamino-4-aryl-5-bromo-isothiazole-1,1-dioxides

2.2.9.1 Synthesis of 5-bromo-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(140)

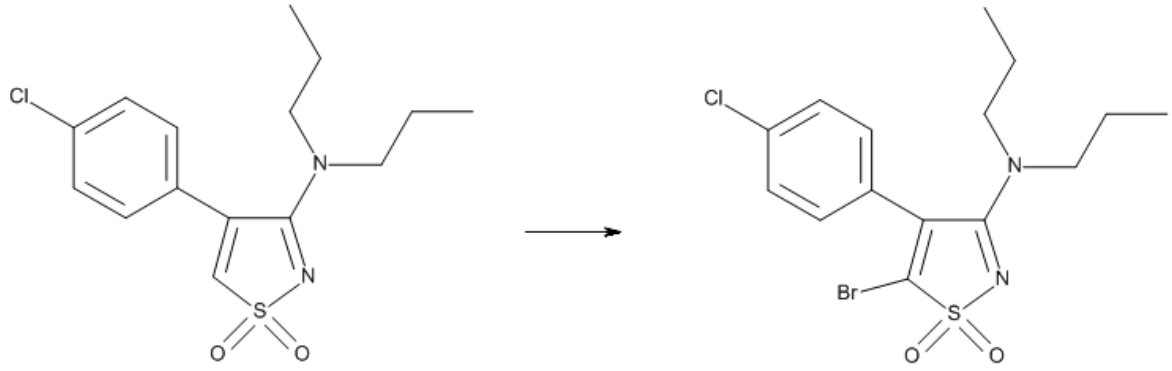
(157)
$C_{16}H_{21}BrN_2O_3S$
MW = 401.32g/mol

Under an atmosphere of nitrogen, a 1M solution of bromine in chloroform (6.20 ml, 6.20 mmol) was added dropwise to a solution of 4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(140)** (2.00 g, 6.20 mmol) in chloroform and stirred at room temperature for 48 hours. Following consumption of the starting material by TLC, triethylamine (0.86 ml, 6.20 mmol) was added dropwise and the reaction mixture stirred for a further 24 hours. The mixture was washed with 10% aqueous sodium metabisulfite (10 ml) and the aqueous layer removed and extracted with dichloromethane (3 x 25 ml). The organics were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a thick dark brown semi-solid (2.20 g, 88%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.33 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.87 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.24-1.33 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.62-1.73 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.85-2.92 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.41-3.48 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.79 (3H, s, $ArOC\mathbf{H}_3$); δ6.96 (2H, d, J=8.7Hz, Ar**H**); δ7.11 (2H, d, J=8.7Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.38 ($NCH_2CH_2\mathbf{C}H_3$), 11.35 ($NCH_2CH_2\mathbf{C}H_3$), 20.04 ($NCH_2\mathbf{C}H_2CH_3$), 22.66 ($NCH_2\mathbf{C}H_2CH_3$), 51.44 ($N\mathbf{C}H_2CH_2CH_3$), 54.16 ($N\mathbf{C}H_2CH_2CH_3$), 55.49 ($ArO\mathbf{C}H_3$), 115.00 (Ar), 123.22 (Ar), 129.09 (Ar), 135.97 (Ar), 138.77 ($SO_2\mathbf{C}H$), 160.64 (C=**C**-Ar), 161.52 (N=**C**-N).

2.2.9.2 Synthesis of 5-bromo-4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(142)

(158)
$C_{15}H_{18}BrClN_2O_2S$
MW = 405.74g/mol

Under an atmosphere of nitrogen, a 1M solution of bromine in chloroform (4.90 ml, 4.90 mmol) was added dropwise to a solution of 4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(142)** (1.60 g, 4.90 mmol) in chloroform and stirred at room temperature for 48 hours. Following consumption of the starting material by TLC, triethylamine (0.68 ml, 4.90 mmol) was added dropwise and the reaction mixture stirred for a further 24 hours. The mixture was washed with 10% aqueous sodium metabisulfite (10 ml) and the aqueous layer removed and extracted with dichloromethane (3 x 25 ml). The organics were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield the product as a brown oil (1.60 g, 80%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.32 (3H, t, J=7.3Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.86 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.21-1.33 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.60-1.71 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.79-2.86 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.39-3.46 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.13 (2H, d, J=8.4Hz, Ar**H**); δ7.43 (2H, d, J=8.4Hz, Ar**H**).

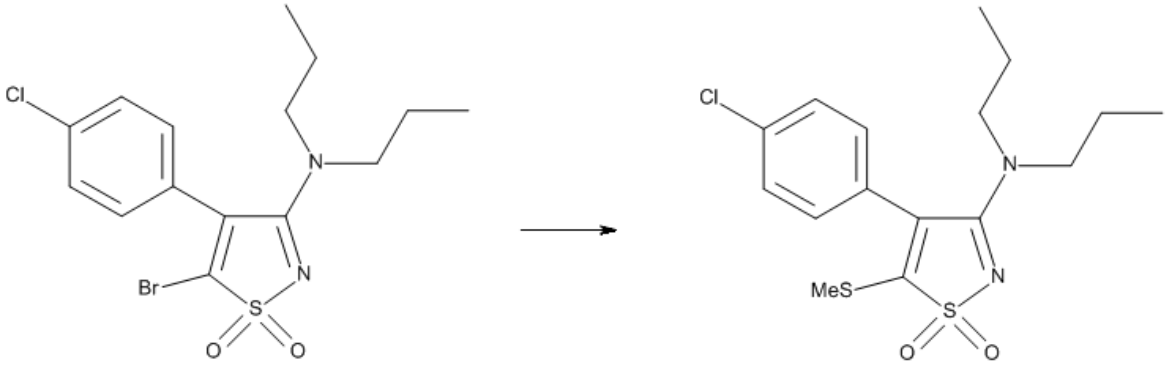
^{13}C NMR (100MHz, $CDCl_3$): δ10.38 ($NCH_2CH_2\mathbf{C}H_3$), 11.33 ($NCH_2CH_2\mathbf{C}H_3$), 20.03 ($NCH_2\mathbf{C}H_2CH_3$), 22.66 ($NCH_2\mathbf{C}H_2CH_3$), 51.44 ($N\mathbf{C}H_2CH_2CH_3$), 54.23 ($N\mathbf{C}H_2CH_2CH_3$), 129.18 (Ar), 129.96 (Ar), 130.00 (Ar), 134.89 (Ar), 136.39 (Ar), 139.70 (Ar), 160.87 (N=**C**-N).

micrOTOF-Q MS m/z $C_{15}H_{18}N_2{}^{79}BrClO_2S$+Na, calculated 426.9853, observed 426.9850.

IR (cm^{-1}): 871, 1011, 1088, 1152, 1307, 1396, 1487, 1560, 1589, 1616.

2.2.10 Experimental Procedures for the Synthesis of 3-Dialkylamino-4-aryl-5-thiomethoxy-isothiazole-1,1-dioxides

2.2.10.1 Synthesis of 4-(4-chlorophenyl)-5-methylsulfanyl-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(158) **(159)**
$C_{16}H_{21}ClN_2O_2S_2$
MW = 372.93g/mol

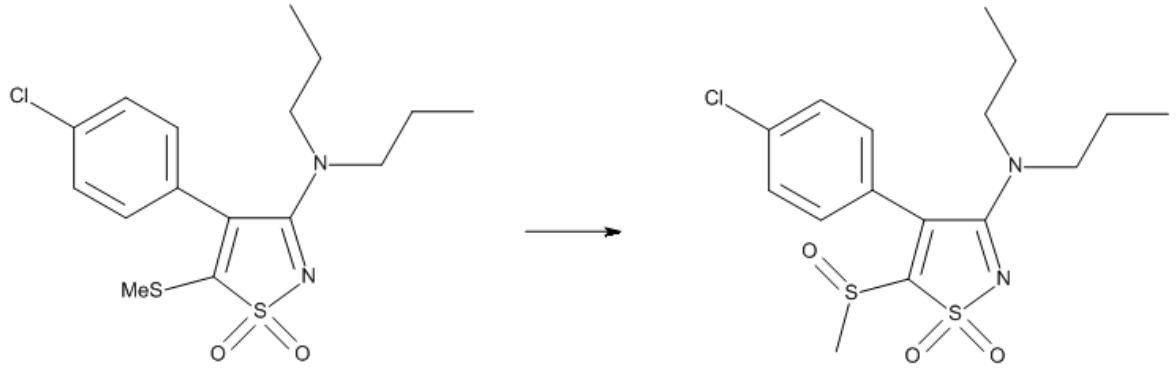
To 5-bromo-4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine **(158)** (1.60 g, 3.94 mmol) in dichloromethane (40 ml) under an atmosphere of nitrogen, sodium thiomethoxide and triethylamine were added and the mixture stirred at room temperature for 24 hours. After this time, the mixture was washed with water (40 ml) and the aqueous layer removed and extracted with dichloromethane (3 x 25 ml). The organics were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a yellow solid (596 mg, 41%).

^{1}H NMR (400MHz, $CDCl_3$): δ0.38 (3H, t, J=7.2Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.92 (3H, t, J=7.1Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.33 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.72 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.78 (3H, s, $SC\mathbf{H}_3$); δ2.88 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.47 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ7.19 (2H, *appt.* d, J=8.6Hz, 2.3Hz, Ar**H**); δ7.47 (2H, *appt.* d, J=9.8Hz, 2.0Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.33 ($NCH_2CH_2\mathbf{C}H_3$), 11.33 ($NCH_2CH_2\mathbf{C}H_3$), 12.96 ($S\mathbf{C}H_3$), 20.22 ($NCH_2\mathbf{C}H_2CH_3$), 22.55 ($NCH_2\mathbf{C}H_2CH_3$), 50.96 ($N\mathbf{C}H_2CH_2CH_3$), 54.11 ($N\mathbf{C}H_2CH_2CH_3$), 124.42 (Ar), 129.75 (Ar), 129.91 (Ar), 130.91 (Ar), 135.58 (Ar), 157.98 (Ar), 160.59 (N=**C**-N).

2.2.11 The Synthesis of 3-Dialkylamino-4-aryl-5-methanesulfonyl-isothiazole-1,1-dioxides

2.2.11.1 Synthesis of 4-(4-chlorophenyl)-5-methylsulfinyl-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(101)

(102)
$C_{16}H_{21}ClN_2O_3S_2$
MW = 388.93g/mol

To 4-(4-chlorophenyl)-5-methylsulfanyl-1,1-dioxo-N,N-dipropyl- isothiazol-3-amine **(101)** (590 mg, 1.58 mmol) in dichloromethane (20 ml) under an atmosphere of nitrogen, mCPBA (545 mg, 3.16 mmol) was added and the mixture allowed to stir at room temperature for 24 hours. After this time, the mixture was washed with 20% w/v aqueous sodium bicarbonate solution (25 ml) and the aqueous layer removed and extracted with dichloromethane (3 x 25 ml). The organics were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a yellow crystalline solid (310 mg, 48%).

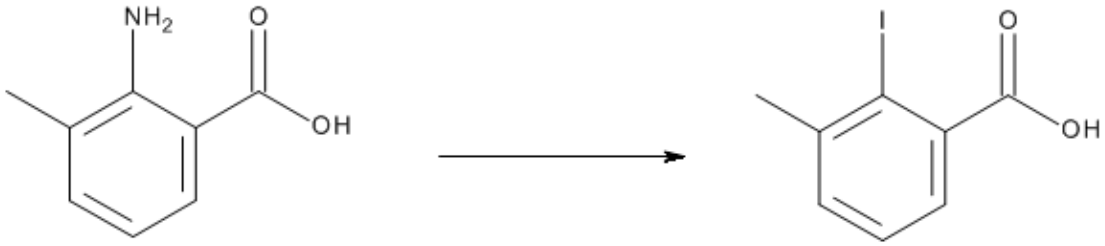
^{1}H NMR (400MHz, $CDCl_3$): δ0.40 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ0.94 (3H, t, J=7.4Hz, $NCH_2CH_2C\mathbf{H}_3$); δ1.36 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ1.75 (2H, m, $NCH_2C\mathbf{H}_2CH_3$); δ2.96 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.52 (2H, m, $NC\mathbf{H}_2CH_2CH_3$); δ3.87 (3H, s, $SO_2C\mathbf{H}_3$); δ7.03 (2H, d, J=8.7Hz, Ar**H**); δ7.18 (2H, d, J=8.4Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ10.48 ($NCH_2CH_2\mathbf{C}H_3$), 11.35 ($NCH_2CH_2\mathbf{C}H_3$), 20.05 ($NCH_2\mathbf{C}H_2CH_3$), 22.67 ($NCH_2\mathbf{C}H_2CH_3$), 51.43 ($N\mathbf{C}H_2CH_2CH_3$), 54.16 ($N\mathbf{C}H_2CH_2CH_3$), 55.48 ($S\mathbf{C}H_3$), 115.00 (Ar), 123.23 (Ar), 129.09 (Ar), 135.95 (Ar), 138.79 (Ar), 160.64 (Ar), 161.52 (N=**C**-N).

2.3 Experimental Procedures for Investigations into the 1,2,4-Oxadiazole Unit as a Structural Feature of Novel, Potential Asymmetric Catalysts

2.3.1 Experimental Procedures for the Synthesis of 2-Iodobenzoic Acids

2.3.1.1 Synthesis of 2-Iodo-3-methylbenzoic acid



(160)

(165)
$C_8H_7IO_2$
MW = 262.04g/mol

At room temperature, 2-amino-3-methylbenzoic acid **(160)** (500 mg, 3.31 mmol) was stirred in sufuric acid/water (5:33 v/v, 8 ml) for 1 hour. Sodium nitrite (228 mg, 3.31 mmol) in water (2 ml) was then added dropwise over 1 hour. An aqueous solution of potassium iodide (714 mg, 4.30 mmol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium chloride solution (10 ml), saturated aqueous sodium thiosulfate solution (10 ml) and the aqueous mixture was removed and extracted with dichloromethane (3 x 10 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to give the product as a white solid with no further purification required (750 mg, 86%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.58 (3H, s, C**H$_3$**); δ7.34 (1H, t, J=7.6Hz, Ar**H**); δ7.43 (1H, dd, J=7.5Hz, 1.1Hz, Ar**H**); δ7.66 (1H, dd, J=8.0Hz, 1.5Hz, Ar**H**); δ8.34-11.39 (1H, broad, O**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ30.11 (**C**H$_3$), 100.70 (Ar), 127.83 (Ar), 128.45 (Ar), 132.89 (Ar), 136.06 (Ar), 143.99 (Ar), 173.05 (**C**=O).

This data is consistent with that reported in the literature[171].

2.3.1.2 Synthesis of 2-Iodo-3-(trifluoromethyl)benzoic acid

(161)

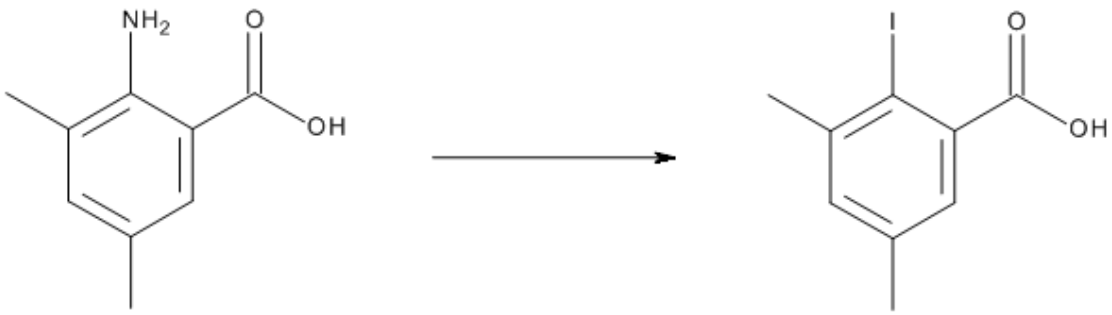
(166)
$C_8H_4F_3IO_2$
MW = 316.06g/mol

At room temperature, 2-amino-3-trifluoromethylbenzoic acid **(161)** (500 mg, 2.44 mmol) was stirred in sulfuric acid/water (5:33 v/v, 8 ml) for 1 hour. Sodium nitrite (168 mg, 2.44 mmol) in water (2 ml) was then added dropwise over 1 hour. An aqueous solution of potassium iodide (526 mg, 3.17 mmol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium chloride solution (10ml), saturated aqueous sodium thiosulfate solution (10 ml) and the aqueous mixture was removed and extracted with dichloromethane (3 x 10 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to give the product as a white solid with no further purification required (711 mg, 92%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.56 (1H, t, J=7.9Hz, Ar**H**); δ7.83 (1H, dd, J=8.2Hz, 1.4Hz, Ar**H**); δ7.87 (1H, dd, J=7.7Hz, 1.4Hz, Ar**H**); δ9.55-11.79 (1H, broad, O**H**).

This data is consistent with that reported in the literature[171].

2.3.1.3 Synthesis of 3,5-Dimethyl-2-iodobenzoic acid



(162)

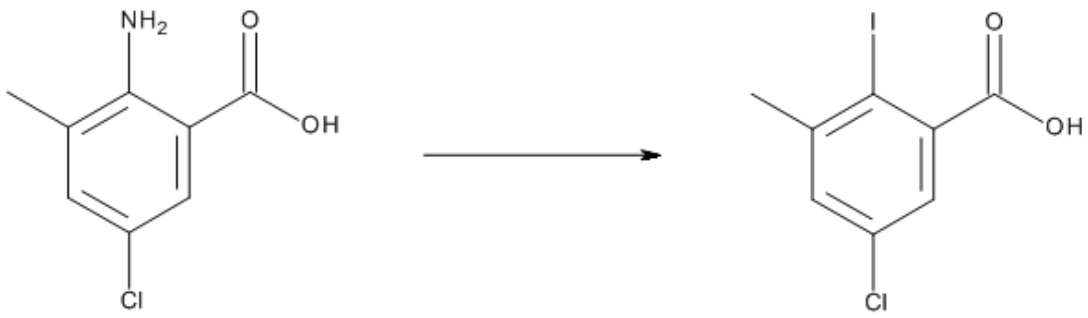
(167)
$C_9H_9IO_2$
MW = 276.07g/mol

At room temperature 2-amino-3,5-dimethylbenzoic acid **(162)** (500 mg, 3.03 mmol) was stirred in sulfuric acid/water (5:33 v/v, 8 ml) for 1 hour. Sodium nitrite (209 mg, 3.03 mmol) in water (2 ml) was then added dropwise over 1 hour. An aqueous solution of potassium iodide (654 mg, 3.94 mmol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium chloride solution (10 ml), saturated aqueous sodium thiosulfate solution (10 ml) and the aqueous mixture was removed and extracted with dichloromethane (3 x 10 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to give the product as a white solid with no further purification required (702 mg, 84%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.34 (3H, s, C**H$_3$**); δ2.53 (3H, s, C**H$_3$**); δ7.24-7.26 (1H, m, Ar**H**); δ7.47-7.49 (1H, m, Ar**H**); δ7.76-7.78 (1H, m, Ar**H**); δ9.79-12.34 (1H, broad, O**H**).

This data is consistent with that reported in the literature[171].

2.3.1.4 Synthesis of 5-Chloro-2-iodo-3-methylbenzoic acid



(163)

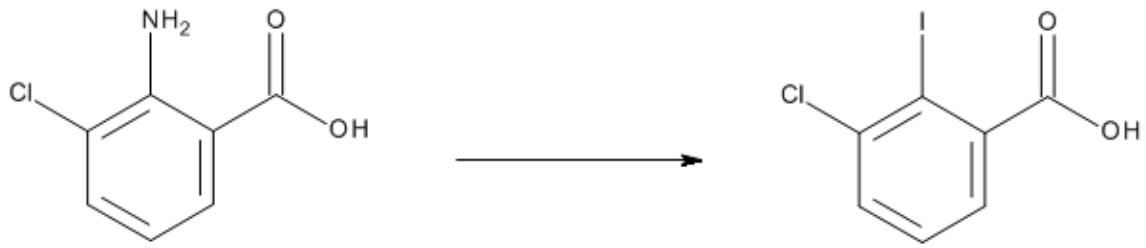
(168)
$C_8H_6ClIO_2$
MW = 296.49g/mol

At room temperature 2-amino-3-methyl-5-chlorobenzoic acid **(163)** (500 mg, 2.69 mmol) was stirred in sulfuric acid/water (5:33 v/v, 8 ml) for 1 hour. Sodium nitrite (186 mg, 2.39 mmol) in water (2 ml) was then added dropwise over 1 hour. An aqueous solution of potassium iodide (581 mg, 3.50 mmol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium chloride solution (10 ml), saturated aqueous sodium thiosulfate solution (10 ml) and the aqueous mixture was removed and extracted with dichloromethane (3 x 10 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to give the product as a white solid with no further purification required (728 mg, 91%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.56 (3H, s, C**H$_3$**); δ7.43 (1H, d, J=2.8Hz, Ar**H**); δ7.64 (1H, d, J=2.2Hz, Ar**H**).

This data is consistent with that reported in the literature[171].

2.3.1.5 Synthesis of 3-Chloro-2-iodobenzoic acid



(164)

(169)
$C_7H_4ClIO_2$
MW = 282.46g/mol

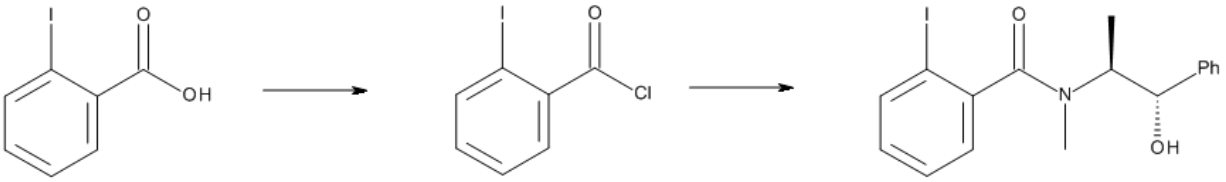
At room temperature 2-amino-3-chlorobenzoic acid **(164)** (500 mg, 2.91 mmol) was stirred in sulfuric acid/water (5:33 v/v, 8 ml) for 1 hour. Sodium nitrite (201 mg, 2.91 mmol) in water (2 ml) was then added dropwise over 1 hour. An aqueous solution of potassium iodide (628 mg, 3.78 mmol) was then added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium chloride solution (10 ml), saturated aqueous sodium thiosulfate solution (10 ml) and the aqueous mixture was removed and extracted with dichloromethane (3 x 10 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to give the product as a white solid with no further purification required (709 mg, 86%).

^{1}H NMR (400MHz, $CDCl_3$): δ7.40 (1H, t, J= 7.8Hz, Ar**H**), δ7.67 (1H, dd, J=8.0Hz, 1.5Hz, Ar**H**); δ7.73 (1H, d, J=8.1Hz, Ar**H**).

This data is consistent with that reported in the literature[171].

2.3.2 Experimental Procedures for the Synthesis of Chiral, Iodine Containing Pre-catalytic Systems

2.3.2.1 Synthesis of N-[(1S,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]-2-iodo-N-methyl-benzamide



(170) **(171)** **(176)**
$C_{17}H_{18}INO_2$
MW = 395.23g/mol

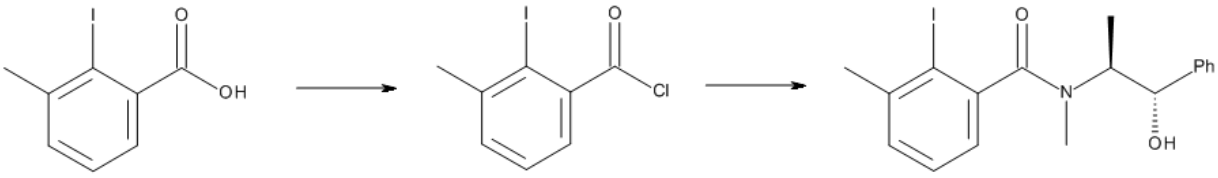
To 2-iodo-3-methylbenzoic acid **(170)** (500 mg, 1.91 mmol) in dichloromethane (5 ml) was added dropwise oxalyl chloride (0.32 ml, 3.82 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction mixture was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(171)** which was immediately dissolved in dry THF (5 ml) under an atmosphere of nitrogen. This was added via cannula to a solution of (1S,2S)-pseudoephedrine hydrochloride (300 mg, 1.82 mmol) and triethylamine (0.29 ml, 2.09 mmol) in dry THF (5 ml) at 0 ^{o}C and allowed to stir and reach room temperature overnight. The reaction mixture was then washed with saturated aqueous sodium chloride solution and the aqueous layer removed and extracted with ethyl acetate (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a thick dark oil (393 mg, 52%), as a mixture of rotamers.

^{1}H NMR (400MHz, $CDCl_3$): (Major rotamer only) δ1.27 (3H, s, CHC**H$_3$**); δ1.36 (3H, s, NC**H$_3$**); δ2.71 (1H, broad, O**H**); δ3.08 (1H, s, C**H**CH_3); δ4.39 (1H, d, J=8.8Hz, C**H**OH); δ6.96-7.02 (1H, m, Ar**H**); δ7.18-7.28 (5H, m, Ar**H**); δ7.30-7.41 (2H, m, Ar**H**).

micrOTOF-Q MS m/z $C_{17}H_{18}O_2NI$+Na, calculated 418.0274, observed 418.0289.

IR (cm^{-1}): 528, 568, 608, 701, 757, 1018, 1256, 1401, 1595, 3350.

2.3.2.2 Synthesis of N-[(1S,2S)-2-Hydroxy-1-methyl-2-phenyl-ethyl]-2-iodo-N-methyl-3-dimethylbenzamide



(165) **(172)** **(177)**
$C_{18}H_{20}INO_2$
MW = 409.26g/mol

To 2-iodo-3-methylbenzoic acid **(165)** (500 mg, 1.91 mmol) in dichloromethane (5 ml) was added dropwise oxalyl chloride (0.32 ml, 3.82 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction mixture was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(172)** which was immediately was dissolved in dry THF (5 ml) under an atmosphere of nitrogen. This was added via cannula to a solution of (1S,2S)-pseudoephedrine hydrochloride (313 mg, 1.55mmol) and triethylamine (0.50 ml, 3.57 mmol) in dry THF (5 ml) at 0 ^{o}C and allowed to stir and reach room temperature overnight. The reaction mixture was then washed with saturated aqueous sodium chloride solution and the aqueous layer removed and extracted with ethyl acetate (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a thick dark oil (461 mg, 59%), as a mixture of rotamers.

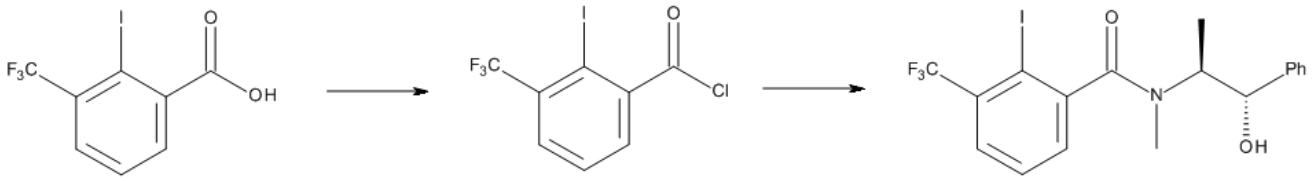
^{1}H NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ0.95 (3H, d, J=6.6Hz, CHC**H$_3$**); δ1.12 (3H, d, J=7.2Hz, CHC**H$_3$**); δ1.15 (3H, d, J=7.0Hz, CHC**H$_3$**); δ1.44 (3H, d, J=7.2Hz, CHC**H$_3$**); δ2.48 (6H, s, ArC**H$_3$**); δ2.49 (3H, s, ArC**H$_3$**); δ2.60 (3H, s, ArC**H$_3$**); δ2.80 (3H, s, NC**H$_3$**); δ2.86 (3H, s, NC**H$_3$**); δ3.16 (3H, s, (NC**H$_3$**); δ3.17 (3H, s, NC**H$_3$**); δ3.67-3.77 (1H, m, C**H**CH$_3$); δ4.24-4.34 (1H, m, C**H**CH$_3$); δ4.54 (1H, d, J=8.4Hz, C**H**OH); δ4.61 (1H, d, J=9.6Hz, C**H**OH); δ4.71 (1H, d, J=8.8Hz, C**H**OH); δ4.88 (1H, d, J=6.9Hz, C**H**OH); δ4.96-5.05 (1H, m, C**H**CH$_3$); δ5.07-5.21 (1H, m, C**H**CH$_3$); δ6.67 (1H, dd, J=6.8Hz, 1.5Hz, Ar**H**); δ6.96-7.05 (2H, m, Ar**H**); δ7.07-7.13 (2H, m, Ar**H**); δ7.21-7.51 (19H, m, Ar**H**).

^{13}C NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ13.79, 13.84, 14.22, 15.55, 26.91, 28.71, 28.77, 28.97, 59.57, 60.44, 60.65, 75.77, 76.07, 76.17, 98.50, 98.83, 99.48, 124.03, 124.13, 124.40, 126.14, 126.88, 126.99, 127.13, 127.61, 128.05, 128.06, 128.32, 128.34, 128.45, 128.59, 128.65, 129.21, 129.37, 129.51, 129.57, 129.65, 129.87, 131.70, 141.39, 141.82, 142.20, 142.37, 142.60, 142.71, 143.67, 143.87, 172.65, 172.93, 173.10.

micrOTOF-Q MS m/z $C_{18}H_{20}INO_2$+Na, calculated 432.0431, observed 432.0427.

IR (cm^{-1}): 618, 699, 748, 761, 786, 1010, 1402, 1441, 1613, 3350.

2.3.2.3 Synthesis of N-[(1S,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]-2-iodo-N-methyl-3-(trifluoromethyl)benzamide



(166) **(173)** **(178)**
$C_{18}H_{17}F_3INO_2$
MW = 463.23g/mol

To 2-iodo-3-(trifluoromethyl)benzoic acid **(166)** (500 mg, 1.58 mmol) in dichloromethane (5 ml) was added dropwise oxalyl chloride (0.27 ml, 3.16 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction mixture was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(173)** which was immediately dissolved in dry THF (5 ml) under an atmosphere of nitrogen. This was added via cannula to a solution of (1S,2S)-pseudoephedrine hydrochloride (262 mg, 1.30 mmol) and triethylamine (0.42 ml, 2.99 mmol) in dry THF (5 ml) at 0 ^{o}C and allowed to stir and reach room temperature overnight. The reaction mixture was then washed with saturated aqueous sodium chloride solution and the aqueous layer removed and extracted with ethyl acetate (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a thick dark oil (557 mg, 65%), as a mixture of rotamers.

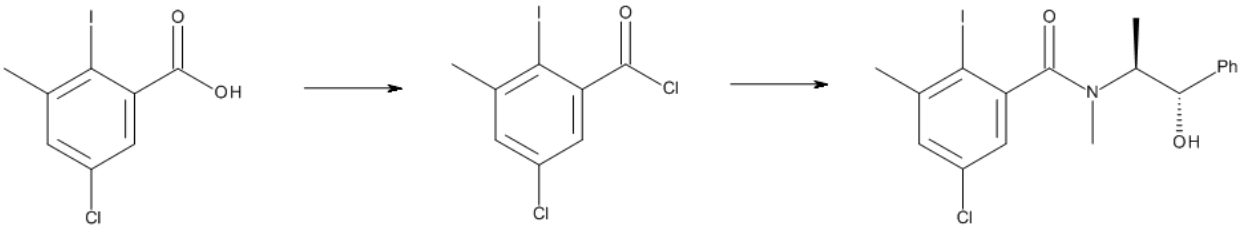
^{1}H NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ0.96 (3H, d, J=7.9Hz, CHC**H$_3$**); δ1.16 (3H, d, J=3.9Hz, CHC**H$_3$**); δ1.18 (3H, d, J=4.1Hz, CHC**H$_3$**); δ1.47 (3H, d, J=7.0Hz, CHC**H$_3$**); δ2.62 (3H, s, NC**H$_3$**); δ2.80 (3H, s, NC**H$_3$**); δ3.19 (3H, s, NC**H$_3$**); δ3.21 (3H, s, NC**H$_3$**); δ3.55-3.65 (1H, m, CHC**H$_3$**); δ4.23-4.36 (1H, m, CHC**H$_3$**); δ4.58 (1H, d, J=9.2Hz, C**H**OH); δ4.73 (1H, d, J=8.4Hz, C**H**OH); δ4.88-4.94 (1H, m, C**H**CH$_3$); δ5.02-5.12 (1H, m (C**H**OH); δ6.96 (1H, *appt.* d, J=7.8, Ar**H**); δ7.06-7.11 (2H, m, Ar**H**); δ7.29-7.39 (6H, m, Ar**H**); δ7.40-7.46 (5H, t, J=7.8Hz, Ar**H**); δ7.46-7.55 (7H, m, Ar**H**); δ7.64 (3H, t, J=7.8Hz, Ar**H**).

^{13}C NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ13.77, 14.21, 15.63, 27.13, 31.85, 34.84, 55.13, 59.67, 60.69, 75.73, 75.87, 75.97, 89.06, 89.30, 89.96, 126.05, 126.81, 126.83, 127.22, 127.28, 127.40, 127.46, 127.51, 127.74, 128.02, 128.08, 128.22, 128.44, 128.50, 128.68, 128.79, 128.88, 129.17, 129.65, 130.02, 131.60, 132.02, 134.16, 134.53, 141.24, 141.58, 142.05, 146.34, 146.53, 146.59, 171.49, 171.75.

micrOTOF-Q MS m/z $C_{18}H_{17}F_3INO_2$+Na, calculated 486.0148, observed 486.0148.

IR (cm^{-1}): 602, 678, 748, 816, 1117, 1148, 1178, 1312, 1606, 3310.

2.3.2.4 Synthesis of 5-chloro-N-[(1S,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]-2-iodo-N-methyl-3-dimethylbenzamide



(168) **(174)** **(179)**
$C_{18}H_{19}ClINO_2$
MW = 443.71g/mol

To 5-chloro-2-iodo-3-methylbenzoic acid **(168)** (500 mg, 1.69 mmol) in dichloromethane (5 ml) was added dropwise oxalyl chloride (0.29 ml, 3.38 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction mixture was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(174)** which was immediately dissolved in dry THF (5 ml) under an atmosphere of nitrogen. This was added via cannula to a solution of (1S,2S)-pseudoephedrine hydrochloride (278 mg, 1.38 mmol) and triethylamine (0.44 ml, 3.17 mmol) in dry THF (5 ml) at 0 ^{o}C and allowed to stir and reach room temperature overnight. The reaction mixture was then washed with saturated aqueous sodium chloride solution and the aqueous layer removed and extracted with ethyl acetate (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a thick dark oil (510 mg, 68%), as a mixture of rotamers.

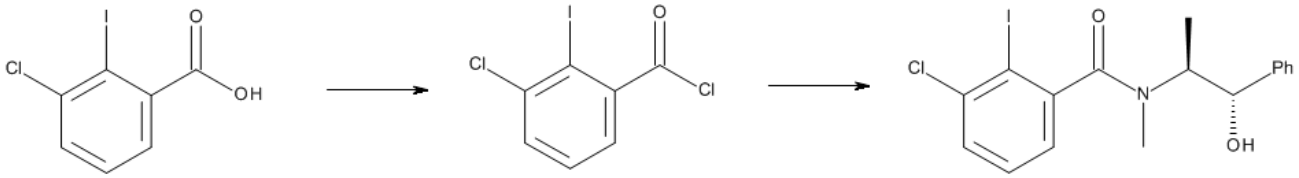
^{1}H NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ0.95 (3H, d, J=6.7Hz, CHC**H$_3$**); δ1.12 (3H, d, J=7.2Hz, CHC**H$_3$**); δ1.14 (3H, d, J=6.9Hz, CHC**H$_3$**); δ1.38 (3H, d, J=7.0Hz, CHC**H$_3$**); δ2.41 (3H, s, ArC**H$_3$**); δ2.43 (6H, s, ArC**H$_3$**); δ2.61 (3H, s, ArC**H$_3$**); δ2.77 (3H, s, NC**H$_3$**); δ3.14 (3H, s, NC**H$_3$**); δ3.55-3.63 (1H, m, CHC**H$_3$**); δ4.24-4.38 (1H, m, CHC**H$_3$**); δ4.49 (1H, d, J=8.4Hz, C**H**OH); δ4.66 (1H, d, J=8.4Hz, C**H**OH); δ4.84 (1H, d, J=7.2Hz, C**H**OH); δ4.95-5.04 (1H, m, CHC**H$_3$**); δ6.65 (1H, d, J=2.3Hz, Ar**H**); δ6.81 (1H, d, J=2.6Hz, Ar**H**); δ6.87 (1H, d, J=2.4, Ar**H**); δ7.07-7.11 (2H, m, Ar**H**); δ7.17-7.20 (3H, m, Ar**H**); δ7.30-7.45 (13H, m, Ar**H**).

^{13}C NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ13.75, 13.77, 15.73, 27.47, 28.58, 28.80, 54.79, 59.60, 60.49, 75.65, 75.70, 75.74, 95.93, 96.26, 96.89, 124.09, 124.31, 126.15, 126.44, 126.67, 126.80, 127.10, 127.74, 127.97, 128.15, 128.41, 128.49, 128.65, 129.13, 129.30, 129.50, 129.68, 130.60, 133.80, 134.18, 134.75, 141.80, 141.81, 141.95, 143.99, 144.39, 144.62, 144.86, 145.04, 145.15, 171.09, 171.19, 171.42.

micrOTOF-Q MS m/z $C_{18}H_{19}ClINO_2$+Na, calculated 466.0041, observed 466.0041.

IR (cm^{-1}): 700, 1011, 1115, 1250, 1350, 1404, 1444, 1614, 3350.

2.3.2.5 Synthesis of 3-chloro-N-[(1S,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]-2-iodo-N-methyl-benzamide



(169) **(175)** **(180)**
$C_{17}H_{17}ClINO_2$
MW = 429.68g/mol

To 3-chloro-2-iodobenzoic acid **(169)** (500 mg, 1.77 mmol) in dichloromethane (5 ml) was added dropwise oxalyl chloride (0.30 ml, 3.54 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(175)** which was immediately dissolved in dry THF (5 ml) under an atmosphere of nitrogen. This was added via cannula to a solution of (1S,2S)-pseudoephedrine hydrochloride (290 mg, 1.44 mmol) and triethylamine (0.46 ml, 3.31 mmol) in dry THF (5 ml) at 0 ^{o}C and allowed to stir and reach room temperature overnight. The reaction mixture was then washed with saturated aqueous sodium chloride solution and the aqueous layer removed and extracted with ethyl acetate (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 3:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a thick dark oil (532 mg, 70%), as a mixture of rotamers.

^{1}H NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ0.97 (3H, d, J=6.7Hz, CHC**H$_3$**); δ1.13 (3H, d, J=6.7, CHC**H$_3$**); δ1.15 (3H, d, J=7.0Hz, CHC**H$_3$**); δ1.45 (3H, d, J=7.0Hz, CHC**H$_3$**); δ2.63 (3H, s, NC**H$_3$**); δ2.83 (3H, s, NC**H$_3$**); δ3.17 (3H, s, NC**H$_3$**); δ3.20 (3H, s, NC**H$_3$**); δ3.63-3.71 (1H, m, CHC**H$_3$**); δ4.25-4.35 (1H, m, CHC**H$_3$**); δ4.57 (1H, d, J=8.5Hz, C**H**OH); δ4.73 (1H, d, J=9.2Hz, C**H**OH); δ4.94 (1H, d, J=7.2Hz, C**H**OH); δ5.01-5.11 (1H, m, CHC**H$_3$**); δ5.48-6.41 (1H, broad, O**H**); δ6.75 (1H, dd, J=7.4Hz, 1.3Hz, Ar**H**); δ7.05-7.10 (3H, m, Ar**H**); δ7.14 (1H, dd, J=7.7Hz, 1.5Hz, Ar**H**); δ7.29-7.44 (17H, m, Ar**H**); δ7.45-7.50 (7H, m, Ar**H**); δ7.61 (1H, d, J=1.5Hz, Ar**H**); δ7.64 (1H, dd, J=3.8Hz, 1.6Hz, Ar**H**); δ7.66 (1H, dd, J=7.7Hz & 1.5Hz, Ar**H**); δ7.69 (1H, dd, J=8.2Hz, 1.4Hz, Ar**H**); δ7.94 (1H, dd, J=8.4Hz, 1.3Hz, Ar**H**).

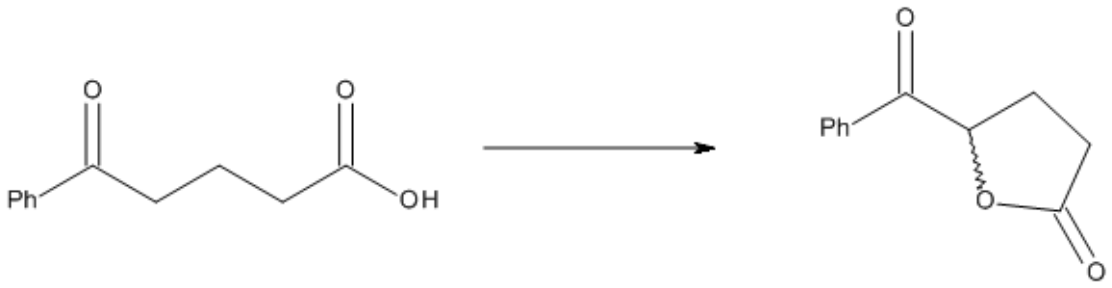
^{13}C NMR (400MHz, $CDCl_3$): (Major three rotamers only) δ13.71, 13.80, 15.58, 55.42, 59.81, 60.49, 75.71, 75.88, 76.03, 96.59, 97.21, 98.64, 124.57, 124.95, 126.07, 126.08, 126.86, 126.88, 127.68, 127.75, 128.26, 128.36, 128.44, 128.53, 128.70, 128.76, 128.78, 129.03, 129.24, 129.30, 129.38, 129.86, 129.96, 130.04, 131.81, 139.46, 139.78, 139.88, 141.00, 141.43, 141.91, 145.61, 169.58, 171.82, 171.83.

micrOTOF-Q MS m/z $C_{17}H_{17}ClINO_2$+Na, calculated 451.9885, observed 451.9885.

IR (cm^{-1}): 699, 748, 803, 1036, 1190, 1246, 1353, 1396, 1608, 3328.

2.3.3 Experimental procedures for Catalyst Screening Reactions

2.3.3.1 Synthesis of 5-Benzoyltetrahydrofuran-2-one



(181)
$C_{11}H_{10}O_3$
MW = 190.20g/mol

To an organoiodine catalyst (0.052 mmol) in the appropriate solvent (2 ml, see Table 3.24), was added 5-oxo-5-phenylpentanoic acid (50 mg, 0.26 mmol), m-chloroperoxybenzoic acid (135 mg, 0.78 mmol) and p-toluenesulfonic acid monohydrate (148 mg, 0.78 mmol). The reaction mixture was set to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated aqueous sodium thiosulfate solution (15 ml) and saturated aqueous sodium bicarbonate solution (15 ml) and the aqueous layer removed and extracted with dichloromethane (3 x 25 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by flash column chromatography with a 5:1 petroleum ether:ethyl acetate solvent to yield the pure product as an pale yellow oil (34 mg, 70%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.41-2.63 (4H, m, CHC**H$_2$**C**H$_2$**CO); δ5.78-5.84 (1H, m, C**H**CH$_2$); δ7.52 (2H, *appt.* t, J=7.0Hz, Ar**H**); δ7.64 (1H, tt, J= 7.4, 1.3Hz, Ar**H**); δ7.95-8.01 (2H, m, Ar**H**).

^{13}C NMR (400MHz, $CDCl_3$): δ25.37 (CH**C**H$_2$CH$_2$CO), 27.21 (CHCH$_2$**C**H$_2$CO), 78.66 (C**H**CH$_2$CH$_2$CO), 129.16 (Ar), 129.42 (Ar), 133.93 (Ar), 134.70 (Ar), 176.69 (Ph**C**=O), 194.72 (O**C**=O).

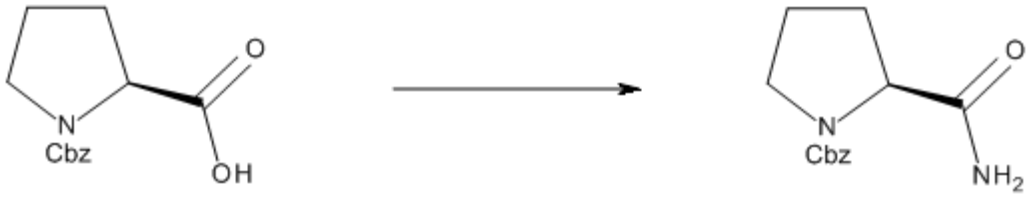
micrOTOF-Q MS m/z $C_{11}H_{10}O_3$+Na, calculated 213.0522, observed 213.0516.

IR (cm^{-1}): 630, 686, 926, 972, 1062, 1172, 1226, 1448, 1692, 1766.

This data is consistent with that reported in the literature[150].

2.3.4 Experimental Procedures for the Synthesis of L-Proline Based, Chiral 1,2,4-oxadiazole Systems

2.3.4.1 Synthesis of (2S)-N-Cbz-pyrrolidine-2-carboxamide



(182)

(183)
$C_{13}H_{16}N_2O_3$
MW = 248.28g/mol

To N-Cbz-L-proline **(182)** (1.00 g, 4.01 mmol) in tetrahydrofuran (50 ml) under an atmosphere of nitrogen, N-hydroxysuccinimide (693 mg, 6.02 mmol) and N,N-dicyclohexylcarbodiimide (827 mg, 4.01 mmol) were added. The mixture was set to stir at room temperature overnight. After this time, concentrated aqueous ammonia (3 ml) was added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was washed with saturated ammonium chloride solution and extracted with ethyl acetate. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. The crude product was purified by gravity column chromatography with a 1:15 petroleum ether:ethyl acetate solvent system to yield the pure product as a pale yellow oil (494 mg, 49%).

^{1}H NMR (400MHz, $CDCl_3$): δ1.83-2.34 (4H, m, NCHC**H_2**C**H_2**); δ3.37-3.57 (2H, m, NC**H_2**); δ4.25-4.37 (1H, m, NC**H**CH_2); δ5.08-5.19 (2H, m, OC**H_2**Ph); δ5.88-6.77 (2H, m, N**H_2**); δ7.27-7.38 (5H, m, Ph**H**).

This data is consistent with that reported in the literature[172].

2.3.4.2 Synthesis of (2S)-N-Cbz-2-cyanopyrrolidine

(183)

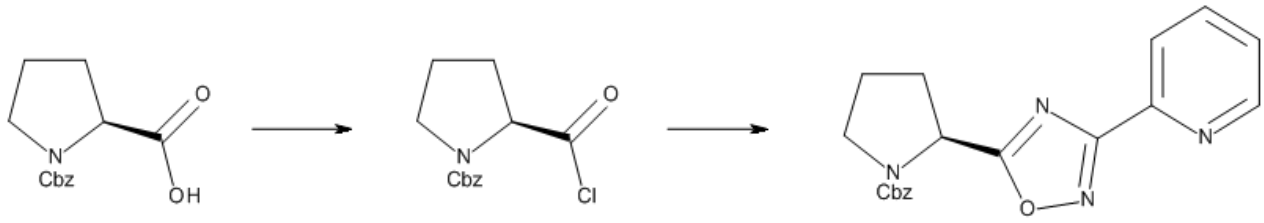
(184)
$C_{13}H_{14}N_2O_2$
MW = 230.26g/mol

To (2S)-N-Cbz-pyrrolidine-2-carboxamide **(183)** (494 mg, 1.98 mmol) under an atmosphere of nitrogen in dichloromethane (20 ml), was added pyridine (0.80 ml, 9.90 mmol) followed by *p*-toluenesulfonyl chloride (755 mg, 3.96 mmol). The reaction mixture was allowed to stir at room temperature for 72 hours. After this time, the reaction mixture was washed with saturated ammonium chloride solution and extracted with ethyl acetate. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated by rotary evaporation. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as a pale yellow oil (217 mg, 48%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.07-2.36 (4H, m, NCHC**H$_2$**C**H$_2$**); δ3.37-3.51 (1H, m, NC**H**$_2$); δ3.56-3.67 (1H, m, NC**H**$_2$); δ4.61 (1H, ddd, J=25.7Hz, 7.5Hz, 2.6Hz, NC**H**CH$_2$); δ5.15-5.26 (2H, m, OC**H$_2$**Ph); δ7.32-7.46 (5H, m, Ph**H**).

This data is consistent with that reported in the literature[172].

2.3.4.3 Synthesis of 5-[(2S)-N-Cbz-pyrrolidin-2-yl]-3-(2-pyridyl)-1,2,4-oxadiazole



(182) **(186)** **(187)**
$C_{19}H_{18}N_4O_3$
MW = 350.37g/mol

To N-Cbz-L-proline **(182)** (500 mg, 2.01 mmol) in dichloromethane (20 ml) was added dropwise oxalyl chloride (0.19 ml, 2.21 mmol) under an atmosphere of nitrogen with a catalytic amount of dimethylformamide (0.1 ml). The reaction mixture was allowed to stir at room temperature overnight. The solvents were removed by rotary evaporation to afford the crude acid chloride **(186)** which was immediately dissolved in xylene under an atmosphere of nitrogen. Immediately to this were added N'-hydroxypyridine-2-carboxamidine (248 mg, 1.81 mmol) and pyridine (0.16 ml, 1.99 mmol) and the reaction mixture was set to stir at reflux overnight. After this time the solvents were removed under reduced pressure. The crude product was purified by gravity column chromatography with a 2:1 petroleum ether:ethyl acetate solvent system to yield the pure product as an orange oil (350 mg, 50%), as a mixture of rotamers.

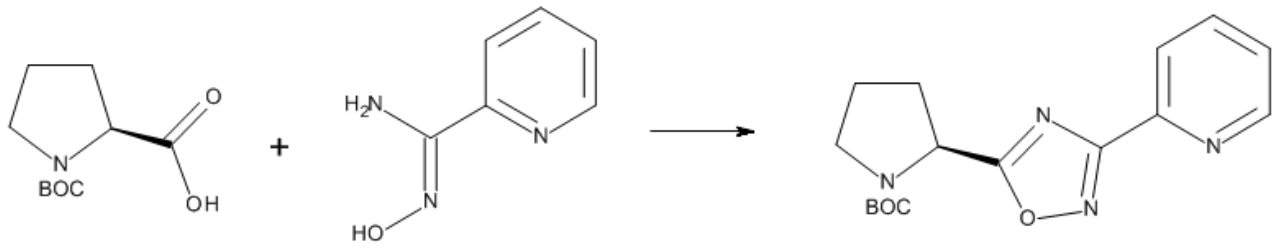
^{1}H NMR (400MHz, $CDCl_3$): (Major rotamer only) δ1.99-2.51 (4H, m, NCHC**H$_2$**C**H$_2$**); δ3.55-3.71 (1H, m, NC**H$_2$**); δ3.76-3.86 (1H, m, NC**H$_2$**); δ5.12 (2H, t, J=17.2Hz, OC**H$_2$**Ph); δ5.29 (1H, dd, J=8.4Hz, 3.4Hz, NC**H**CH$_2$); δ7.13-7.22 (3H, m, Ph**H**); δ7.32-7.40 (2H, m, Ph**H**); δ7.42-7.49 (1H, m, Ar**H**); δ7.82-7.90 (1H, m, Ar**H**); δ8.11 (1H, dd, J=26.4Hz, 7.8Hz, Ar**H**); δ8.80-8.85 (1H, m, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ23.62 (Major and minor rotamers) (NCH$_2$**C**H$_2$), 24.44 (NCH$_2$**C**H**$_2$**), 31.56 (NCH**C**H$_2$), 32.49 (NCH**C**H$_2$), 46.58 (N**C**H$_2$), 47.00 (N**C**H$_2$), 53.77 (N**C**HCH$_2$), 54.29 (N**C**HCH$_2$), 67.28 (O**C**H$_2$Ph), 67.33 (O**C**H$_2$Ph), 123.27 (Ar), 123.35 (Ar), 125.47 (Ar), 125.57 (Ar), 127.85 (Ar), 127.90 (Ar), 128.03 (Ar), 128.11 (Ar), 128.34 (Ar), 128.52 (Ar), 136.08 (Ar), 136.40 (Ar), 136.98 (Ar), 137.01 (Ar), 146.21 (Ar)146.37 (Ar), 150.41 (Ar), 150.44 (Ar), 154.08 (Ar), 154.82 (Ar), 168.18 (Ar), 168.30 (Ar), 180.64 (**C**=O), 180.73 (**C**=O).

micrOTOF-Q MS m/z $C_{19}H_{18}N_4O_3$+Na, calculated 373.1266, observed 373.1271.

IR (cm^{-1}): 724, 908, 1090, 1114, 1176, 1353, 1408, 1447, 1581, 1700.

2.3.4.4 Synthesis of 5-[(2S)-N-boc-pyrrolidin-2-yl]-3-(2-pyridyl)-1,2,4-oxadiazole



(189) **(44)** **(191)**
$C_{15}H_{20}N_4O_3$
MW = 316.36g/mol

To N-boc-L-proline **(189)** (1.00 g, 4.65 mmol) in dichloromethane (50 ml) under an atmosphere of nitrogen, N-hydroxysuccinimide (1.22 g, 6.98 mmol) and N,N-dicyclohexylcarbodiimide (959 mg, 4.65 mmol) were added. The mixture was set to stir at room temperature overnight. After this time, N'-hydroxypyridine-2-carboxamidine **(44)** (638 mg, 4.65 mmol) was added and the reaction mixture was allowed to stir at room temperature overnight. After this time, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residues were redissolved in toluene and the reaction mixture was set to stir at reflux overnight. The crude product was purified by gravity column chromatography with a 1:2 petroleum ether:ethyl acetate solvent system to yield the pure product as a mixture of rotamers as a pale yellow oil (1.21 g, 82% two steps).

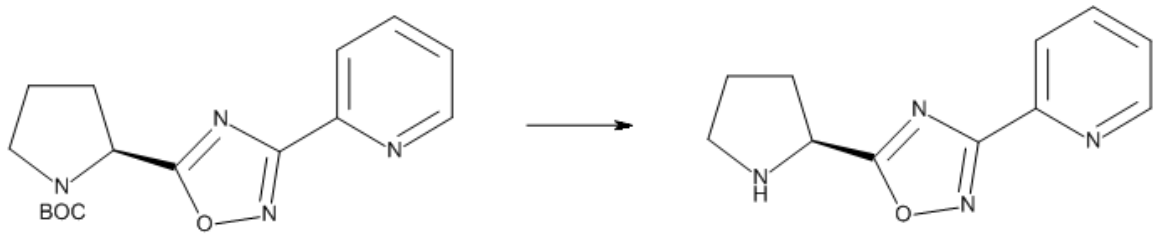
^{1}H NMR (400MHz, $CDCl_3$): (Major rotamer only) δ1.27-1.51 (9H, m, OC(C**H$_3$**)$_3$); δ1.97-2.49 (4H, m, NCHC**H$_2$**C**H$_2$**); δ3.40-3.77 (2H, m, NC**H$_2$**); δ5.09-5.27 (1H, m, NC**H**CH$_2$); δ7.39-7.47 (1H, m, Ar**H**); δ7.81-7.89 (1H, m, Ar**H**); δ8.12 (1H, d, J=7.7Hz, Ar**H**); δ8.77-8.83 (1H, m, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): (Major rotamer only) δ28.15 (OC(**C**H$_3$)$_3$), 28.39 (OC(**C**H$_3$)$_3$), 31.60 (O**C**(CH**$_3$**)$_3$), 33.54 (O**C**(CH$_3$)$_3$), 33.23 (NCH$_2$**C**H$_2$), 33.61 (NCH$_2$**C**H$_2$), 46.39 (NCH**C**H$_2$), 46.71 (NCH**C**H$_2$), 53.86 (N**C**H$_2$), 53.94 (N**C**H$_2$), 80.38 (N**C**HCH$_2$), 80.56 (N**C**HCH$_2$), 123.17 (Ar), 123.31 (Ar), 125.42 (Ar), 125.60 (Ar), 136.97 (Ar), 137.12 (Ar), 146.24 (Ar), 150.33 (Ar), 150.50 (Ar), 153.31 (Ar), 168.22 (Ar), 181.09 (**C**=O), 181.47 (**C**=O).

micrOTOF-Q MS m/z $C_{16}H_{20}N_4O_3$+Na, calculated 339.1428, observed 339.1429.

IR (cm^{-1}): 745, 771, 1117, 1157, 1247, 1364, 1387, 1693, 2931, 2975.

2.3.4.5 Synthesis of 3-(2-pyridyl)-5-[(2S)-pyrrolidin-2-yl]-1,2,4-oxadiazole



(191)

(188)
$C_{11}H_{12}N_4O$
MW = 216.24g/mol

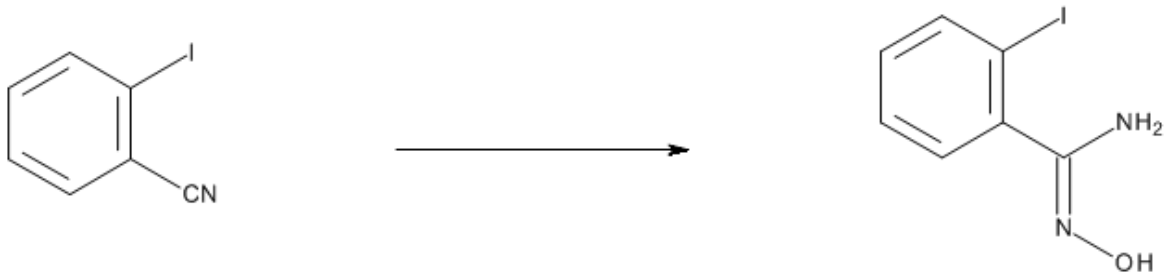
To [(2S)-N-boc-pyrrolidin-2-yl]-3-(2-pyridyl)-1,2,4-oxadiazole **(191)** (1.00 g, 3.16 mmol) under an atmosphere of nitrogen was added a 1:20 solution of trifluoroacetic acid in dichloromethane (10ml). The reaction mixture was allowed to stir at room temperature overnight. After this time, the solvents were removed under reduced pressure and the residues redissolved in water (20 ml) and extracted with diethyl ether (3 x 20 ml). The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to yield the product as a pink semi-solid (567 mg, 83%).

^{1}H NMR (400MHz, $CDCl_3$): δ2.15-2.34 (2H, m, $NCH_2C\mathbf{H_2}$); δ2.42-2.69 (2H, m, $NCHC\mathbf{H_2}$); δ3.54-3.69 (2H, m, $NC\mathbf{H_2}$); δ5.28 (1H, t, J=8.0Hz, $NC\mathbf{H}CH_2$); δ7.41 (1H, dd, J=7.7Hz, 5.1Hz, Ar**H**); δ7.82 (1H, t, J=7.3Hz, Ar**H**); δ8.03 (1H, d, J=8.0Hz, Ar**H**); δ8.69 (1H, d, J=4.4Hz, Ar**H**); δ8.80-10.20 (1H, broad, N**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ25.40 ($NCH_2\mathbf{C}H_2$), 31.19 ($NCH\mathbf{C}H_2$), 46.94 ($N\mathbf{C}H_2$), 54.44 ($N\mathbf{C}HCH_2$), 123.25 (Ar), 125.53 (Ar), 137.06 (Ar), 146.29 (Ar), 150.45 (Ar), 168.02 (Ar), 182.79 (Ar).

micrOTOF-Q MS m/z $C_{11}H_{12}N_4O$+Na, calculated 239.0903, observed 239.0906.

2.3.4.6 Synthesis of N'-hydroxy-2-iodo-benzamidine



(194)

(195)
$C_7H_7IN_2O$
MW = 262.05g/mol

To hydroxylamine hydrochloride (500 mg, 7.20 mmol) in water (50 ml) was added in small portions, sodium carbonate (670 mg, 7.20 mmol). To this, 2-iodobenzonitrile **(194)** (1.50 g, 6.55 mmol) in ethanol (50 ml) was added and the reaction mixture set to stir at reflux for 24 hours. After this time, the reaction mixture was extracted with dichloromethane. The organics were dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation to yield the product as a white solid (240 mg, 61%).

^{1}H NMR (400MHz, $CDCl_3$): δ5.85-6.21 (2H, broad doublet, N**H$_2$**); δ7.14 (1H, *appt.* td, J=7.7Hz, 1.6Hz, Ar**H**); δ7.41 (1H, *appt.* t, J=7.3Hz, Ar**H**); δ7.49 (1H, dd, J=7.5Hz, 1.5Hz, Ar**H**); δ7.91 (1H, d, J=7.8Hz, Ar**H**).

^{13}C NMR (100MHz, $CDCl_3$): δ91.97, 128.14, 128.19, 131.40, 140.09, 141.21.

IR (cm^{-1}): 1021, 1448, 2830, 2942, 3315.

M.p.: 139-140 ^{o}C.

3 Results and Discussion

This chapter is divided into three sub-chapters, each discussing in detail a particular area of research in which the 1,2,4-oxadiazole unit has been explored.

The first of these subchapters concerns the potential suitability of the chemistry of the 1,2,4-oxadiazole unit as a useful component in ligands in supramolecular chemistry.

The second of these sub-chapters looks at the potential incorporation of 1,2,4-oxadiazloles/oxadiazolines and subsequent biological effects of the products in extensions of our group's work on β-sultams, γ-sultams and similar, related systems. In this chapter a competing reaction resulted in the formation of isoxazoles/isoxazolines rather than 1,2,4-oxadiazoles/oxadiazolines.

The third sub-chapter considers the 1,2,4-oxadiazole unit as a feature of asymmetric organocatalysis. This subchapter involves the incorporation of the 1,2,4-oxadiazole into novel L-proline bases and moves on to look at their potential in hypervalent iodine based systems.

3.1 The 1,2,4-Oxadiazole as a Key Feature in Ligand Systems

As introduced earlier, the 1,2,4-oxadiazole nucleus carries major potential as a coordination unit in ligand strands, though remains relatively unexplored in any depth. There are several reasons for this potential. The first is that each nitrogen atom of the 1,2,4-oxadiazole is fully available for co-ordination to metal ions. This is because the oxygen atom donates one of its lone pairs to the π-electron system of the ring, thus enabling one or both of the oxadiazole nitrogen atoms to utilise their lone pairs and form dative, co-ordinate bonds to metal ions without loss of aromaticity. The imine-nitrogen (N4) and oxime-nitrogen sites (N2) provide two realistic co-ordination options and thus give the 1,2,4-oxadiazole versatility as a potential component in ligand systems.

A second highly suitable feature of the 1,2,4-oxadiazole unit in ligand systems, is the attractive bite angle created when the unit is 3,5-disubstituted with other potential binding domains, such as 2-pyridyl units, for example. The lone pairs of the pyridine nitrogen and oxadiazole nitrogens are angled very nicely towards a central focus, at approximately 50^0. The oxadiazole nitrogens and those of adjacent 2-*N*-heterocycles provide a perfect potential bidentate binding domain for metal ions.

Another interesting feature of the 1,2,4-oxadiazole in ligand synthesis is the fact that they are so under-researched in this area. There are a handful of 1,2,4-oxadiazole containing ligands in the literature and these are detailed in the introduction.

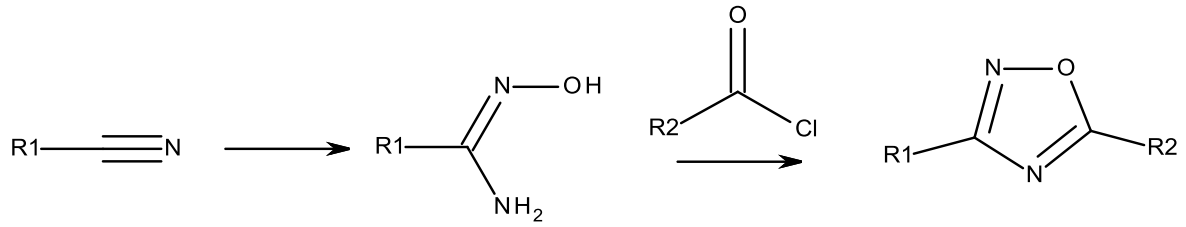
The work in this section was inspired through collaboration with Prof. Craig Rice of the University of Huddersfield. Rice and co-workers have focussed largely on thiazole containing ligand systems. The parallels between the thiazole and 1,2,4-oxadiazole units were highlighted in the introduction.

3.1.1 The Synthesis of 1,2,4-Oxadiazole-Containing Ligand Precursor Materials

The precursor materials required for the synthesis of the 1,2,4-oxadiazole ligand were not all commercially available and thus were synthesised in-house where necessary.

Initially, the 1,3-dipolar cycloaddition route to the 1,2,4-oxadiazole nucleus served as our primary mode of synthesis. However, following a series of practical difficulties with some of the ligand precursor materials, it was decided to switch focus to the amidoxime/reactive-carboxylic mode.

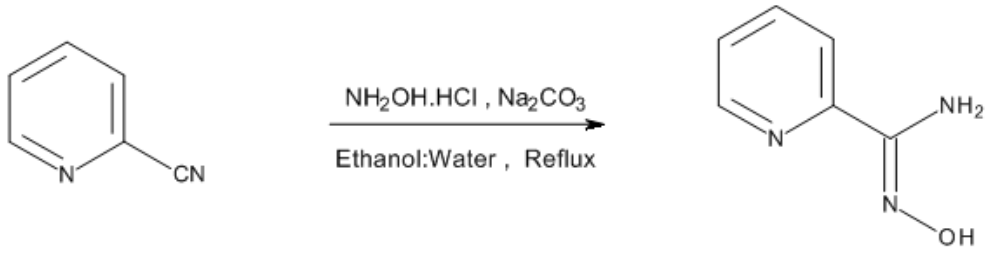
The general scheme for ligand construction is shown below:



Scheme 3.1

Occasionally, some of the cyano- compounds also had to be synthesised. These syntheses and those of the corresponding ligand-metal complexes are detailed below.

3.1.1.1 Synthesis of N'-Hydroxypyridine-2-carboxamidine



(43) **(44)**

Scheme 3.2

The synthesis of the simple pyridine-2-amidoxime **(44)** was achieved in 77% yield through reaction with hydroxylamine in a water-ethanol solvent under reflux.

This simple precursor was used to synthesise several ligands in this chapter and was an important and regularly utilised precursor.

The synthesis of the product was confirmed by ^{1}H NMR spectroscopy. The broad NH_2 signal is seen clearly at δ5.67. The OH is visible as a broad singlet also, at δ8.58. The four pyridine protons resonate as doublets of varying multiplicity at δ7.24, δ7.64, δ7.86 and δ8.50.

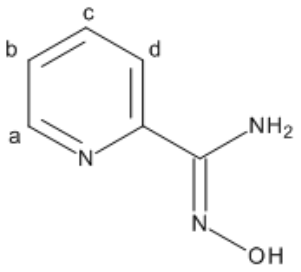
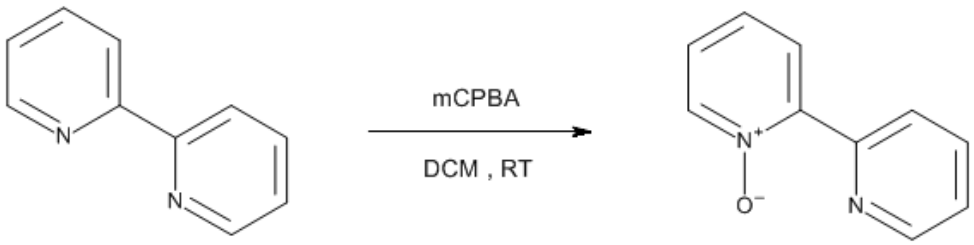


Figure 3.1

3.1.1.2 Synthesis of 1-Oxido-2-(2-pyridyl)pyridin-1-ium



(45) **Scheme 3.3** **(46)**

Mono-oxidation of 2,2'-bipyridine **(45)** to yield **(46)** was achieved through treatment with mCPBA in dichloromethane. This was achieved in 50% yield. The product was purified by column chromatography to remove remaining mCPBA starting material and the mCBA by-product.

The use less than 1eq of mCPBA minimised oxidation of both pyridine nitrogen atoms.

The structure of the product was confirmed by ^{1}H NMR spectroscopy. The apparent triplet of doublets at δ7.05 and δ7.60 and the multiplet at δ7.10-7.16 are likely to resonate from protons *b,c, f* and *g*. The four remaining split doublets at δ7.95, δ8.11, δ8.51 and δ8.69 are likely to resonate from protons *a, d, e* and *h*. The signal at δ8.69 is likely to be proton *a*, due to the deshielding influence of the nearby pyridinium oxide.

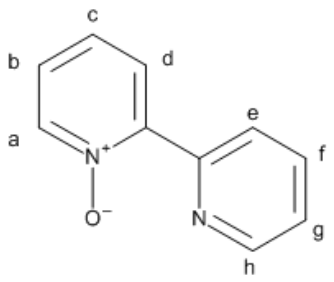
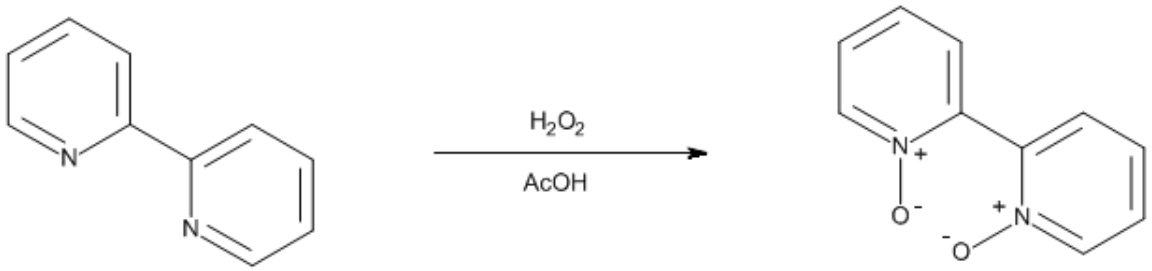


Figure 3.2

The identity of the product was further confirmed by ^{13}C NMR spectroscopy which showed the correct number of aromatic signals, and by HRMS which measured an accurate mass of the $[M+Na]^{+}$ ion as 195.0536 for 195.0529 calculated.

3.1.1.3 Synthesis of 1-Oxido-2-(1-oxidopyridin-1-ium-2-yl)pyridin-1-ium



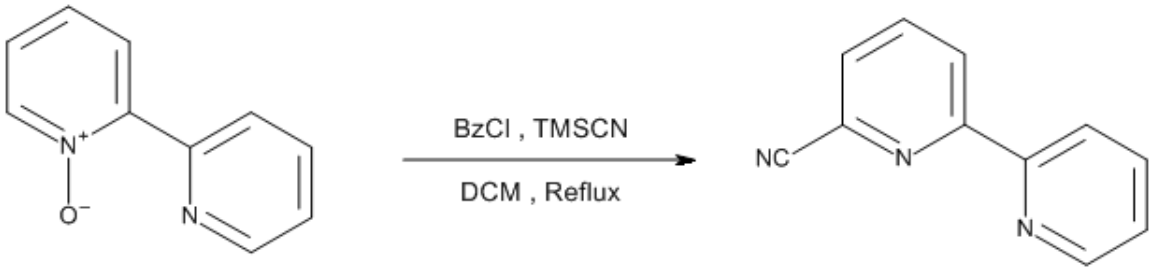
(45) **(47)**

Scheme 3.4

The bipyridine bis-N-oxide **(47)** was synthesised by oxidation with hydrogen peroxide in glacial acetic acid and was achieved in 93% yield.

The structure of this symmetrical product was strongly suggested by ^{1}H NMR spectroscopy, and confirmed by HRMS which delivered an accurate mass for the $[M+Na]^{+}$ ion of 211.0482 for the theoretical figure of 211.0478 for this ion.

3.1.1.4 Synthesis of 6-(2-Pyridyl)pyridine-2-carbonitrile



(46) **Scheme 3.5** **(48)**

The nucleophilic substitution by cyanide to the 2-position of the bipyridine mono-N-oxide **(46)** was achieved in 55% yield through treatment of the N-oxide with a total of two equivalents of benzoyl chloride and two equivalents of trimethylsilyl cyanide in refluxing dichloromethane. The mono-2-

cyanated product **(48)** was purified by column chromatography to remove benzoic acid and trimethylsilyl side products.

The structure of the product was confirmed by ^{1}H NMR spectroscopy. Assignment of signals suggests that the clean, apparent triplet at δ7.86 is proton *b.* The doublet of doublets of doublets and apparent triplet of doublets at δ7.29 and δ7.76 respetively are likely to account for protons *e* and *f*. The remaining doublets at δ7.62, δ8.35, δ8.57 and δ8.59 correspond to protons in positions *a, c, d,* and *g.*

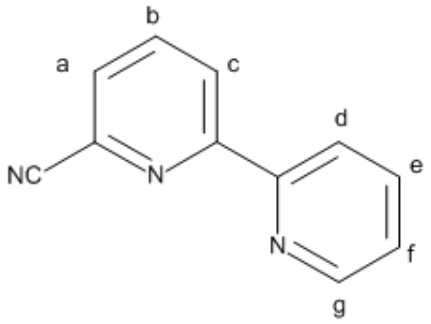
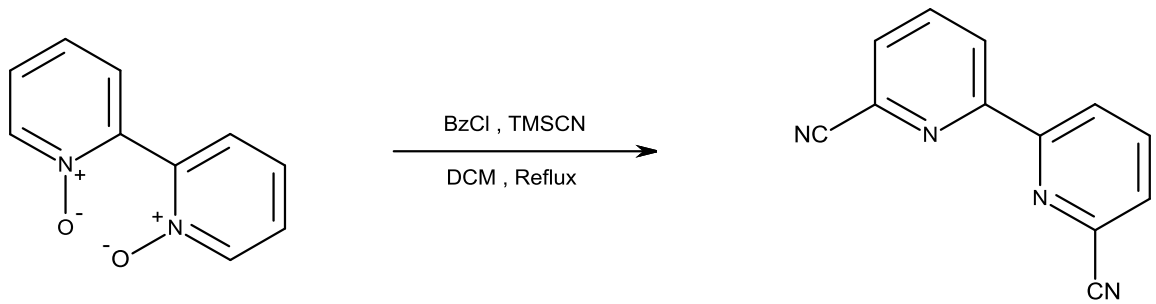


Figure 3.3

The structure of the product was confirmed by HRMS with the accurate mass of the $[M+Na]^{+}$ ion measured as 204.0537 for the calculated figure of 204.0532.

3.1.1.5 Synthesis of 6-(6-Cyano-2-yridyl)pyridine-2-carbonitrile



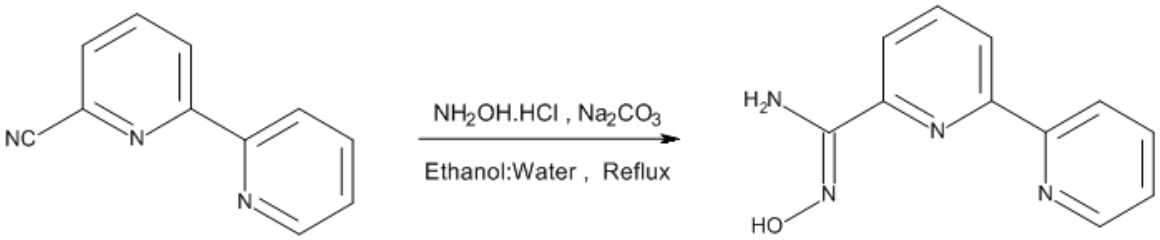
(47) **(49)**

Scheme 3.6

The bipyridine bis-cyano compound **(49)** was synthesised in 74% yield by reaction of **(47)** with a total of 2.5 equivalents of both benzoyl chloride and trimethylsilyl cyanide in refluxing dichloromethane.

The structure of the product was suggested by ^{1}H NMR spectroscopy, and confirmed by HRMS which delivered an accurate mass for the $[M+Na]^{+}$ ion of 229.0488 for the calculated figure of 229.0485 for this ion.

3.1.1.6 Synthesis of N'-Hydroxy-6-(2-pyridyl)pyridine-2-carboxamidine



(48) **(50)**

Scheme 3.7

The 2,2'-bipyridyl-2-amidoxime **(50)** was synthesised in 90% yield by applying the same conditions as per the synthesis of **(44)**. The primary amine of the amidoxime was clearly present as a broad singlet at δ5.69 in the ^{1}H NMR spectrum. Two split doublets were observed, at δ7.89 and δ8.64, together with a multiplet resonating at δ8.35-8.40. Considering the splitting patterns, the doublet of doublets doublets at δ7.28 and the overlapping apparent triplet of doublets and doublet of doublets at δ7.78 and δ7.79 correspond to protons *b, e* and *f* respectively.

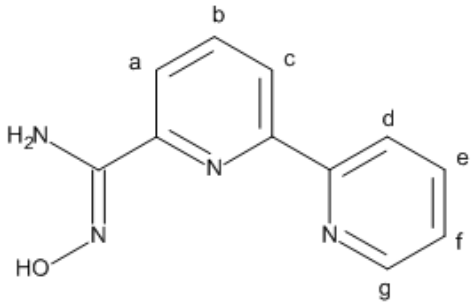
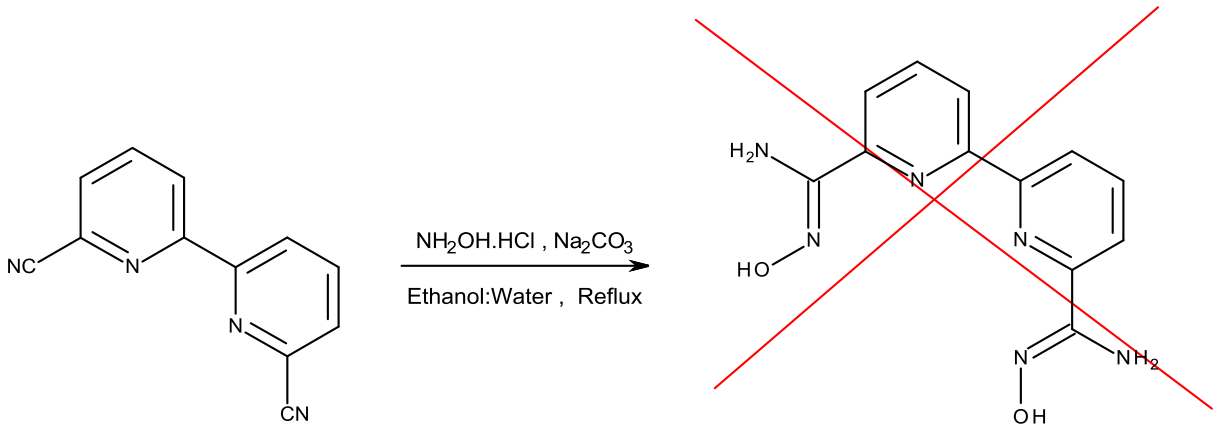


Figure 3.4

The ^{13}C NMR supports this structure, giving the appropriate number of signals.

The IR spectrum shows good support for this structure, the absorption band at 1651.8cm^{-1} is most likely resultant from the amidoxime imine bond. The broader stretch at approx. 2750-3100cm^{-1} and 3100cm^{-1} are likely to be caused by the amidoxime OH and NH bonds respectively.

3.1.1.7 Synthesis of N'-hydroxy-6-[6-[(Z)-N'-hydroxycarbamimidoyl]-2-pyridyl] pyridine-2-carboxamidine

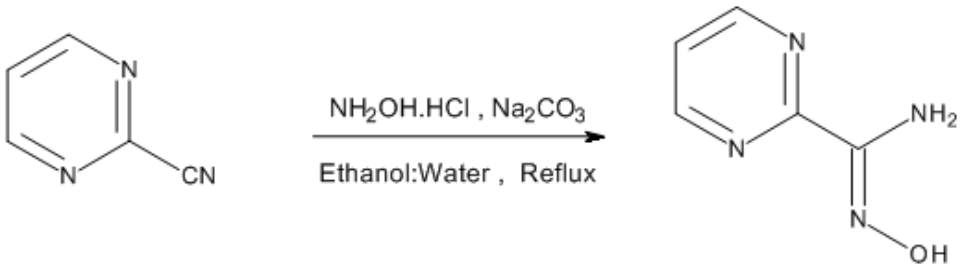


(49) **(51)**

Scheme 3.8

The 2,2'-bipyridine bis-amidoxime **(51)** was not successfully synthesised by the above means. This was largely due to an extremely impractical reaction mixture which, upon extraction attempts, formed an unworkable emulsion.

3.1.1.8 Synthesis of N'-Hydroxypyrimidine-2-carboxamidine



(52) **(53)**

Scheme 3.9

The synthesis of the pyrimidine-2-amidoxime **(53)** from pyrimidine-2-carbonitrile **(52)** was achieved in 68% via the same synthetic protocol as **(44)**. This particular amidoxime product was isolated as a brilliant yellow/golden crystalline solid.

The ^{1}H NMR spectrum is predictably simple with the primary amine protons resonating as a broad singlet at δ5.85 and the OH proton observable further upfield at δ10.21. The aromatic protons are observed at δ7.51 and δ8.84. The doublet at δ8.84 and triplet at δ7.51 are likely to correspond to protons *a* and *b*, respectively.

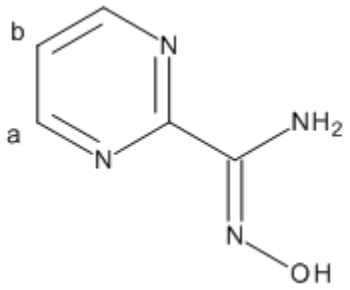
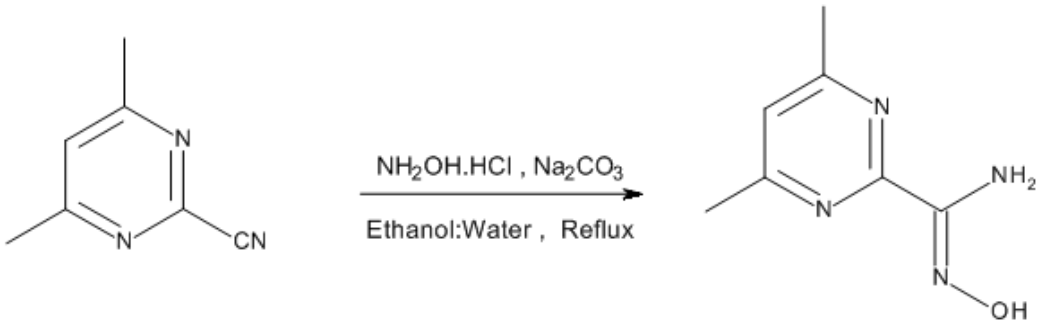


Figure 3.5

This structure was confirmed by ^{13}C NMR, IR spectroscopy and HRMS which delivered an accurate mass of the $[M+Na]^{+}$ ion of 161.0438 for the theoretical figure of 161.0434.

3.1.1.9 Synthesis of N'-Hydroxy-4,6-dimethyl-pyrimidine-2-carboxamidine



(54) **(55)**

Scheme 3.10

The synthesis of the dimethyl pyrimidine amidoxime **(55)** from **(54)** was also achieved also via the same process as amidoxime **(44)**.

As with previous amidoximes, ^{1}H NMR spectroscopy remains a strongly diagnostic tool with the primary amine protons seen as a broad singlet at δ5.63 and the OH proton a little higher at δ6.87. The lone aromatic proton *b* resonates as the expected singlet at δ7.06 with the methyl protons *a* as a singlet at δ2.55.

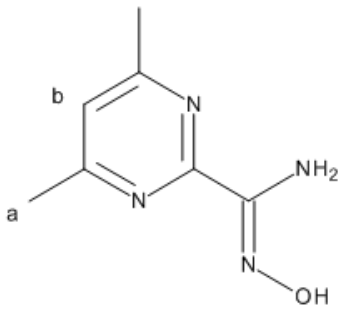
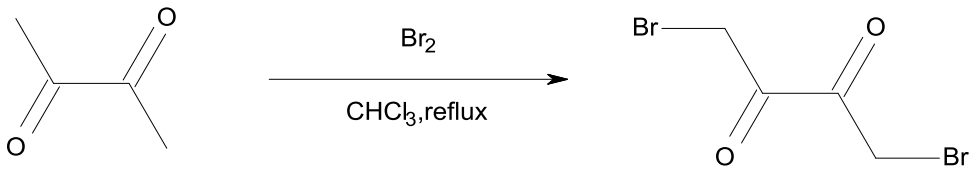


Figure 3.6

The structure was further confirmed by ^{13}C NMR and HRMS which measured an accurate mass of the $[M+Na]^{+}$ ion of 189.0752 for the expected figure of 189.0747.

3.1.1.10 Synthesis of 1,4-Dibromobutane-2,3-dione



(56) **(57)**

Scheme 3.11

This precursor was synthesised in order to generate two thiazole ligands, **(75)** and **(77)** (see sections 3.1.2.16 and 3.1.2.17). The synthesis was achieved via the dropwise addition of 2 equivalents of bromine in chloroform to 2,3-butanedione **(56)** in refluxing chloroform in 91% yield. The di-α-brominated product **(57)** was purified by recrystallisation from chloroform[92,167,168].

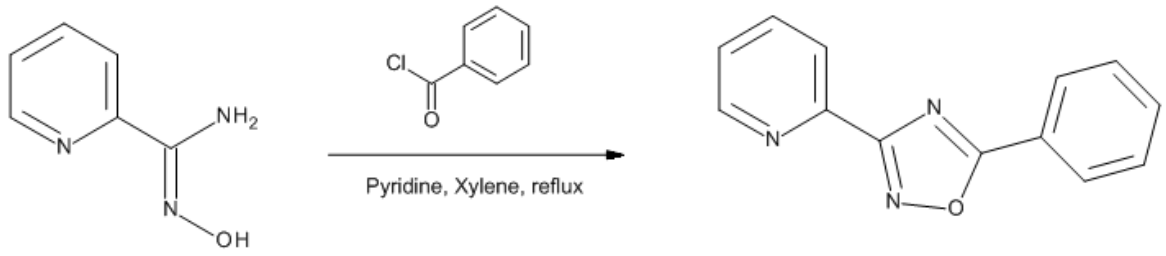
The structure of the product was confirmed by ^{1}H NMR spectroscopy, the methylene protons resonating at δ4.34, noticeably higher than the methyl protons of the starting material dione.

3.1.2 The Synthesis of Novel 1,2,4-Oxadiazole Ligand Systems

The vast majority of ligands in this section are novel. A handful of the ligands in this section [compounds **(58)**, **(75)** and **(77)**] have been synthesised previously. Crystallisation of ligands with divalent metal ions was achieved using acetonitrile and nitromethane solvents, with slow diffusion from various co-solvents including dichloromethane, chloroform, diethyl ether, ethyl acetate and diisopropyl ether. To aid dissolution, small amounts (2/3 drops) of methanol were occasionally added where necessary. The divalent metal ions selected were used consistently throughout all synthesised ligand systems and included in all cases; cadmium(II), mercury(II), zinc(II), copper(II), iron(II), nickel(II), cobalt(II) and lead(II) perchlorates. Occasionally, the more reactive zinc(II) and lead(II) triflates were used, pending availability.

In most cases, the ligands reacted with the metal ions to form aggregated complexes visible with the naked eye, however only complexes of a crystalline nature were examinable by X-ray diffraction. X-ray crystal structures of such crystalline materials are included where applicable. The synthetic schemes for each ligand are similar; however, it is important to show the subtle differences in these syntheses since they ultimately lead to drastically different crystalline materials.

3.1.2.1 Synthesis of 5-phenyl-3-(2-pyridyl)-1,2,4-oxadiazole



(44) **(58)**

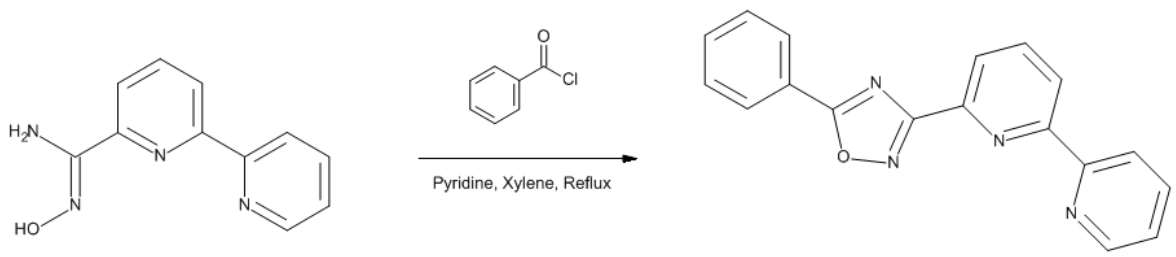
Scheme 3.12

The synthesis of ligand **(58)** was achieved in 32% yield by treating amidoxime **(44)** with benzoyl chloride and pyridine in refluxing xylene. The reaction was also attempted in toluene; however this choice of solvent limited the reaction to very low yields. This ligand was synthesised previously by Pace in 2011[61], and explored as a ligand with copper, nickel and zinc.

The data was fully consistent with the proposed structure and with that published by Pace.

This is the simplest ligand in our synthetic library. With just three nitrogen atoms in total, only two of which able to coordinate to any one metal ion, the ligand is only able to operate as a basic bidentate unit, as Pace and co-workers have shown[61]. With metals other than those used by Pace, no crystalline materials were observed.

3.1.2.2 Synthesis of 5-phenyl-3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazole



(50) **(59)**

Scheme 3.13

In an extension from the previous ligand **(58)**, ligand **(59)** was developed through reaction of the previously synthesised 2,2'-bipyridine amidoxime **(50)** with benzoyl chloride in the presence of pyridine in refluxing xylene. The product was obtained in 98% yield.

The ligand features a phenyl group substituted at the 5-position of the oxadiazole and the 2,2'-bipyridine unit at the 3-position. The ligand poses potentially interesting metal ion coordination options, since the bipyridine ring, whilst an attractive bidentate possibility in itself, forms an attractive tridentate domain with one of either oxadiazole ring nitrogens.

Analysis by ^{1}H NMR spectroscopy reveals a complex aromatic region. Individual signals are not split cleanly. Multiplicity is not obvious and coupling constants are somewhat compromised. The ^{13}C NMR spectrum showed the correct number of unique carbon atoms. HRMS confirms the structure with an accurate mass for the $[M+H]^{+}$ ion measured to be 301.1085, comparing well with the theoretical figure of 301.1070.

Reaction of **(59)** with an equimolar amount of $Cd(ClO_4)_2 \cdot 6H_2O$ in MeCN resulted in a colourless solution. Following slow diffusion of ethyl acetate, colourless crystalline materials were observed. Analysis of these materials by single crystal X-ray diffraction revealed a mononuclear complex. The crystal structure in Figure 3.8 shows **(59)** coordinating as a tridentate ligand, with binding through the nitrogen atoms of the bipyridine unit and through the N4 nitrogen of the oxadiazole. Just as previous literature concerning 1,2,4-oxadiazole units in ligands has suggested, the N4 nitrogen of the oxadiazole is able to form an attractive bite angle with 2-pyridyl nitrogens substituted at the oxadiazole 3- or 5-positions. This coordination represents one of very few examples of the 1,2,4-oxadiazole unit coordinating as part of a successful tridentate domain in ligand systems[58].

Please see Tables 3.1 and 3.2 for bond distances and angles.

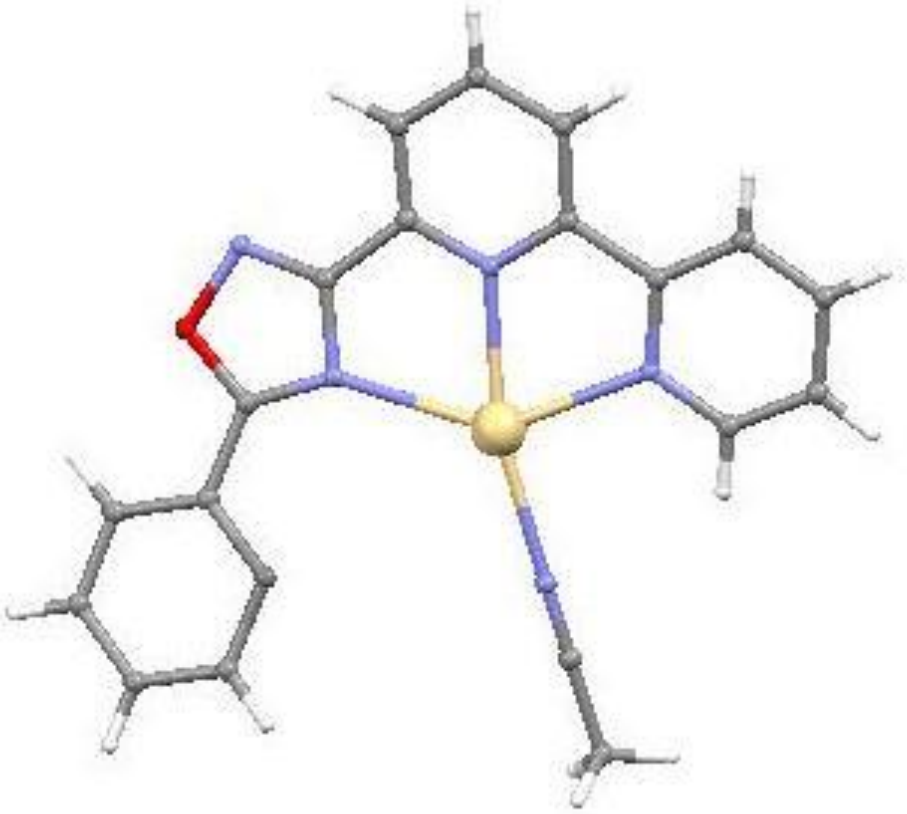


Figure 3.7 – Crystal structure of mononuclear complex featuring ligand **(59)** and Cd^{2+}.

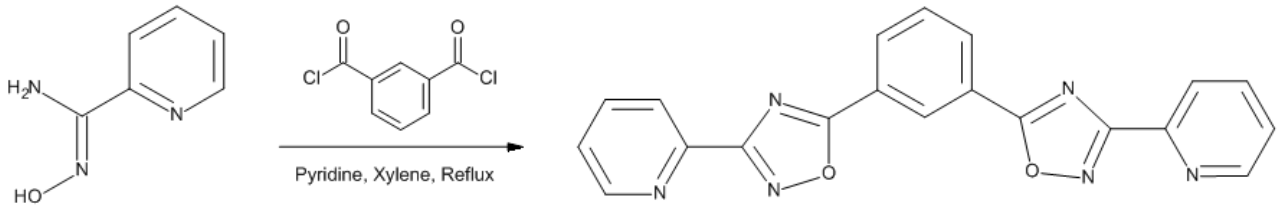
Bond	Bond Distance (Å)
Cd(1) – O(2)	2.241(3)
Cd(1) – O(3)	2.283(2)
Cd(1) – N(6)	2.305(3)
Cd(1) – N(2)	2.305(2)
Cd(1) – N(1)	2.343(2)
Cd(1) – N(3)	2.419(2)

Table 3.1 – Bond distance data for **(59)** complex.

Bond	Bond Angle (^{0})
O(2) – Cd(1) – O(3)	157.01(11)
O(2) – Cd(1) – N(6)	83.91(10)
O(3) – Cd(1) – N(6)	80.73(10)
O(2) – Cd(1) – N(2)	101.21(9)
O(3) – Cd(1) – N(2)	97.68(9)
N(6) – Cd(1) – N(2)	166.26(9)
O(2) – Cd(1) – N(1)	97.62(11)
O(3) – Cd(1) – N(1)	101.00(9)
N(6) – Cd(1) – N(1)	96.45(10)
N(2) – Cd(1) – N(1)	70.35(8)
O(2) – Cd(1) – N(3)	87.87(10)
O(3) – Cd(1) – N(3)	85.98(8)
N(6) – Cd(1) – N(3)	122.22(9)
N(2) – Cd(1) – N(3)	71.03(8)
N(1) – Cd(1) – N(3)	141.33(8)

Table 3.2 - Bond angle data for **(59)** complex.

3.1.2.3 Synthesis of 3-(2-pyridyl)-5-[3-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(44) **(60)**

Scheme 3.14

The crystallisation of the previous ligand **(59)** with Cd^{2+} ions resulting in a simple mononuclear complex provided our oxadiazole research with good credibility and merited further ligand development. Taking the promising oxadiazole-pyridine bidentate system **(58)** developed by Pace and co-workers[61] as a model, our group developed the dimeric ligand **(60)** with the introduction of a phenylene spacer unit. This interesting prospect introduced symmetry to the ligand, and distance between the oxadiazoles. The result of this oxadiazole separation is two potential pyridine-oxadiazole bidentate binding domains. At a glance, this provides a highly attractive prospect for metal ion coordination.

Ligand (**19**) was synthesised via the usual method in 27% yield. Isophthaloyl chloride was reacted with two equivalents of pyridine amidoxime **(44)** to yield the desired 5-ringed system.

The structure of the product was confirmed by the ^{1}H NMR spectrum. Though assignment of each individual proton is tricky, the multiplicity and integration is as expected. The triplet integrating as one proton at δ7.80 must originate from proton *f*. Likewise, the singlet at δ9.23 is likely caused by the bridging phenylene proton *g*.

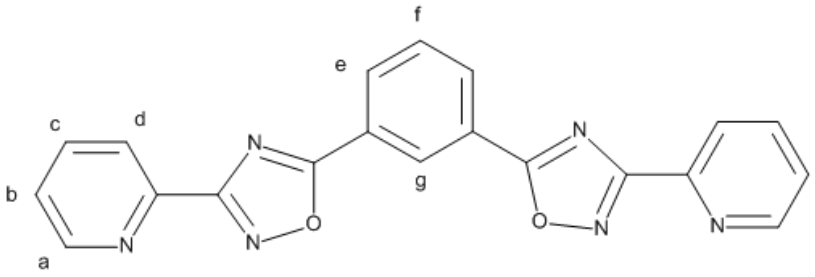
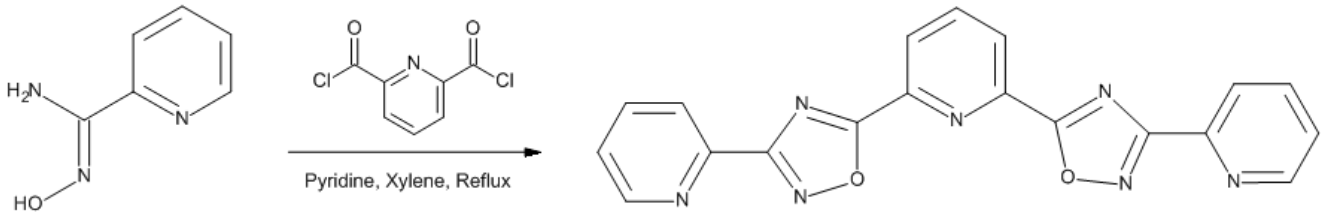


Figure 3.8

Confirmation of the structure was provided by ^{13}C NMR spectroscopy, which indicated the 11 environmentally unique carbons atoms, and via HRMS which delivered an accurate mass for the $[M+Na]^+$ ion of 391.0915. The theoretical mass for this compound was calculated to be 391.0901.

Whilst some products of ligand **(60)** with various metal ions were observed, these products did not possess crystallinity that made them suitable for x-ray crystallographic analysis.

3.1.2.4 Synthesis of 3-(2-pyridyl)-5-[6-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(44) **(61)**

Scheme 3.15

Ligand **(61)** was synthesised in 15% yield through reaction of pyridine-2,6-dicarbonyl dichloride with amidoxime **(44)**.

Whist the function of the spacer units is to partition potential binding domains, the installation of a further potential nitrogen binding domain in the spacer unit was attractive. At a glance, this nitrogen atom sits in the middle of a potential tridentate domain with the oxadiazole nitrogens with what appears to be a reasonably attractive (though perhaps slightly tight/convergent) bite angle. Amongst other denticities of this ligand are the oxadiazole-pyridine bidentate domains either side of the central pyridine unit and also the theoretical possibility of pentadenticity across the length of the ligand. Due to the high potential of this ligand and in spite of the lack of crystalline products observed with the analogous phenylene spaced ligand **(60)**, it was considered very worthwhile attempting crystallisation with this interesting, pentadentate ligand.

Analysis of ligand **(61)** by ^1H NMR spectroscopy is not entirely diagnostic. The triplet integrating as one proton at δ8.24 must account for proton *f,* in the 4-position of the central pyridine unit.

Doublets at δ8.33, δ8.68, the multiplet-type doublet at δ8.89 and the multiplet at δ7.51 complete the NMR spectrum which shows some complex long range coupling.

Fortunately the ^{13}C NMR spectrum provides good evidence for this structure with all carbon signals present and correct. HRMS measured an accurate mass of the $[M+Na]^+$ ion of 392.0866 for the calculated figure of 392.0864.

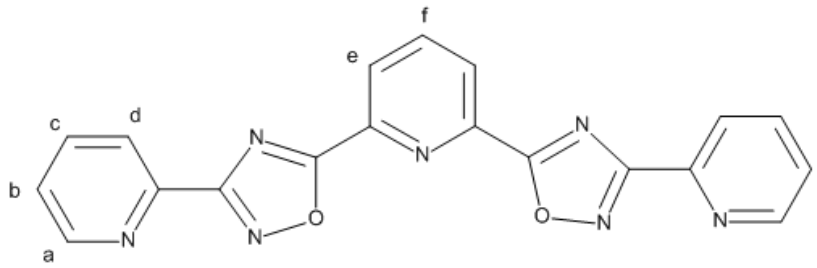
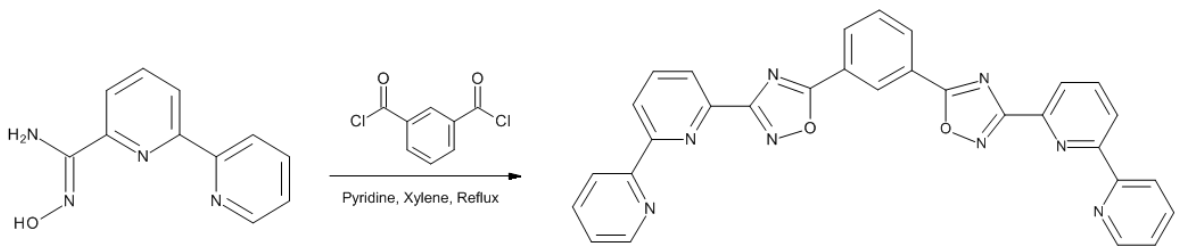


Figure 3.9

Unfortunately, the inclusion of the nitrogen atom within the spacer unit proved to be an unsuccessful venture since no crystalline products were formed with divalent metal ions.

Whilst no crystals were observed, it was felt that the inclusion of a central pyridine unit remained a reasonably attractive option. The bite angle between central pyridine nitrogen and oxadiazole nitrogen atoms appears too appealing to ignore. This central tridentate domain may be marginally more sterically congested than the outer bi- and tridentate domains. Similar ligands will be discussed later.

3.1.2.5 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[3-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(50) **(62)**

Scheme 3.16

The heptacyclic ligand **(62)**, analogous with ligand **(60)**, was synthesised in 35% yield by reaction of isophthaloyl chloride with the 2,2'-bipyridine amidoxime **(50)** in the presence of pyridine in refluxing xylene.

This ligand features a central phenylene unit serving to partition the ligand and create two uniform, tridentate binding domains in the shape of the proven oxadiazole-pyridine-pyridine system. This system appears highly attractive at a glance. The metallocrystallisation observed with **(59)** provided much encouragement with this ligand, however the lack of metal ion crystallisation with ligands **(60)** and **(61)** was an unpredicted disappointment.

The ^{1}H NMR spectrum is consistent with the assigned structure of this product. The spectrum shows two doublets of doublets potentially accounting for protons *b* and *c,* and two triplets for protons *f* and *i*. Three further doublets were present together with a series of multiplets at δ7.71-7.77 and δ8.81-8.88 integrating overall for the correct number of protons. The singlet visible at δ9.17 is diagnostic of phenylene proton *j*.

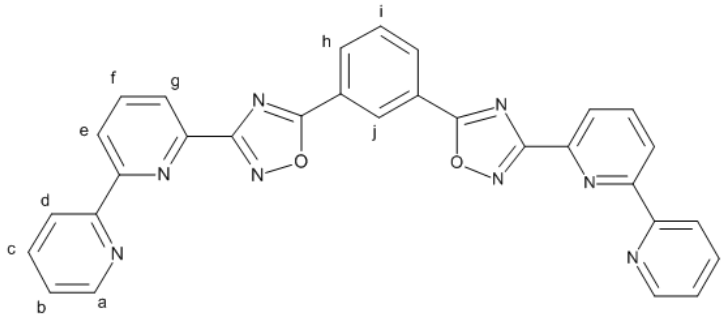
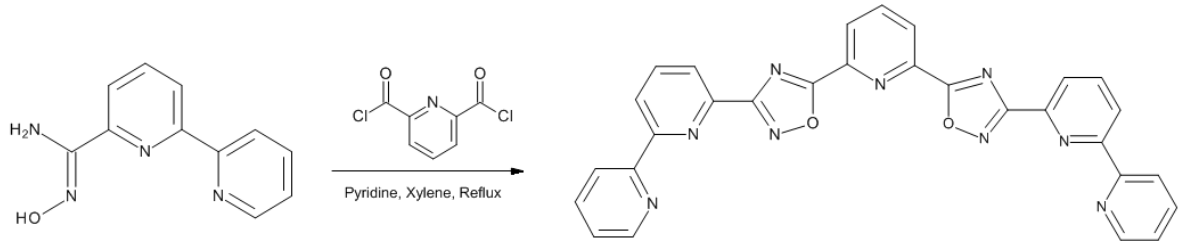


Figure 3.10

The ^{13}C NMR spectrum is consistent with the suggested structure, indicating the presence of sixteen environmentally unique carbon atoms. The structure was confirmed unequivocally by HRMS which provided a value of 523.1648 for the $[M+H]^{+}$ ion, correlating with the calculated figure of 523.1626.

To our surprise and disappointment, this ligand did not produce any crystalline products. This was extremely disappointing since, as described before, the ligand seems perfectly set up for intricate metal ion complexation and thus the possibility of self-assembled, metallosupramolecular structures. Unfortunately, though semi-crystalline materials were harvested, none were suitable for analysis by X-ray crystallography.

3.1.2.6 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[6-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(50) **(63)**

Scheme 3.17

The seven-heterocycle-strong ligand **(63)** was synthesised via the conventional method with the pyridine 2,6-diacid chloride and **(50)** in refluxing xylene with pyridine as base, in 11% yield.

Following the disappointment of the phenylene and pyridine spaced, pyridine and bipyridine, oxadiazole ligands, there seemed little chance of any crystalline structures forming from this particular ligand. However, this ligand completed a series and so the synthesis and crystallisation setup was carried out as per the usual methods.

The ligand itself has a plethora of potential metal binding sites. Bidentate domains through the bipyridine units, tridentate domains through the bipyridine-oxadiazole systems, a potential tridentate domain across the central oxadiazole-pyridine-oxadiazole system and even a potential tetradentate domain across four heterocycles through the bipyridine-oxadiazole-pyridine system; the potential bite angles of which look highly attractive.

The ^{1}H NMR spectrum is strongly supportive of this structure. The triplet integrating as one proton at δ8.52 is highly likely to be generated by proton *i* of the central pyridine unit, suggesting that both acid chlorides of the 2,6-pyridine diacid chloride have reacted with the amidoxime to form the symmetrical ligand. Further exact assignment is difficult, since the aromatic region is predictably crowded. Despite the signals integrating well, the splitting patterns are not clearly observed, with only three doublets of doublets (or apparent triplets) being seen.

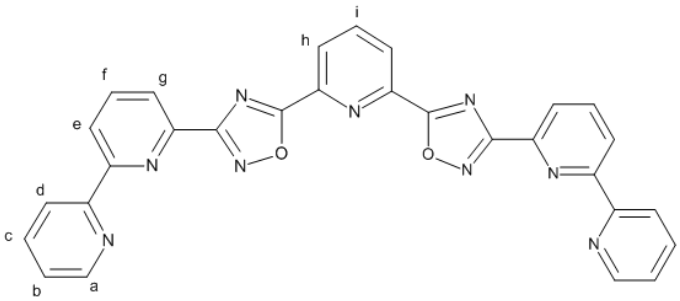


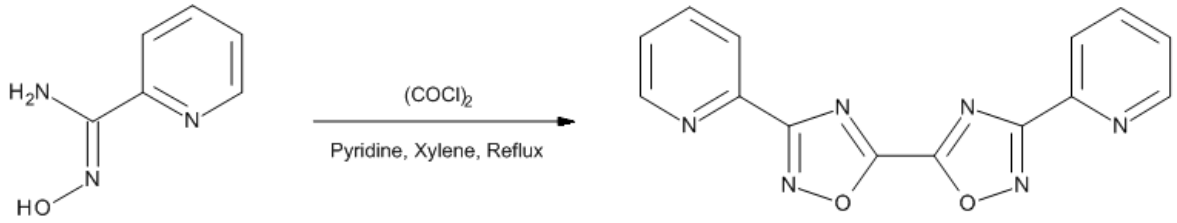
Figure 3.11

On this occasion, ^{13}C NMR was not available due to the extremely poor organic solubility of the ligand. Fortunately the mass spectrum provided an accurate mass of 546.1396 for the $[M+Na]^+$ ion with the calculated figure determined to be 546.1397.

Unfortunately, in keeping with the trend of previous ligands of this nature, no crystalline products were formed. Again this is highly surprising given the number of alluring coordination prospects throughout this molecule.

Whilst Rice and co-workers observed remarkable results with many thiazole ligands featuring spacer units[65-69], it appears that the spacer unit is a poor feature in 1,2,4-oxadiaozole systems. Whilst we have shown that the bipyridine-oxadiazole system is capable of behaving as a tridentate domain, it appears that the presence of spacer units partitioning two such domains does not afford crystalline, self-assembled, metallosupramolecular structures.

3.1.2.7 Synthesis of 3-(2-pyridyl)-5-[3-(2-pyridyl)-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(44) **Scheme 3.18** **(64)**

The potentially tetradentate ligand **(64)** was synthesised in 10% yield by switching to the simple two-carbon diacid chloride, oxalyl chloride. The reaction was set up under the usual conditions.

In a change of strategy, we decided to leave the spacer unit tactic and explore ligands with a central, bis-oxadiazole core. In this particular ligand the bis-oxadiazole core, linked at the 5-positions, is flanked by single 2-pyridyl units. In terms of potential metal ion coordination, this ligand is more compact with two potential bidentate pyridine-oxadiazole units. The theoretical prospect of the ligand behaving as a tetradentate ligand seems unlikely. It has been shown by Steel and co-workers that the parent bis-oxadiazole unit can coordinate with metal ions to form simple mononuclear assemblies[53]. This undesired coordination is a potential consequence. However, it was thought that the inclusion of pyridine units at the 3-positions of the bis-oxadiazole core would modify this coordination.

The ^{1}H NMR spectrum of the product is simple, showing doublets at δ8.29 and δ8.88 corresponding to protons *a* and *d*, along with an apparent triplet of doublets at δ7.95 and a doublet of doublet of doublets at δ7.54. These split signals are protons *b* and *c*. ^{13}C NMR spectroscopy supports this structure very well. The structure was confirmed by HRMS which measures an accurate mass for the $[M+Na]^{+}$ ion of 315.0601, correlating well with the calculated figure of 315.0612.

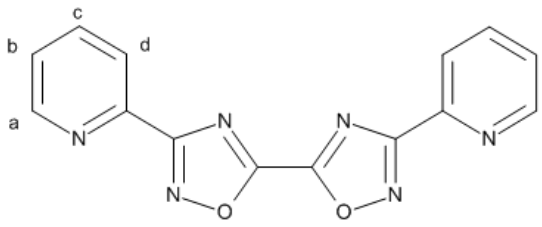
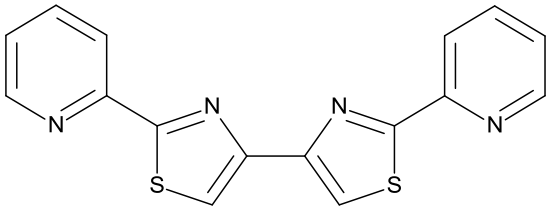


Figure 3.12

To our surprise, this ligand produced some quite unexpected and spectacular results when crystallised with metal ions.

Thiazole ligand **(75)** containing the bis-thiazole core flanked by pyridine units, has been demonstrated to react with divalent metal ions capable of octahedral geometry to produce a dinuclear double helicate $[M_2(\mathbf{L^{75}})_3]^{4+}$[65,115,116]. Since strong molecular comparisons between the thiazole unit and 1,2,4-oxadiazole unit can be drawn, it was hoped that if any self-assembled

architecture were to form, it may be of the same dinuclear double helicate format, although such predictions are often inaccurate.



(75)

Figure 3.13

Though analogous to the thiazole ligand **(75)**, it seems that the 1,2,4-oxadiazole unit displays distinctly different coordination behaviour since no dinuclear double helicates were observed.

Reaction of **(64)** with an equimolar amount of $Hg(ClO_4)_2 \cdot 6H_2O$ in MeCN resulted in a colourless solution. Following slow diffusion of ethyl acetate, colourless crystals were observed. Analysis of these materials by single crystal X-ray diffraction revealed a tetranuclear cyclic helicate complex. This elaborate metallosupramolecular system features the ligand **(64)** partitioned into two bidentate pyridine-oxadiazole domains (clearly the spacer units were unnecessary to promote this effect). The Hg^{2+} ions adopt octahedral geometry, coordinating as they do with the bidentate pyridine-oxadiazole domains of two ligands **(64)**. The remaining equatorial positions of the Hg^{2+} ion are filled by coordination to perchlorate counter anions. Coordination of the oxadiazole unit occurs via the imine-N-4 atom rather than the oxime N-2 atom. The second bidentate domain of each ligand coordinates a second Hg^{2+} ion in the same manner with an approximate 180^0 twist of the central oxadiazole-oxadiazole bond. This twist is often a common, diagnostic theme of helicate assemblies. In grid-type assemblies the twist is absent, creating a more linear architecture. The twisting helicate creates a quite beautiful, overlap-underlap effect about the metals ions. This coordination is extended through four Hg^{2+} metal ions resulting in a self-assembled, tetranuclear cyclic helicate (Figure 3.14). Bond angle and bond distance data is currently in refinement.

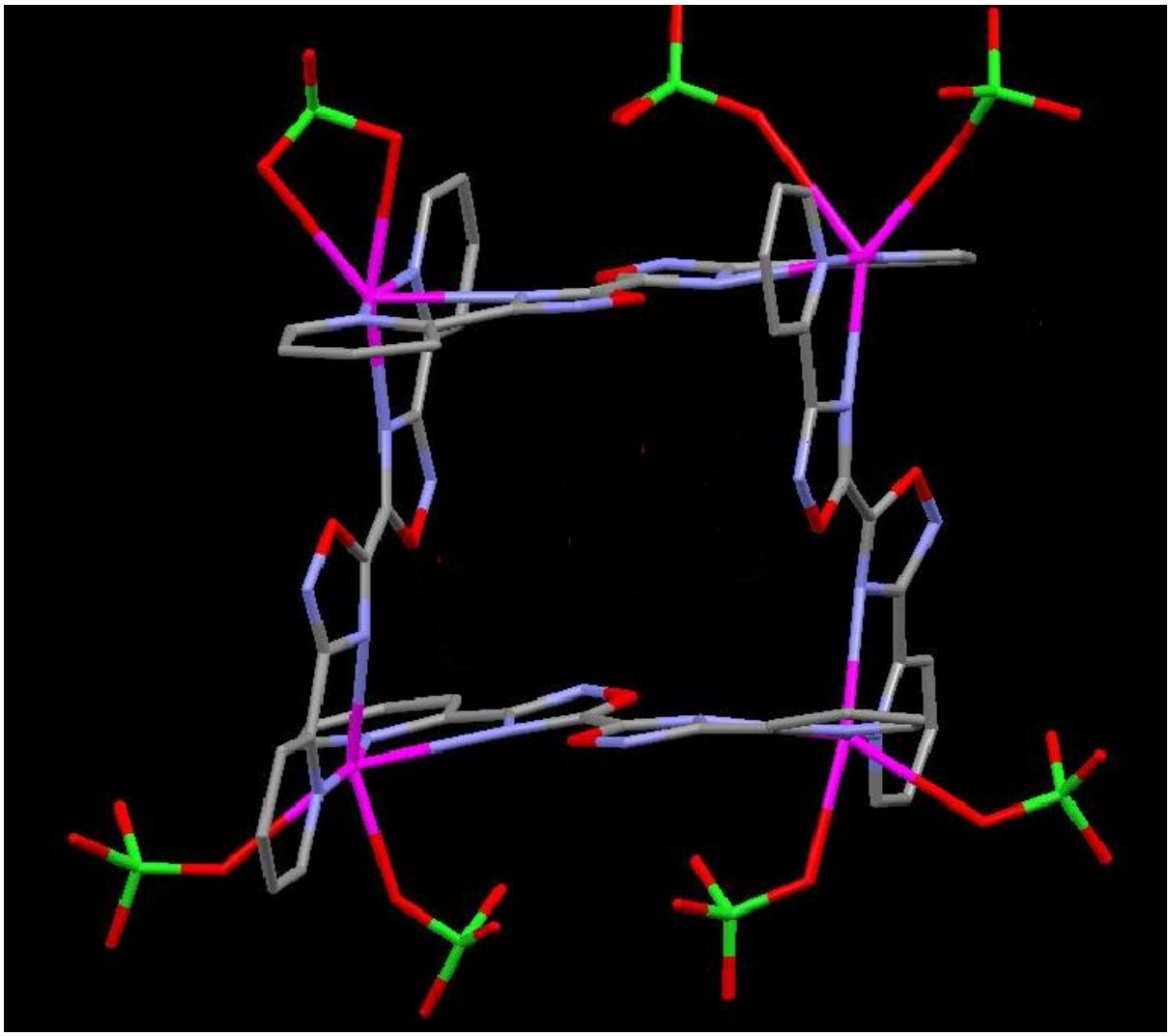


Figure 3.14 – Crystal structure of tetranuclear complex featuring ligand **(64)** and Hg^{2+}.

Further exploration of this ligand with alternative metal ions led to another completely unexpected and rather remarkable result. The reaction of ligand **(64)** with $Pb(ClO_4)_2 \cdot 6H_20$ in MeCN produced a pale yellow solution. Following slow diffusion of diisopropyl ether, pale yellow, perfectly cubic crystals were observed. Examination of these materials by single crystal X-ray diffraction revealed a two-dimensional helicate polymer. This 2D-polymer exists as chains of ligand **(64)** and Pb^{2+} ions, which are linked by a further molecule of **(64)**. Close examination of the structure shows a Pb^{2+} ion coordinated to the pyridine-oxadiazole bidentate domain of a total of three ligands. The Pb^{2+} ion however, does not sit in octahedral geometry as above, but in an 8-coordinate state due to the coordination of two perchlorate counter anions. Each Pb^{2+} ion coordinates a bidentate pyridine-oxadiazole domain of two ligands; the remaining bidentate units are coordinated by other Pb^{2+} ions forming a helicating chain. In this helicating chain, coordination of the oxadiazole unit is achieved solely through the imine N4 atoms. The helicating chain is linked to another helicating chain by a third ligand, the bidentate pyridine-oxadiazole domains each coordinating a Pb^{2+} ion of separate chains. This chain-linking coordination is achieved through the very rarely observed oxime N2 atom of the oxadiazole. Overall, this results in a very beautiful, two-dimensional helicate polymer, structural images of which are shown in Figures 3.15 and 3.16, with crystal structures shown in Figures 3.17 and 3.18. Bond distance and angle data is shown in Tables 3.3 and 3.4.

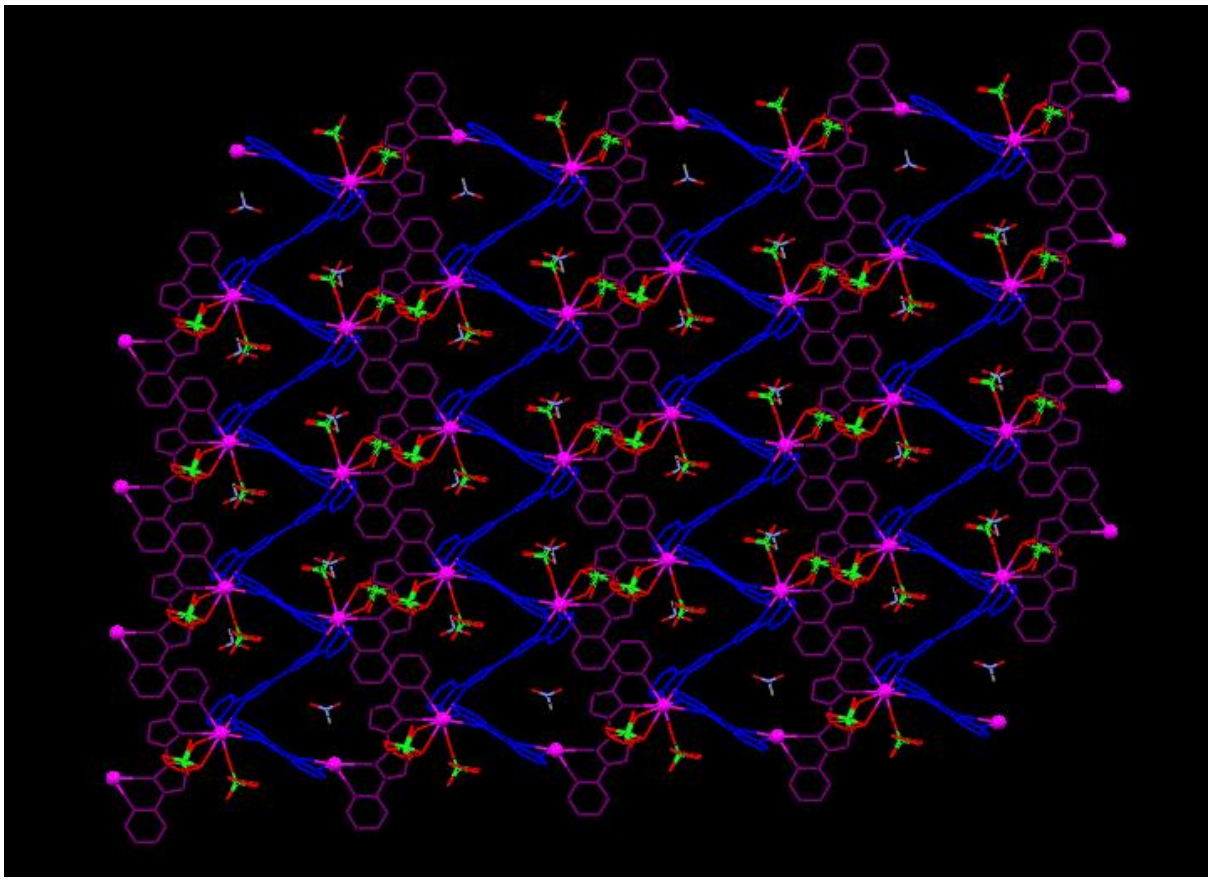


Figure 3.15 – Image of helicate polymer complex featuring **(64)** and Pb^{2+}.

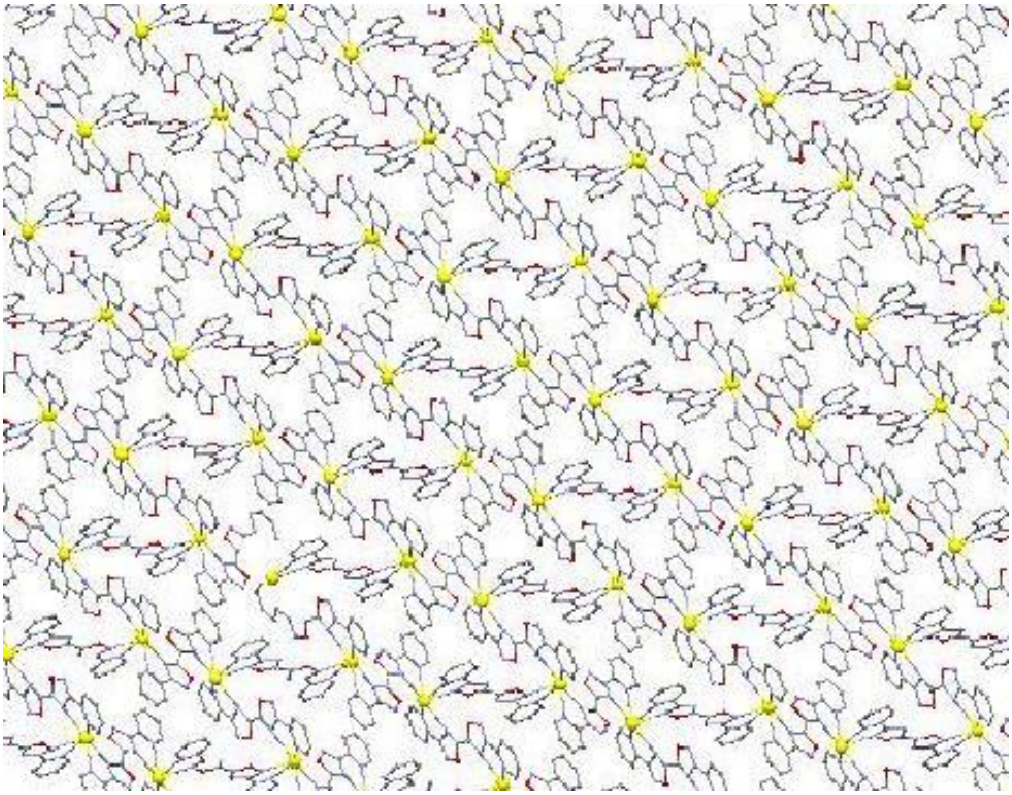


Figure 3.16 – Alternative image of helicate polymer complex featuring **(64)** and Pb^{2+}.

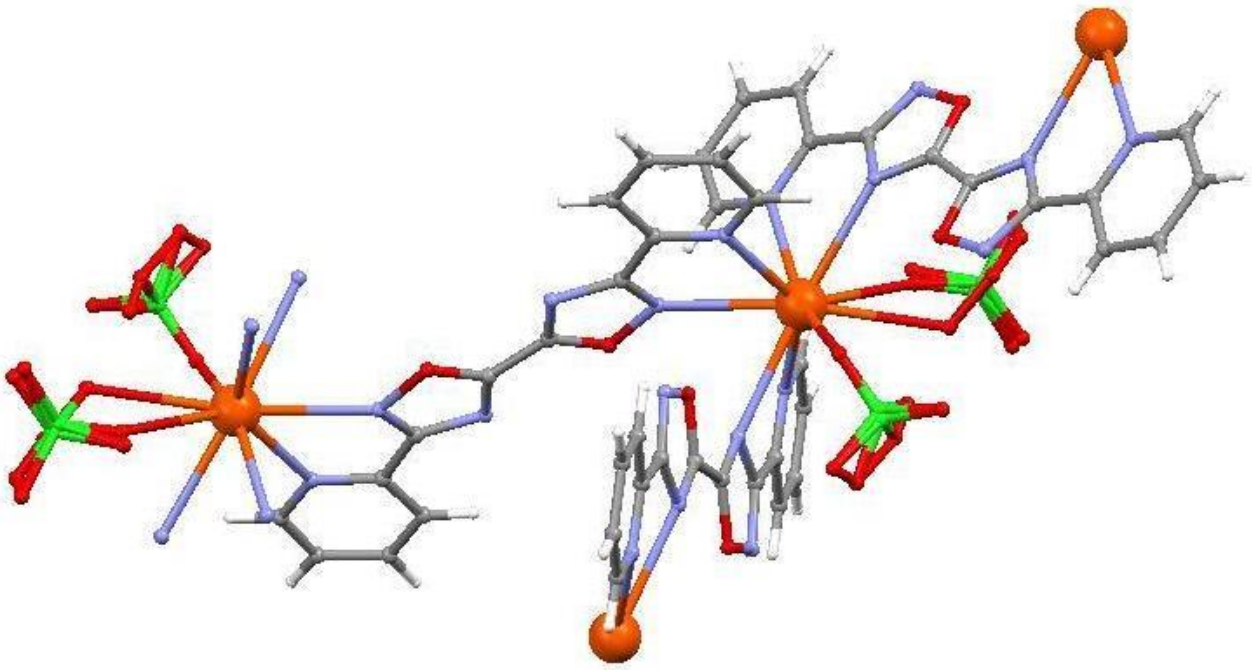


Figure 3.17 - Crystal structure of approximate unit cell of helicate polymer complex featuring **(64)** and Pb^{2+}, with bridging ligand on left.

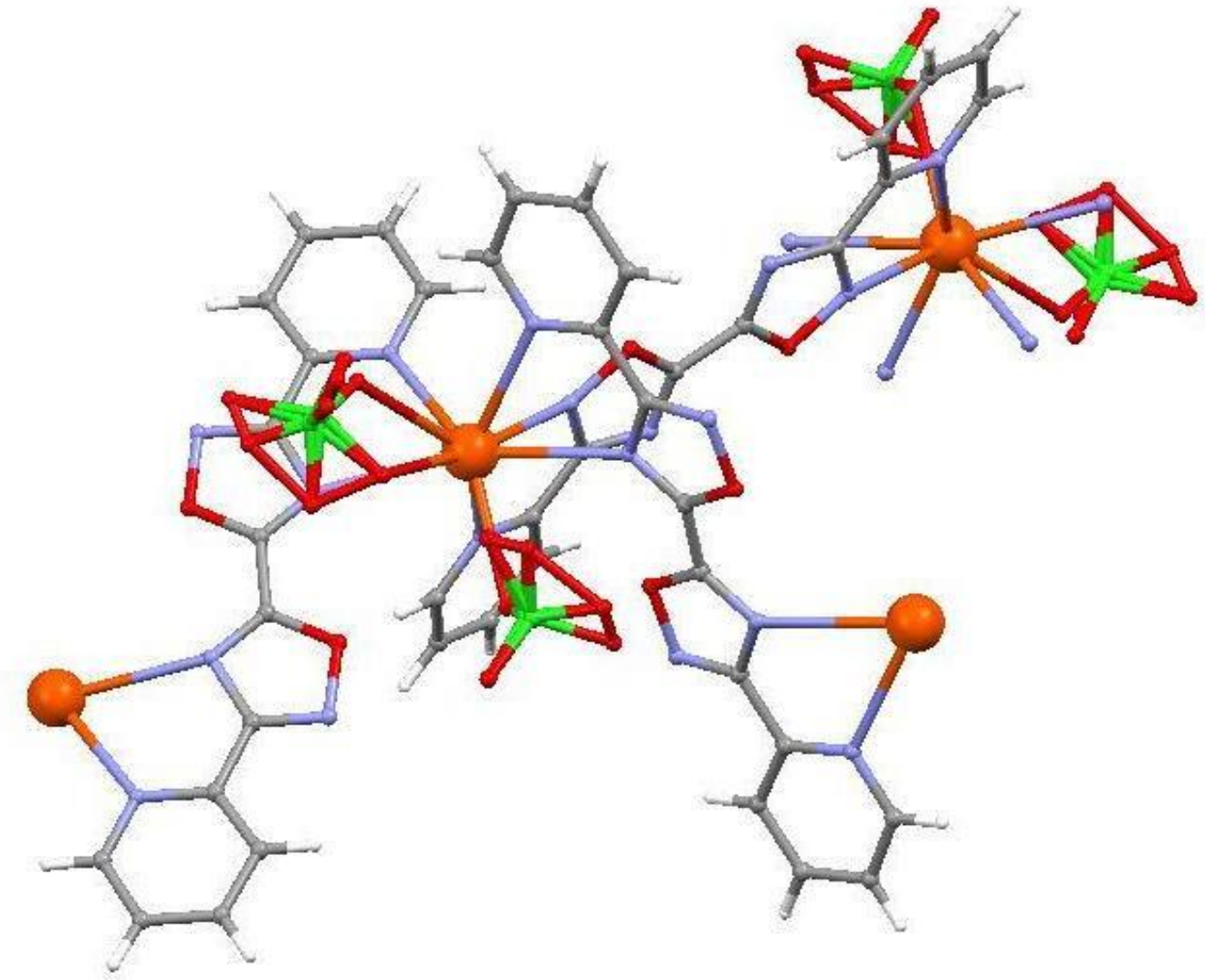


Figure 3.18 - Crystal structure of approximate unit cell of helicate polymer complex featuring **(64)** and $Pb^{2+,}$ (alternative view) with bridging ligand in background.

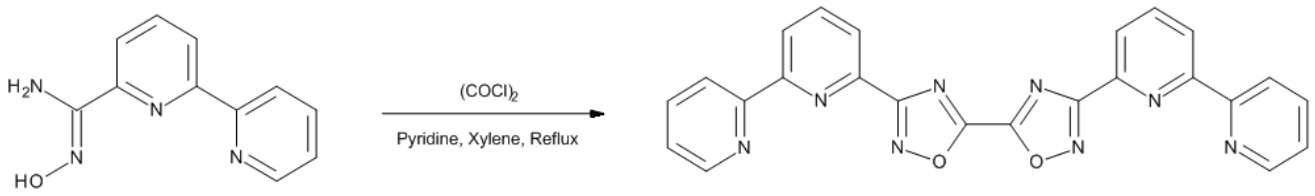
Bond	Bond Distance (Å)
Pb(1) – N(7)	2.618(2)
Pb(1) – N(4)	2.697(2)
Pb(1) – N(5)	2.7358(18)
Pb(1) – N(1)	2.737(2)
Pb(1) – N(2)	2.800(2)
Pb(1) – N(8)	2.800(2)

Table 3.3 – Bond distance data for helicate polymer complex featuring **(64)** and Pb^{2+}.

Bond	Bond Angle (^{0})
N(7) – Pb(1) – N(4)	85.01(6)
N(7) – Pb(1) – N(5)	74.36(6)
N(4) – Pb(1) – N(5)	60.72(6)
N(7) – Pb(1) – N(1)	86.13(7)
N(4) – Pb(1) – N(1)	140.72(6)
N(5) – Pb(1) – N(1)	80.04(6)
N(7) – Pb(1) – N(2)	130.67(6)
N(4) – Pb(1) – N(2)	97.76(6)
N(5) – Pb(1) – N(2)	64.99(6)
N(1) – Pb(1) – N(2)	61.04(6)
N(7) – Pb(1) – N(8)	62.86(6)
N(4) – Pb(1) – N(8)	75.66(6)
N(5) – Pb(1) – N(8)	120.51(6)
N(1) – Pb(1) – N(8)	131.89(6)
N(2) – Pb(1) – N(8)	165.09(6)

Table 3.4 – Bond angle for helicate polymer complex featuring **(64)** and Pb^{2+}.

3.1.2.8 Synthesis of 3-[6-(2-pyridyl)-2-pyridyl]-5-[3-[6-(2-pyridyl)-2-pyridyl]-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(50) **(65)**

Scheme 3.19

In light of the excellent results obtained with the previous ligand, it was decided to extend the ligand by one pyridine unit at either end by utilising the bipyridine amidoxime **(50)**. This extended ligand length, would possibly eliminate the formation of the polymeric system observed with **(64)**. The ligand itself contains the bis-oxadiazole core as previous. Coordination solely through this central bidentate system is possible as shown by Steel and coworkers[53], however since this coordination was not observed with **(64)** this was not considered a likelihood. Instead, the main potential of the ligand in coordination terms was thought to be through the two tridentate pyridine-pyridine-oxadiazole domains.

The potentially hexadentate ligand **(65)** was synthesised via the usual amidoxime-acid chloride method. The 2,2'-bipyridyl-amidoxime was reacted with oxalyl chloride in refluxing xylene with pyridine as the scavenger for the HCl. The yield for this product was very low at just 8%.

Protons *a, d, e,* and *g* were expected to resonate as doublets, however only three of these doublets are observed. Three triplets are observed as one would expect however, a triplet observed at δ8.60 is peculiar since it integrates as four protons. Therefore it was assumed that the missing doublet resides beneath this signal. However, there is no sign of any overlap whatsoever as the triplet is very clean. The ^{13}C NMR showed twelve environmentally unique carbon atoms offering support for the assigned structure. HRMS delivered an accurate mass of 447.1320 for the $[M+H]^+$ ion, consistent with the calculated figure of 447.1312, which all but confirmed the structure and permitted attempts at crystallisation.

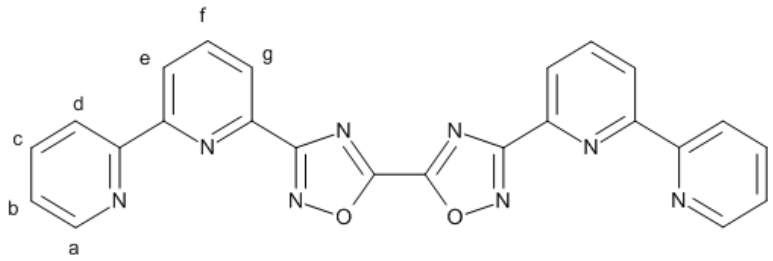


Figure 3.19

When reacted with $Cu(ClO_4)\cdot 6H_2O$ in acetonitrile via slow diffusion of ethyl acetate, this ligand produced an elaborate tetranuclear cyclic helicate in much the same style as the previous ligand **(64)**. The differences between the two metallosupramolecular structures are subtle. The differences are caused by the extra coordination potential from the terminal pyridine units around the Cu^{2+} ion (see Figure 3.20). The ligand is, as before, partitioned into two polydentate domains; the tridentate nature of these domains enables the ligand to wrap further around the metal ion, thus producing a larger assembly. The metal ions remain in octahedral geometry, with the oxadiazole N4 atom and terminal pyridine N-donor atom coordinating in opposite equatorial positions, the internal pyridine N-donor atom coordinates in the axial position with no coordination to solvent molecules. Interestingly, the same self-assembling structure was also obtained in reaction with Ni^{2+} ions, presumably since copper and nickel atoms are of similar size. Bond angle and bond distance data for these helicates are currently in refinement.

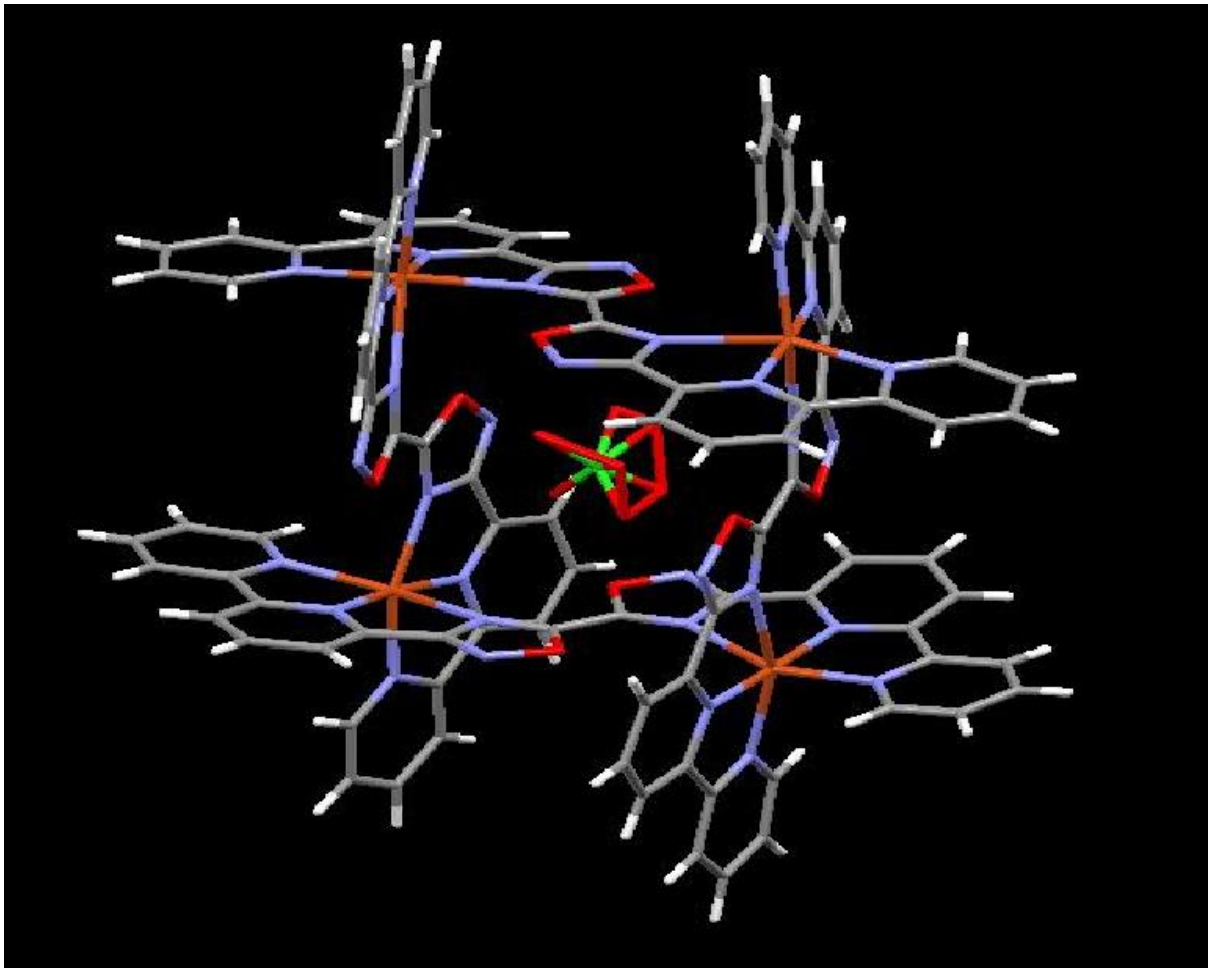
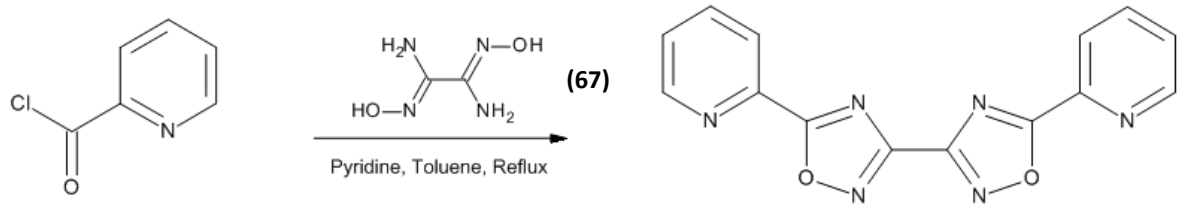


Figure 3.20 – Crystal structure of tetranuclear helicate complex featuring **(65)** and Cu^{2+}.

3.1.2.9 Synthesis of 5-(2-pyridyl)-3-[5-(2-pyridyl)-1,2,4-oxadiazol-3-yl]-1,2,4-oxadiazole



(66) **(68)**

Scheme 3.20

In a marginal change from the usual reaction of a 2-pyridyl amidoxime with an acid chloride, this synthesis involves the simplest diamidoxime (diaminoglyoxime) **(67)** in reaction with picolinoyl chloride **(66)** in the usual basic, refluxing xylene conditions. This furnished the ligand **(68)** in 8% yield.

This simple change reverses the N-O bond of the oxadiazole. The oxadiazole core is now bound at the 3-position rather than the 5-position. It was anticipated that this change might have an interesting impact on the synthesis of the cyclic helicates observed with ligand **(64)** since coordination in all cases is through the oxadiazole N4. However, the reversal of the N-O bond may alter the formation of the previously observed Pb^{2+} polymer since the coordinating N4 atom is now in a different position.

The structure of this ligand is supported by the ^{1}H NMR spectrum. Comparison with the ^{1}H NMR spectrum produced by **(64)** shows a strong correlation. The doublet of doublet of doublets observed at δ7.62 and the apparent triplet of doublets at δ8.01 correspond to protons *b* and *c* respectively. The split doublets at δ8.48 and δ8.92 likely represent protons *a* and *d*. A minor impurity is present at δ7.15-7.30. ^{13}C NMR spectroscopy was unavailable due to poor sample solubility.

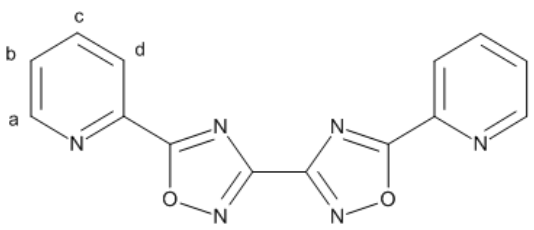


Figure 3.21

The presence of the desired product was confirmed by HRMS which delivered an accurate mass of the $[M+Na]^+$ ion of 315.0605 for the calculated figure of 315.0601.

Reaction of this ligand with $Pb(ClO_4)_2 \cdot 6H_2O$ in MeCN gave a colourless solution which, upon slow diffusion of diisopropyl ether, produced colourless crystalline materials. Examination of these crystals by X-ray diffraction afforded the crystal structure shown in Figure 3.23. This metallosupramolecular system is similar to the helicate polymer formed from reaction of **(64)** with Pb^{2+}. The system produced by **(68)** is similar to the helicating chain observed with the two-dimensional helicate polymer from **(64)**, but lacks the third bridging ligand between chains. As such, this new system exists as a one-dimensional helicate polymer. Coordination through the oxadiazole is in all cases through the N4 nitrogen.

Each Pb^{2+} ion exists in seven-coordinate geometry. Each Pb^{2+} ion coordinates to the bidentate pyridine-oxadiazole domain of two separate ligands, two water molecules and one perchlorate molecule. Below is a picture of a segment of this helicating polymer chain.

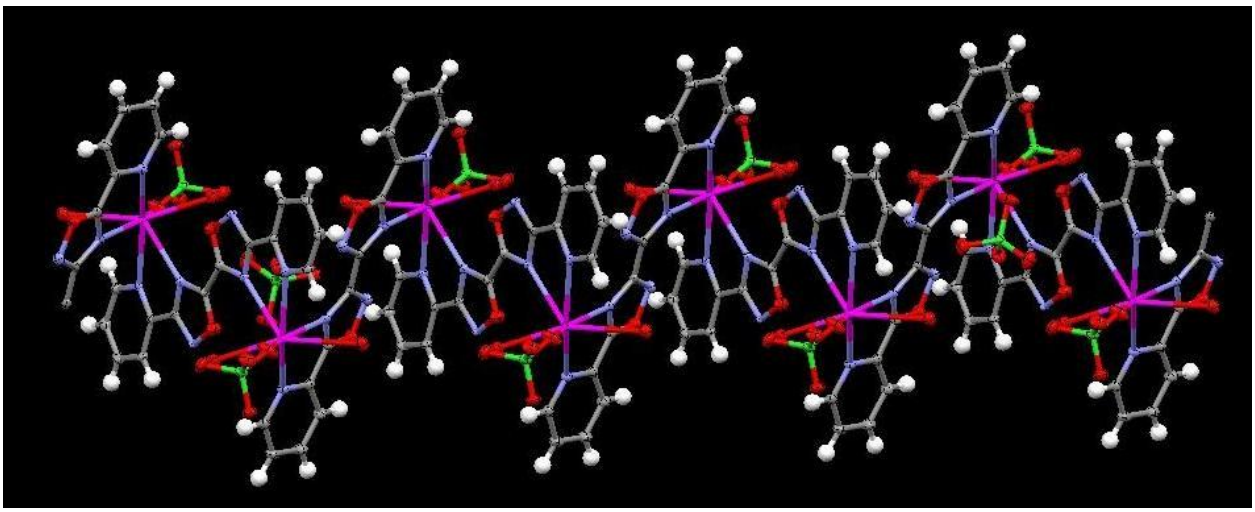


Figure 3.22 – Image of 1D helicating polymer featuring **(68) and** Pb^{2+}.

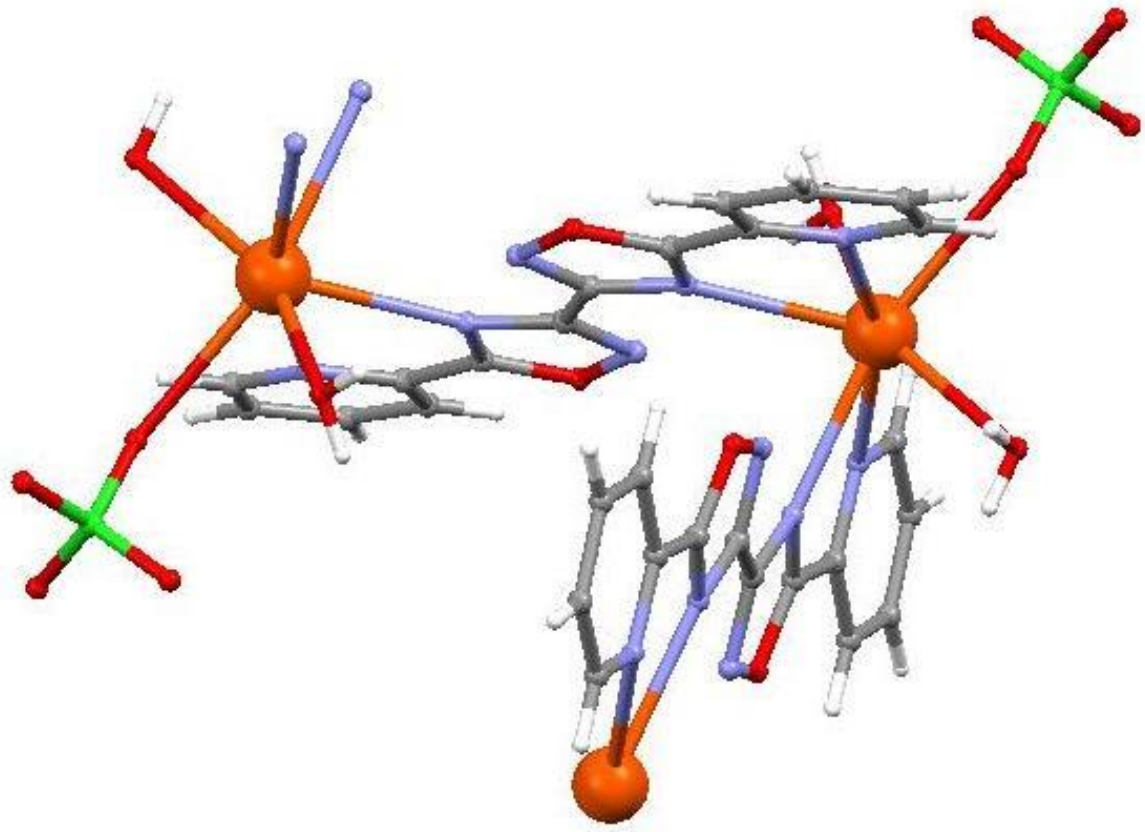


Figure 3.23 - Crystal structure of approximate unit cell of 1D helicate polymer complex featuring **(68)** and Pb^{2+}.

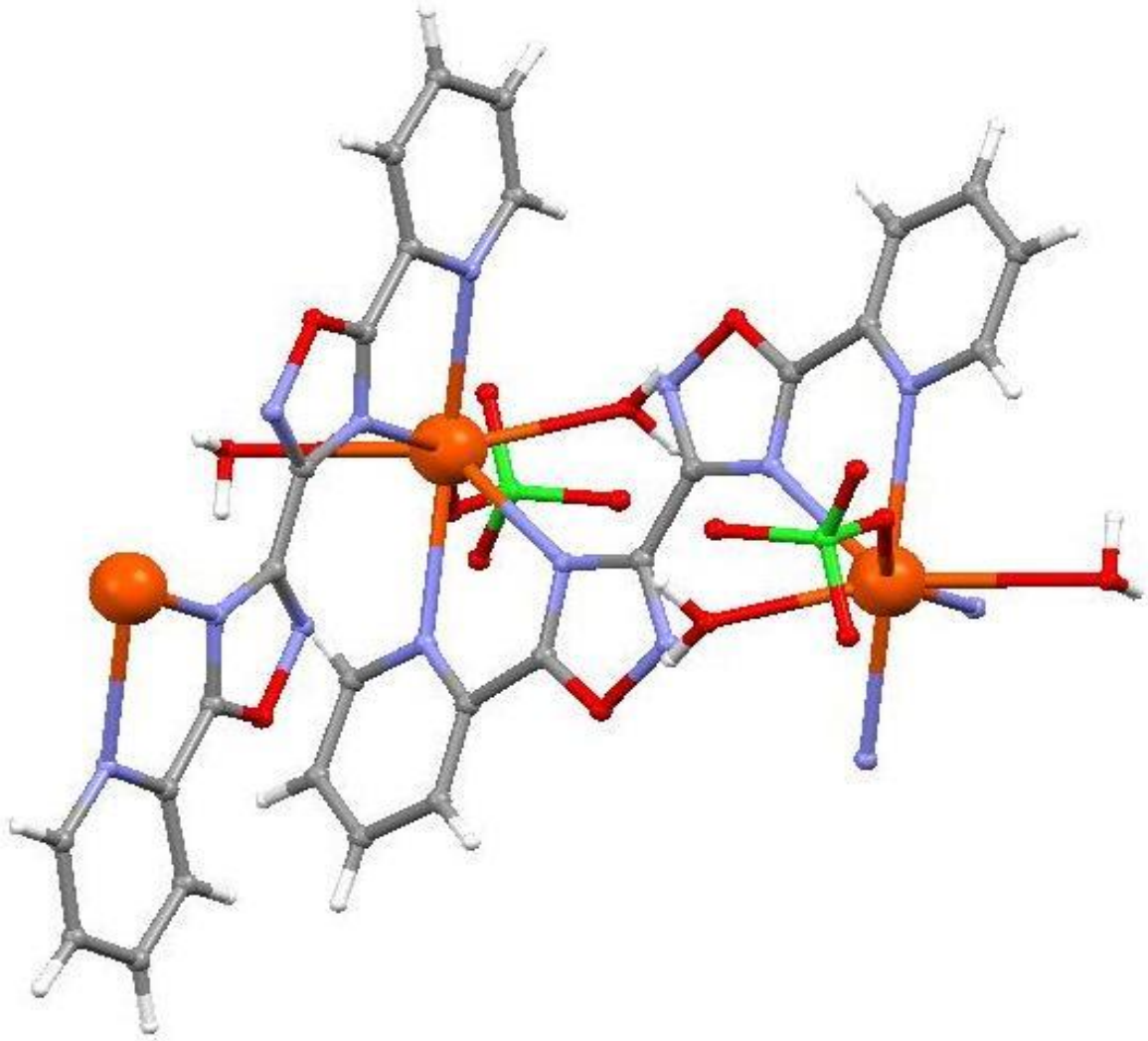


Figure 3.24 - Crystal structure of approximate unit cell of 1D helicate polymer complex featuring **(68)** and Pb^{2+} (alternative view).

Bond	Bond Distance (Å)
Pb(1) – O(3)	2.4632(19)
Pb(1) – N(5)	2.689(2)
Pb(1) – N(4)	2.690(2)
Pb(1) – N(1)	2.717(2)
Pb(1) – N(2)	2.728(2)

Table 3.5 – Bond distance data for 1D helicate polymer complex featuring **(68)** and Pb^{2+}.

Bond	Bond Angle (^{0})
O(3) – Pb(1) – N(5)	77.19(6)
O(3) – Pb(1) – N(4)	107.87(7)
N(5) – Pb(1) – N(4)	62.34(6)
O(3) – Pb(1) – N(1)	79.13(7)
N(5) – Pb(1) – N(1)	102.44(6)
N(4) – Pb(1) – N(1)	159.95(7)
O(3) – Pb(1) – N(2)	126.04(7)
N(5) – Pb(1) – N(2)	76.17(6)
N(4) – Pb(1) – N(2)	99.77(6)
N(1) – Pb(1) – N(2)	62.30(6)

Table 3.6 – Bond angle data for 1D heliacte polymer complex featuring **(68)** and Pb^{2+}.

3.1.2.10 On the Formation of Cyclic Helicates from Ligands Featuring a Bis-oxadiazole Core

The interesting array of structures obtained with ligands **(64)**, **(65)** and **(68)** reflect the enormous impact that minor heterocyclic changes in ligand systems can have on the ultimate supramolecular assembly. The metallosupramolecular structures observed with the thiazole ligands produced by Rice and co-workers are very different from those obtained with the analogous 1,2,4-oxadiazole ligands developed in this project.

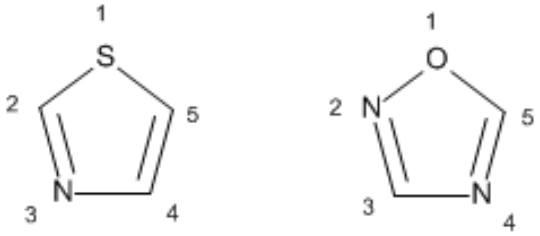


Figure 3.25 – Structural comparison of thiazole (*left*) and 1,2,4-oxadiazole (*right*).

The additional nitrogen atom of the oxadiazole gives this heterocycle extra versatility; as exemplified with coordination through both the N2 and N4 nitrogens in the helicate polymer formed from ligand **(64)**. Comparison of the two heterocycles above reveals some interesting features. Coordinations at the 3-position of the thiazole and 4-position of the oxadiazole, (i.e opposite the chalcogen) are analogous. At the thiazole 2-position, the sp^2 hybridised imine carbon is comparable to the oxime N2 nitrogen of the oxadiazole. These atoms are of very similar size and thus (unless N2 coordination is observed) one would not expect these atomic changes to have dramatic effects on the resultant self-assembled structure. The same can be said of nitrogen/sp^2 carbon comparisons in the 3 position of the thiazole and 3 position of the oxadiazole. Since the 5-positions are identical, the major difference in supramolecular behaviour must be attributed to the influence of the chalcogen atoms at the 1-position.

Molecular modelling studies of these two tetradentate ligands (see 3.1.2.10.1 for details), Rice's thiazole **(75)** and our group's new oxadiazole **(64)**, reveal some subtle but very interesting and significant contrasts. These contrasts serve to strongly impact upon the bite angles of the thiazole/2-pyridyl nitrogens in **(75)** and the oxadiazole-N4/2-pyridyl nitrogens in **(64)**.

Extrapolation along the thiazole-thiazole bond and thiazole-pyridine bond in **(75)** (see Figure 3.26) reveals a bond angle of 134.6^0. Very interestingly, extrapolation of similar bonds in the oxadiazole ligand **(64)** reveals a bond angle of 149.6^0- substantially larger than that of the thiazole. This larger angle translates as a wider bite angle between N-donor atoms.

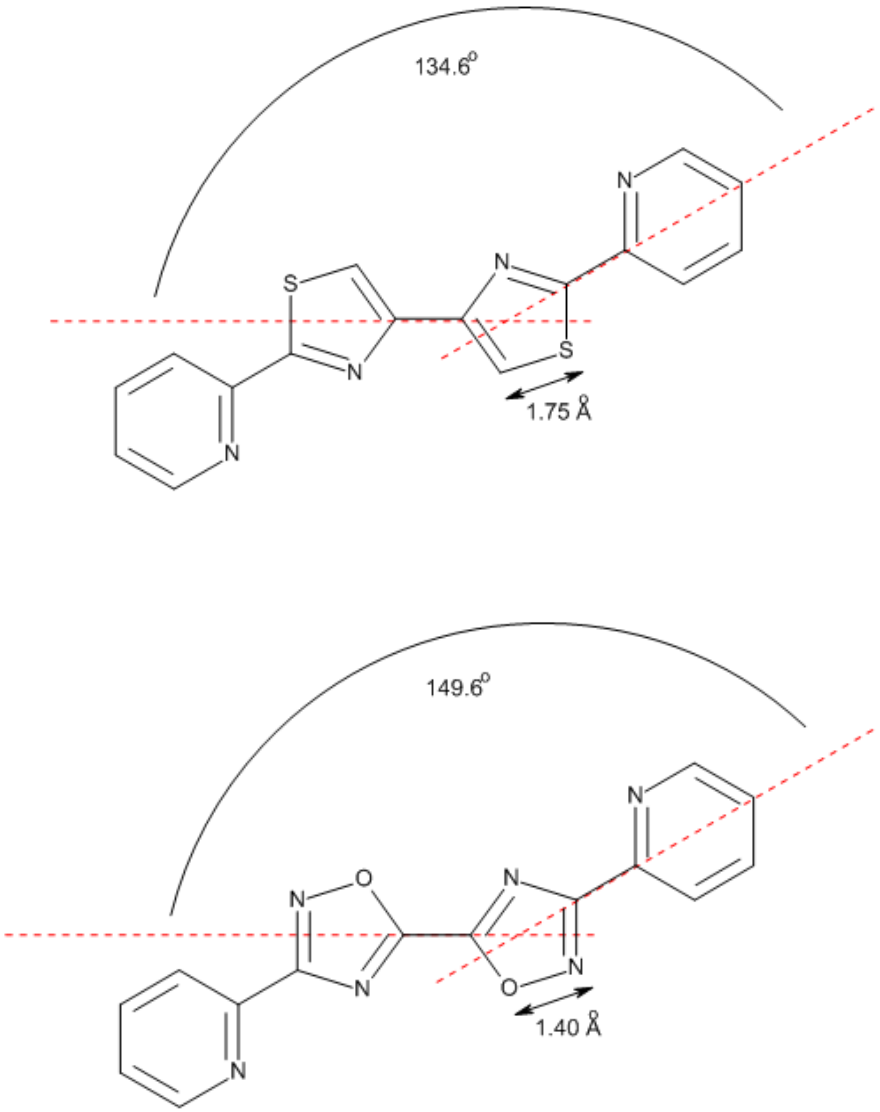


Figure 3.26 – Bond angle and bond length diagram, contrasting thiazole and oxadiazole ligands.

In the thiazole ligand **(75)**, the carbon-sulfur bond length is on average 1.75Å. In the oxadiazole containing ligand **(64)**, the nitrogen-oxygen bond length is on average 1.40Å, considerably shorter than that observed with the thiazole ligand. This is attributed to the larger covalent radius of the sulfur atom. The shorter N-O bond at the 'back' of the of the oxadiazole serves to effectively pull the

pyridine ring round towards this N-O bond thus increasing the linearity of the molecule and creating a more divergent bite angle of 149.6^0. By contrast, the larger sulfur atom and consequentially longer C-S bond length forces the thiazole-pyridine bidentate domain to act as a tighter, more convergent system. This explains the nuclearity and the overall nature of the self-assembled, supramolecular structures formed with the thiazole and oxadiazole ligands. The more divergent nature of the bidentate domains of the oxadiazole ligand enables the overall ligand strand to adopt a greater 'reach'. The lesser reach of the thiazole restricts it from forming longer and larger helicate structures. The more convergent nature of the thiazole ligand only enables shorter, sharper, dinuclear double and triple helicate systems[65,67], compared with the more elaborate, larger, tetranuclear systems observed with the 1,2,4-oxadiazole ligands.

3.1.2.10.1 Molecular Modelling Data for Ligands (64) and (75)

The relaxed structures of **(75)** and **(64)** in the gas phase were determined using the computational package GAMESS-UK[125-127] using the hybrid B3LYP methodology with 20% contribution from Hartree-Fock and 80% from Density Functional theory, employing the 6-31G* basis set[128-129]. The convergence threshold in the optimization run was 0.001 eV (~1 kJ mol^{-1}).

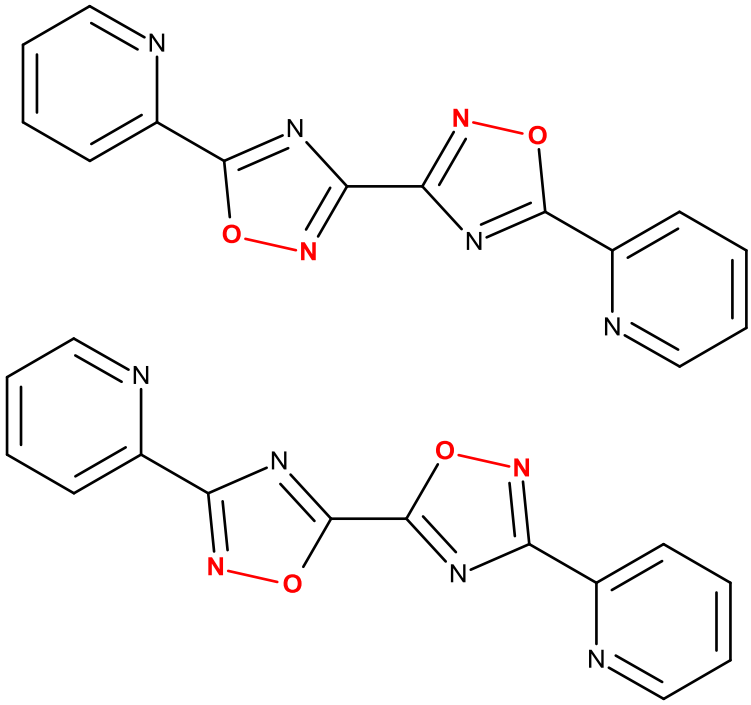
The angle between bonds described by the vectors r_1 and r_2 was calculated for each molecule using the formula:

$$\text{Cos } \vartheta = r_1 \bullet r_2 \,/\, |r_1||r_2|$$

where $r_1 \bullet r_2$ is the dot product of the two vectors and $|r_1|\ |r_2|$ are the magnitudes of the two vectors (essentially the bond length in this context).

3.1.2.11 On the Formation of Helicate Polymers from Ligands Featuring a Bis-oxadiazole Core

The bis-oxadiazole centred ligands **(64)** and **(68)** (Figure 3.27) each formed very interesting helicate polymers in reaction with Pb^{2+} ions. The critical structural difference in these ligands is the positions of oxygen and N2 nitrogen atoms. With **(64)**, the bis-oxadiazole core is linked at the 5-positions of each oxadiazole whereas with **(68)** the oxadiazoles are linked at the 3-position. This effectively swaps the positions of the oxygen and N2 nitrogen in the ligands strands.



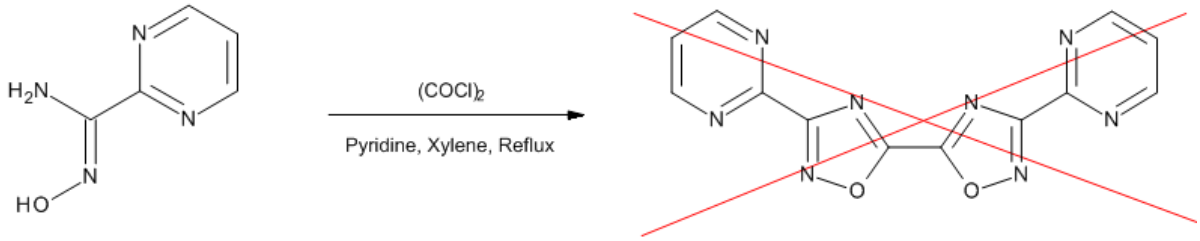
(68)

(64)

Figure 3.27 – Structural comparison of bis-oxadiazole centred ligands.

With the 2-dimensional helicate polymer observed with ligand **(64)**, very interestingly, the pyridine-oxadiazole binding domains of the ligands linking the helicating chains are coordinated to the Pb^{2+} ion through the N2 nitrogens. This is particularly interesting since, as discussed previously, the oxime nitrogen (N2) is less nucleophilic than the N4 nitrogen, therefore coordination through this atom is far less observed than with the N4 nitrogen. This peculiar, alternative, oxime nitrogen coordination showcases the versatility of the 1,2,4-oxadiazole unit in ligand systems. As far as our group are aware, this is only the second occasion (see section 1.2.5.2) where N2 coordination has been observed in 1,2,4-oxadiazole ligand systems. However, examination of the helicate polymer observed when ligand **(68)** is reacted with Pb^{2+} ions shows the helicating chain very similar to that obtained with **(64)**, but without any 'bridging' ligand. Due to the absence of these bridging ligands, it can be determined that the shift of N2 nitrogen from 'outside' the oxadiazole (i.e near the 2-pyridyl unit) to 'inside' the oxadiazole (i.e. closer to the bis-oxadiazole centre), denies a third ligand the opportunity to coordinate favourably with the Pb^{2+} ions of two separate chains. The 'outer' position of the N2 nitrogen it appears is critical for this rare, highly interesting N2 coordination and the subsequent development of the two-dimensional helicate polymer.

3.1.2.12 Synthesis of 3-pyrimidin-2-yl-5-(3-pyrimidin-2-yl-1,2,4-oxadiazol-5-yl)-1,2,4-oxadiazole



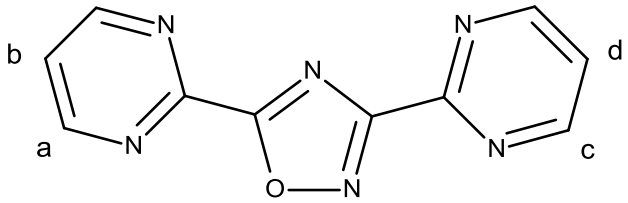
(53) **(69)**

Scheme 3.21

In a bid to extend the ligand series an attempt was made at incorporating 2,6-pyrimidine units into the system, instead of regular 2-pyridyls units. It was hoped that this would offer some possible alternative assemblies due to the extra coordination options made possible by the inclusion of pyrimidine functionality.

Unfortunately, the desired compound **(69)** was not synthesised through the amidoxime route. No evidence of product **(69)** was observed upon analysis. However, a new product was observed. The ^{1}H NMR spectrum shows two triplets at δ7.78 and δ7.85, both integrating as one proton and two doublets higher up at δ9.10 and δ9.16, both integrating as two protons. This is consistent with two different pyrimidine rings rather than the two identical pyrimidine rings that would be seen in **(69)**. The product was eventually identified as the dipyrimidine oxadiazole **(70)** (see Figure 3.28).

Unfortunately due to poor solubility in NMR solvents, we were not able to examine the compound by ^{13}C NMR spectroscopy or by HRMS. The decision was made to proceed on the mediocre strength of the ^{1}H NMR spectrum and set up the ligand with metal ions for possible crystallisation. Fortunately, some crystalline products were observed.



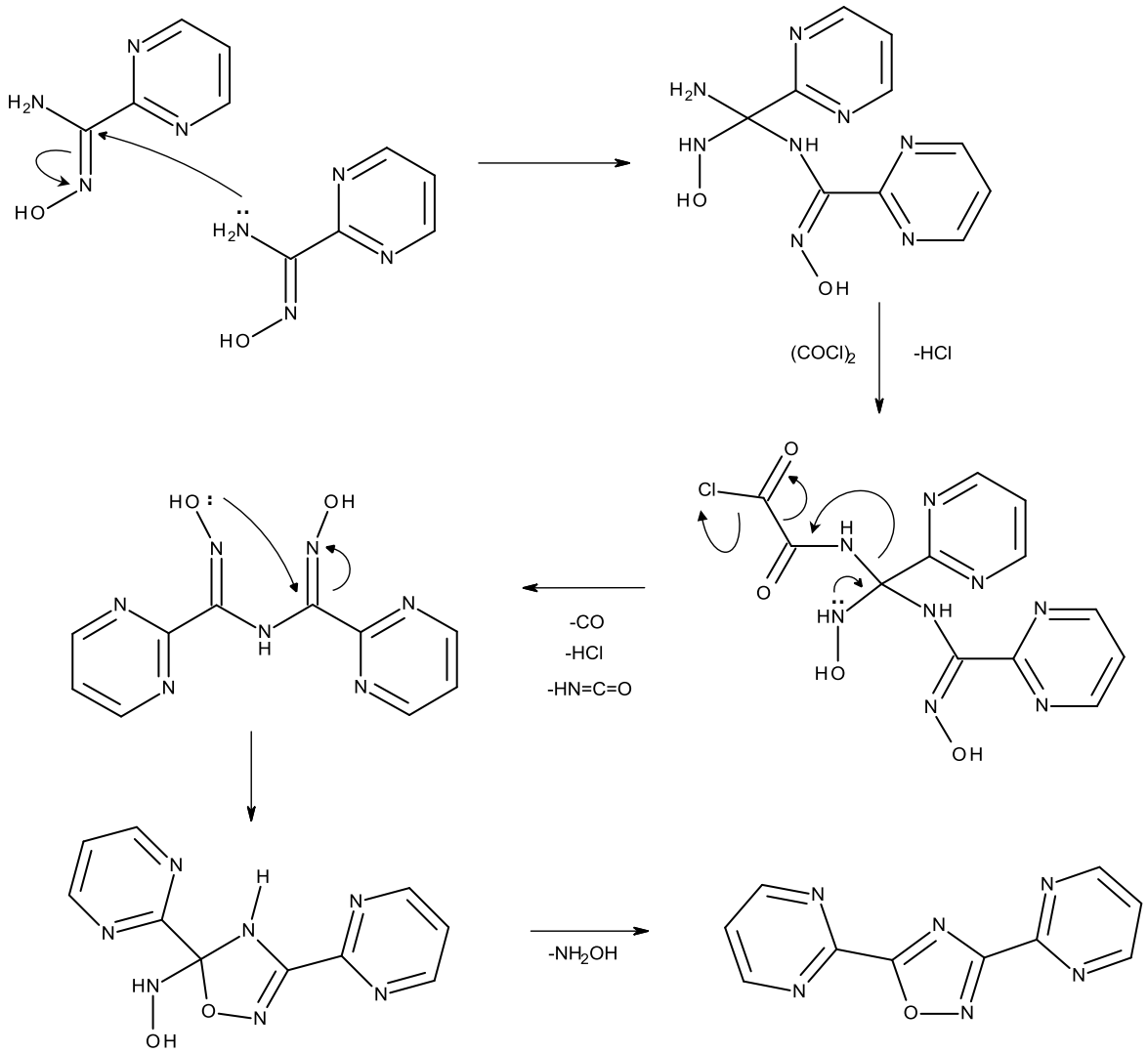
(70)

Figure 3.28

Reaction of this ligand with an equimolar amount of $Cd(ClO_4)_2 \cdot 6H_2O$ in MeCN gave a colourless solution. Following slow diffusion of diethyl ether a colourless crystalline material was observed. Subsequent examination of these materials by single crystal X-ray diffraction revealed a mononuclear double helicate complex formed from ligand **(70)**. The ligands coordinate to the Cd^{2+} ion via the bidentate pyrimidine-oxadiazole domain. The oxadiazole N4 nitrogen and a pyrimidinyl nitrogen at the oxadiazole 3-position coordinate to the Cd^{2+} centre. The metal ion retains octahedral geometry through coordination with two molecules of MeCN in equatorial positions, with the bidentate ligands opposed in an approximate 90^0 dihedral angle (Figures 3.29 and 3.30).

The successful complexation behaviour of this ligand draws interesting parallels with Pace's ligand, re-synthesised in this project as **(58)** (see Scheme 3.18). Using this ligand, no crystalline materials were observed with Cd^{2+} ions. The crystal structure for **(70)** with Cd^{2+} ions appears to be in strong correlation with that obtained by Pace in 2011 with their 3-(2-pyridyl)-5-phenyl-1,2,4-oxadiazole ligand (Figure 1.20). However, most interestingly, despite ligand **(70)** being more similar in nature and denticity to Pace's 3,5-bi(2-pyridyl)-1,2,4-oxadiazole ligand (Figure 1.18), no similar structures were observed with ligand **(70)**.

Research into this result is continuing with much focus around the mechanism of the reaction that formed ligand **(70)**. It should be noted at this stage that the yield of this product was just 3%. One possible mechanism is shown below; variations are clearly possible:



(70)

Scheme 3.22

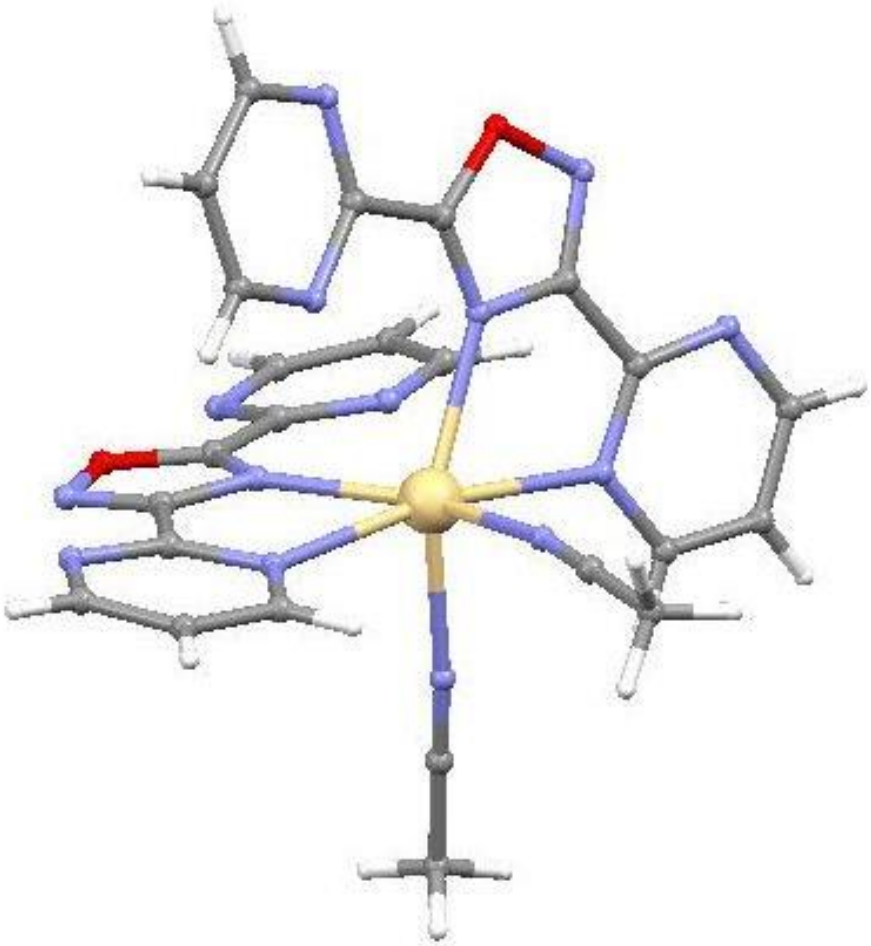


Figure 3.29 – Crystal structure mononuclear complex featuring **(70)** and Cd^{2+}.

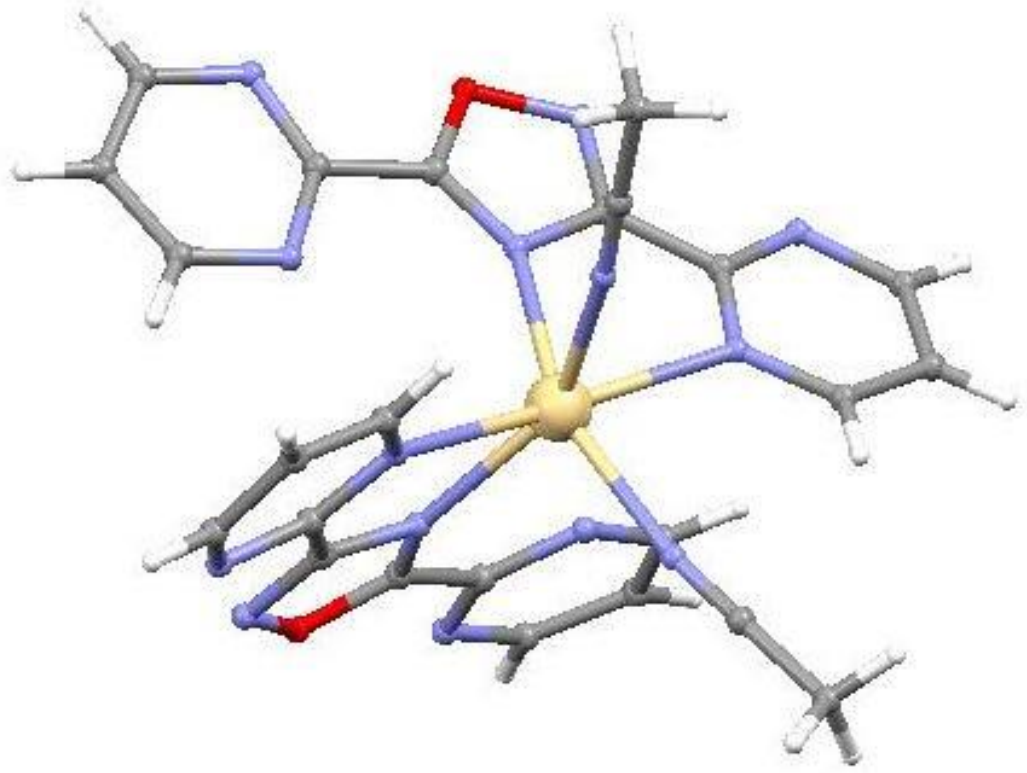


Figure 3.30 - Crystal structure mononuclear complex featuring **(70)** and Cd^{2+} (alternative view).

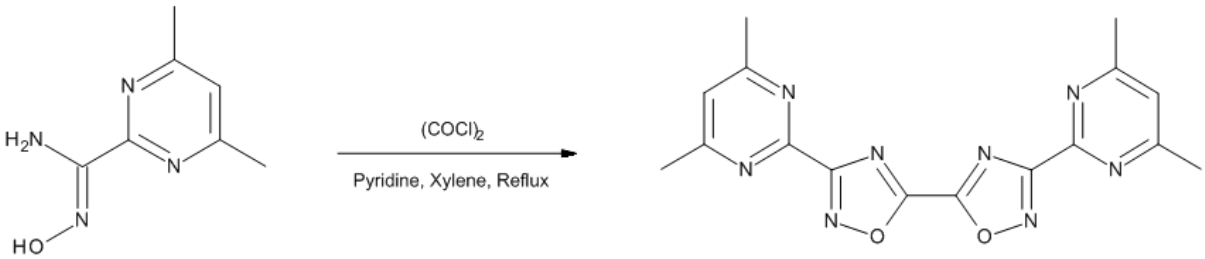
Bond	Bond Distance (Å)
Cd(1) – N(13)	2.287(3)
Cd(1) – N(4)	2.289(3)
Cd(1) – N(14)	2.290(4)
Cd(1) – N(1)	2.344(3)
Cd(1) – N(8)	2.473(3)
Cd(1) – N(2)	2.539(3)

Table 3.7 – Bond distance data for complex featuring **(70)** and Cd^{2+}.

Bond	Bond Angle (^{0})
N(13) – Cd(1) – N(4)	95.65(10)
N(13) – Cd(1) – N(14)	96.81(11)
N(4) – Cd(1) – N(14)	146.75(10)
N(13) – Cd(1) – N(1)	154.05(10)
N(4) – Cd(1) – N(1)	94.12(9)
N(14) – Cd(1) – N(1)	87.90(10)
N(13) – Cd(1) – N(8)	84.30(10)
N(4) – Cd(1) – N(8)	121.40(10)
N(14) – Cd(1) – N(8)	90.48(11)
N(1) – Cd(1) – N(8)	70.12(9)
N(13) – Cd(1) – N(2)	92.81(10)
N(4) – Cd(1) – N(2)	68.67(10)
N(14) – Cd(1) – N(2)	80.02(11)
N(1) – Cd(1) – N(2)	113.14(9)
N(8) – Cd(1) – N(2)	169.70(10)

Table 3.8 - Bond angle data for complex featuring **(70)** and Cd^{2+}.

3.1.2.13 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]-1,2,4-oxadiazole



(55) **(71)**

Scheme 3.23

In light of the curious case of the absent oxadiazole observed in the synthesis of **(70)**, the decision was made to attempt the synthesis of an analogous pyrimidine system in a bid to see if similar unexpected products were formed.

The dimethyl-pyrimidine ligand **(71)** was synthesised in the conventional manner, though again in very low yield at 3%. In this case, the expected di-(1,2,4-oxadiazole) was formed.

Ligand **(71)** itself boasts a wealth of coordination potential. The pyrimidine-oxadiazole systems offer bidentate domains on both the imine-N4 and oxime-N2 sides and a further bidentate domain across the central bis-oxadiazole N4-N4 system, therefore housing a total of five potential bidentate domains. The ligand itself includes a possible tetradentate domain across its length. The ligand is of highly condensed denticity with the four likely pyrimidine-oxadiazole bidentate units spanning just four heterocyclic units, thus rendering this ligand one of the most interesting of the series.

The structure of the product was largely confirmed through ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum is very simple as one would expect due to the high degree of symmetry. The pyrimidine-4,6-dimethyl protons *a* can be observed at δ2.67 and the unsubstituted pyrimidine 5-position protons (*b*) can be observed at δ7.24 in the ^{1}H NMR spectrum.

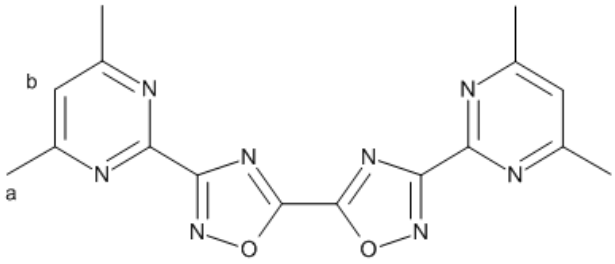


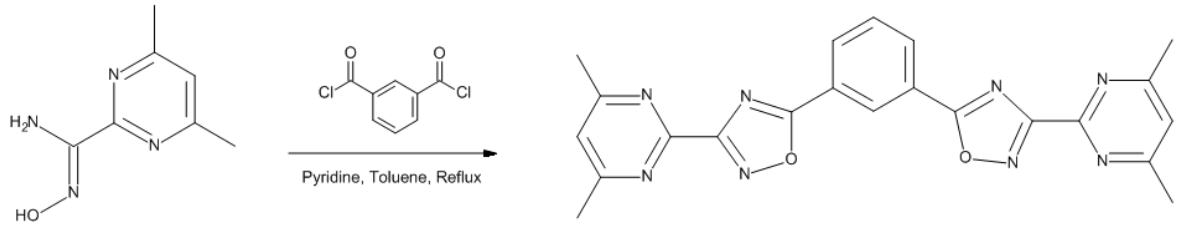
Figure 3.31

The ^{13}C NMR spectrum was extremely simple; the methyl carbons resonated predictably low in the spectrum at δ24.14. The remaining five carbon atoms are visible in the typical aromatic region.

Analysis by HRMS delivered an accurate mass of the $[M+Na]^+$ ion of 373.1133 for the calculated figure of 373.1132.

Several crystalline products featuring this ligand are awaiting analysis by XRD, and are part of the future work section of this project.

3.1.2.14 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[3-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]phenyl]-1,2,4-oxadiazole



(55) **(72)**

Scheme 3.24

The phenylene spaced pyrimidine ligand **(72)** was synthesised in 7% yield. A switch to toluene as solvent was made in order to afford a cleaner, more isolable product.

The ligand itself is split into two bis-bidentate oxadiazole-dimethylpyrimidine domains. With coordination possible on both sides of the oxadiazole through both the imine-N4 and oxime-N2 donor atoms and both sides of the pyrimidine units, this ligand carries immense potential.

The assignment of the structure of the ligand is supported by ^{1}H NMR spectroscopy. The spectrum shows the very intense singlet at δ2.69, integrating as 12 protons, corresponding to pyrimidine methyl protons *a*.

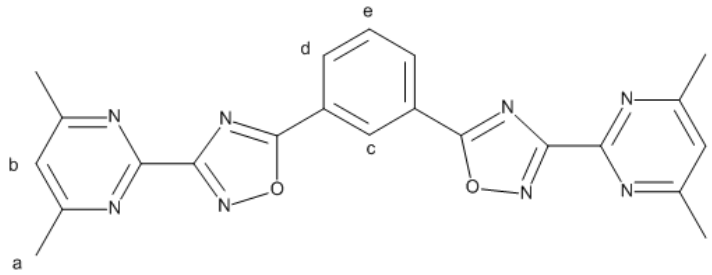


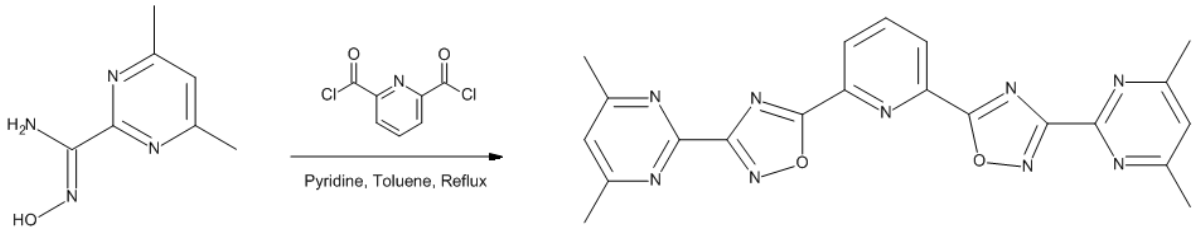
Figure 3.32

The singlet at δ7.23 corresponds to protons *b* since this signal integrates for two protons. The very slightly split singlet at δ9.27, integrating as one, is likely to correspond to proton *c*. A remaining doublet at δ8.60 and a triplet at δ7.80 account for protons *d* and *e*. The ^{13}C NMR spectrum provides further confirmation by accounting for all ten unique carbon atoms, the methyl signal significant at δ24.25 and the nine aromatic carbons between δ121.55 and δ175.75.

Analysis by HRMS delivered an accurate mass of the $[M+Na]^{+}$ ion of 449.1452 comparing well with the calculated value of 449.1445.

Several crystalline products featuring this ligand are awaiting analysis by XRD and again form part of the future work section of this project.

3.1.2.15 Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-5-[6-[3-(4,6-dimethylpyrimidin-2-yl)-1,2,4-oxadiazol-5-yl]-2-pyridyl]-1,2,4-oxadiazole



(55) **(73)**

Scheme 3.25

The pyridine spaced dimethylpyrimidine ligand **(73)** was synthesised in 4% yield, again using toluene as solvent, which gave a cleaner reaction mixture than xylene, an easier work-up and consequently a cleaner product.

As an extension of the previous ligand **(72)**, this ligand features a central pyridine unit in place of the phenylene unit. With the additional prospect of a central tridentate, oxadiazole-pyridine-oxadiazole domain, this ligand is an interesting prospect. The wealth of coordination options throughout the ligand makes it a good candidate for potentially self-assembling structures.

Analysis by ^{1}H NMR spectroscopy supported the assigned structure. The methyl protons *a*, are observed as a singlet at δ2.70. The lone proton of the pyrimidine rings, *b*, is observed as a singlet at δ7.25. The remaining protons *c* and *d* resonate as the doublet and triplet seen at δ8.22 and δ8.72, integrating as two and one protons, respectively.

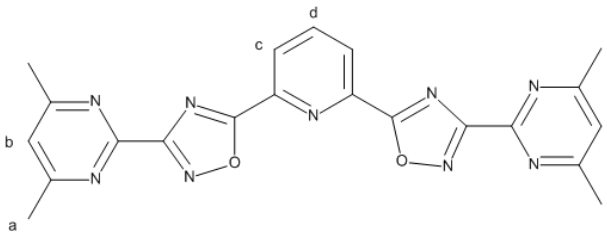
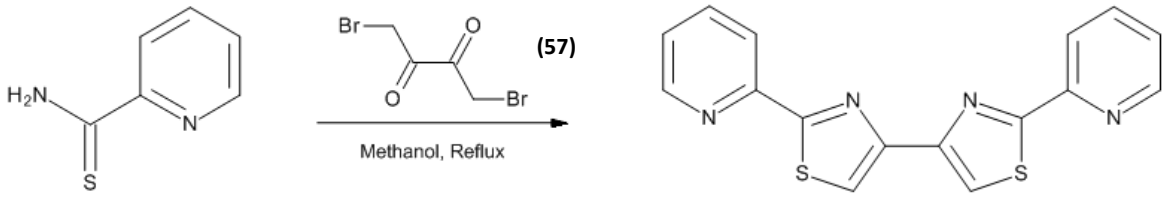


Figure 3.33

The ^{13}C spectrum lends support to this structure, with all nine signals present and correct. The accurate mass of the compound was determined by HRMS. The measured figure for the $[M+Na]^+$ ion was 450.1407 with the theoretical figure determined to be 450.1397.

Several crystalline products featuring this ligand are also awaiting future analysis by XRD.

3.1.2.16 Synthesis of 2-(2-pyridyl)-4-[2-(2-pyridyl)thiazol-4-yl]thiazole



(74) **(75)**

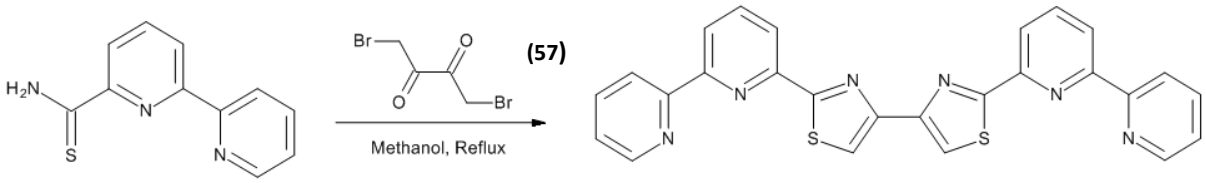
Scheme 3.26

The supramolecular chemistry of thiazole ligand **(75)** has been thoroughly explored by Rice, Ward and co-workers as explained in the introduction. The synthesis involves combination of pyridine-2-thioamide and dibromodiacetyl in refluxing methanol.

It was necessary to synthesise this ligand in a bid to draw full comparison with ligand **(64)**. This was due to the fact that this particular ligand, though thoroughly explored by Rice, had not seen any attempt at crystallisation with Pb^{2+} ions, whereas **(64)** formed interesting complexes with this metal.

This known compound gave identical spectroscopic data to that reported previously[92]. Unfortunately, no crystalline products were observed with Pb^{2+}.

3.1.2.17 Synthesis of 2-[6-(2-pyridyl)-2-pyridyl]-4-[2-[6-(2-pyridyl)-2-pyridyl]thiazol-4-yl]thiazole



(76) **(77)**

Scheme 3.27

As with ligand **(75)**, this particular thiazole ligand has been synthesised and thoroughly explored by Rice and co-workers[65-69]. Again however, the ligand had not seen attempts at crystallisation with Pb^{2+} ions whereas the oxadiazole analogue **(65)** had. Thus the ligand was synthesised via the same refluxing methanol protocol as **(75)** and gave spectroscopic data consistent with the literature.

No further self-assembled products were observed through reaction of ligand **(77)** with Pb^{2+} ions.

3.1.3 Conclusions

It has been demonstrated in this section of the thesis that the 1,2,4-oxadiazole unit, despite a distinct lack of recent research, is a highly effective coordination unit in ligand strands in metallosupramolecular chemistry,

The 1,2,4-oxadiazole unit was shown to be a very versatile unit, with coordination through both the N4 nitrogen and, for only the second time in the history of its coordination chemistry, through the N2 nitrogen.

It has also been demonstrated that the use of spacer units is unnecessary, since ligands with a bis-oxadiazole centre partition effectively into both bidentate and tridentate domains with suitable 2-pyridyl and 2,2'-bipyridyl substitution.

For the first time in metallosupramolecular chemistry, the 1,2,4-oxadiazole has been shown to be a feature of ligand systems promoting the self-assembly of one and two-dimensional helicate polymers.

Additionally, we have further underlined that very subtle differences in the electronics and heteroatomic content of 5-membered heterocycles drastically affects the nature of the metallosupramolecular structures formed.

Several new ligands have been synthesised, from which crystals have been prepared and crystal structures obtained. Further crystals have been obtained for analysis in future crystallographic programmes.

3.2 The 1,2,4-Oxadiazole in Extensions of Biologically Active Isothiazole and Thiazete Dioxides

This part of the thesis looks at 1,2,4-oxadiazoles and derivatives as potential biologically active compounds based on some systems of existing interest in our research group.

Our group have long been interested in the organic and medicinal chemistry of β-sultams, γ-sultams and larger ring systems. This chapter of the thesis discusses some of the advances our group have made towards novel thiazete- and isothiazole-1,1-dioxides (i.e. β- and γ-sultams) and cycloaddition products thereof, and the investigation into their biological properties. The inspiration for this exploration into sultam chemistry was taken from previous successes of the group. As described in the introduction, the group have successfully synthesised a 3-amino-4-aryl-isothiazole-1,1-dioxide (see Figure 3.34). The chemical reactivity of this isothiazole-1,1-dioxide and the corresponding thiazete-1,1-dioxide has been a major focal point within our research group, and the objective in this thesis is to make further examples. This isothiazole was synthesised in accordance with the pioneering synthetic work of Francesca Clerici and co-workers. A previous worker in our group explored its chemistry and the biological activity of the compound and its cycloadducts. The chemistry to be explored is summarised in Scheme 3.28.

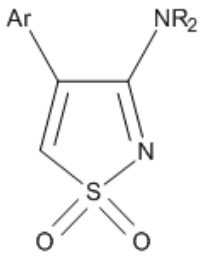
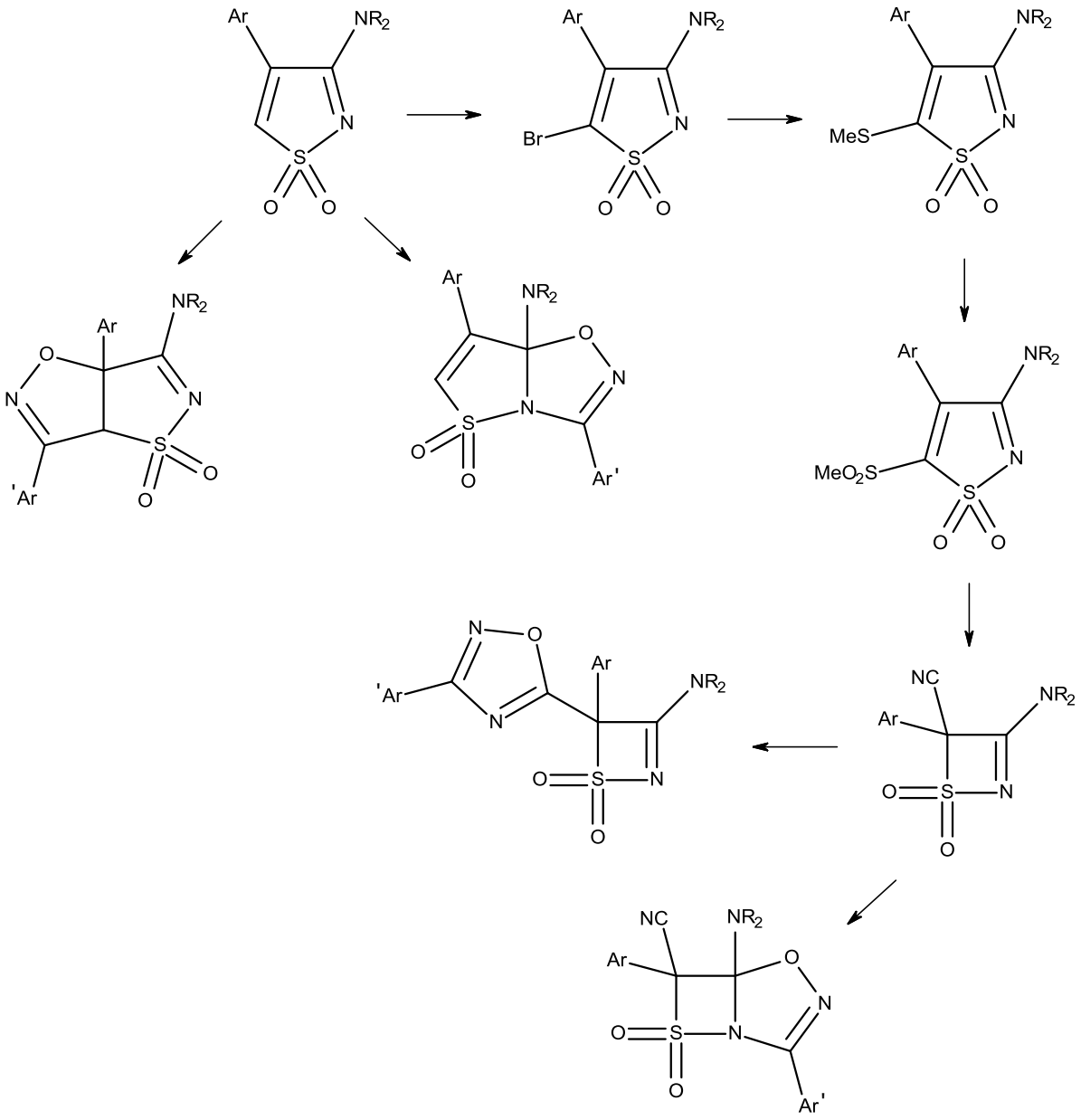


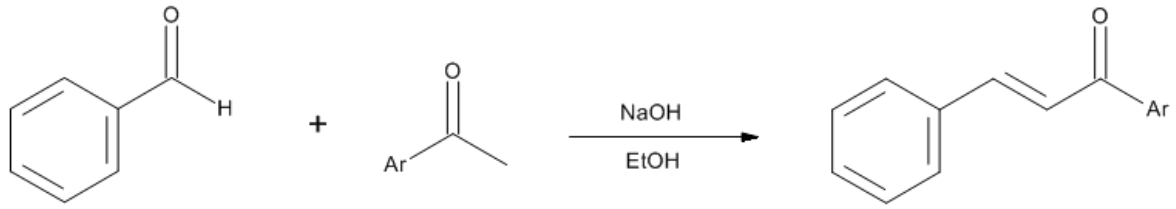
Figure 3.34 – The 3-amino-4-arylisothiazole-1,1-dioxide.

Variation in the Ar and NR_2 groups gives some scope for exploration, but it is the reactivity of this system that offers the most scope. As shown below in Scheme 3.28, this system can be converted into a β-sultam with two potential dipolarophilic sites and offers two dipolarophilic sites of its own (along with those offered by the intermediates).



Scheme 3.28

3.2.1 The Synthesis 3-Phenyl-α,β-unsaturated Arylketones



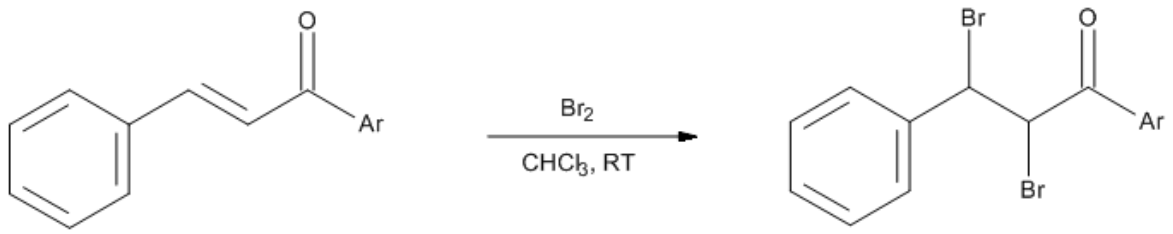
Scheme 3.29

The campaign towards the isothiazole-1,1-dioxides shown in Scheme 3.28 and the subsequent cycloaddition products begins with a simple base catalysed aldol reaction between benzaldehyde and an acetophenone to give a range of simple α,β-unsaturated ketones, as shown in Table 3.9.

Entry	Aryl Acetophenone	Product	Yield (%)
1	Ph	**(80)**	61
2	4-NO_2Ph	**(82)**	16
3	4-MeOPh	**(84)**	71
4	4-ClPh	**(86)**	91
5	4-MePh	**(88)**	52

Table 3.9

3.2.2 The Synthesis of 3-phenyl-α,β-dibrominated Arylketones



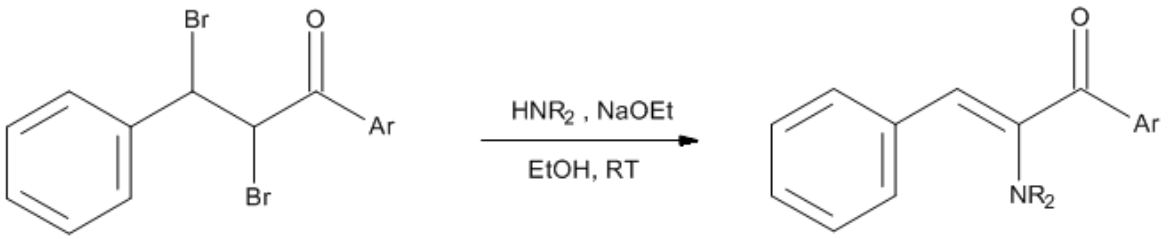
Scheme 3.30

The second step of the synthesis was a simple alkene dibromination. This was achieved by reacting the 1-aryl-3-phenyl-α,β-unsaturated ketones with bromine in chloroform at room temperature. All the reactions proceeded smoothly and gave useable quantities of the desired products, shown in Table 3.10.

Entry	Acyl Arene	Product	Yield (%)
1	Ph	**(89)**	34
2	4-NO_2Ph	**(90)**	67
3	4-MeOPh	**(91)**	30
4	4-ClPh	**(92)**	21
5	4-MePh	**(93)**	47

Table 3.10

3.2.3 The Synthesis of α,β-unsaturated-3-phenyl-2-dialkylamino Arylketones



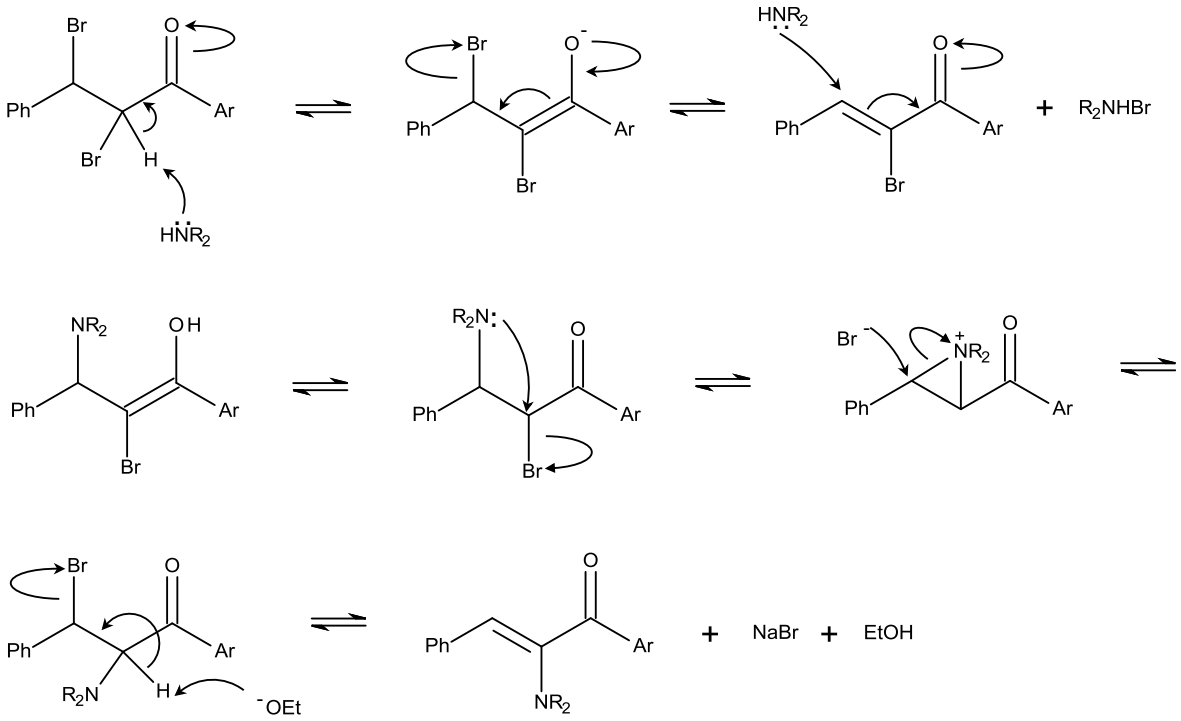
Scheme 3.31

The synthesis of the enamines proved to be the most inconvenient step of the synthesis. It is at this point that the amine functionality is introduced, in the form of a nucleophilic secondary amine. The synthesis is achieved by room temperature reaction of the α,β-dibrominated ketone with a secondary amine in ethanol[80,81]. After 24 hours, the reaction mixture is treated with sodium ethoxide to generate the enamine product[81].

In all cases, the product did not form cleanly. This made for an extremely challenging separation, meaning that the products were never isolated in a pure enough quality to permit characterisation.

In addition to this problem, the semi-clean product often took the form of a very adhesive, viscous, unworkable semi-solid. Thus, in light of the practical difficulties associated with purity and physical state, the enamine was taken forward to the next stage as a crude material. Fortunately in most cases, this had little effect on the next stage of the synthesis, at which point the product could be purified and characterised.

A mechanism for this reaction is shown in Scheme 3.32 below[80,118]:



Scheme 3.32

The highly reversible nature of the steps in this mechanism, as well as alternative avenues, may well account for the highly impure nature of the reaction mixture. It is very possible that several of the intermediate materials in this mechanism may be present by TLC.

No attempts were made to isolate the intermediate components of this reaction.

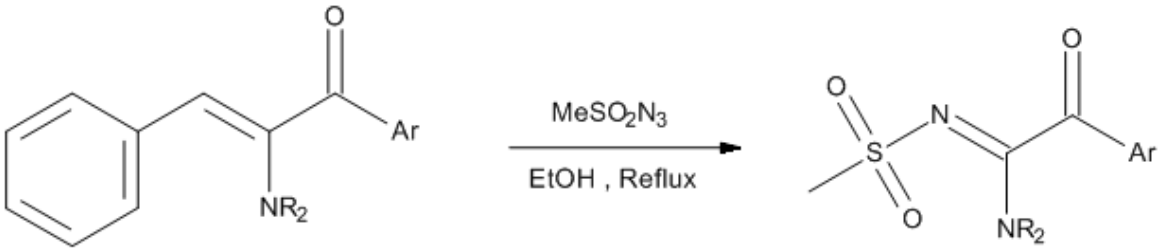
The range of amines and dibromo compounds used is shown in Table 3.11. It is notable that only entry 4 failed in the next step.

Entry	Arene	Amine	Product	Evidence of Formation*
1	Ph	Et_2	**(94)**	Y
2	Ph	Pr_2	**(95)**	Y
3	Ph	Piperidinyl	**(96)**	Y
4	4-NO_2Ph	Et_2	**(97)**	N
5	4-MeOPh	Pr_2	**(98)**	Y
6	4-MeOPh	Piperidinyl	**(99)**	Y
7	4-MeOPh	Morpholinyl	**(100)**	Y
8	4-ClPh	Et_2	**(101)**	Y
9	4-ClPh	Pr_2	**(102)**	Y
10	4-ClPh	Piperidinyl	**(103)**	Y
11	4-MePh	Et_2	**(104)**	Y
12	4-MePh	Piperidinyl	**(105)**	Y

Table 3.11

(*) Evidence of formation refers to the success of the following amidine synthesis, as discussed below.

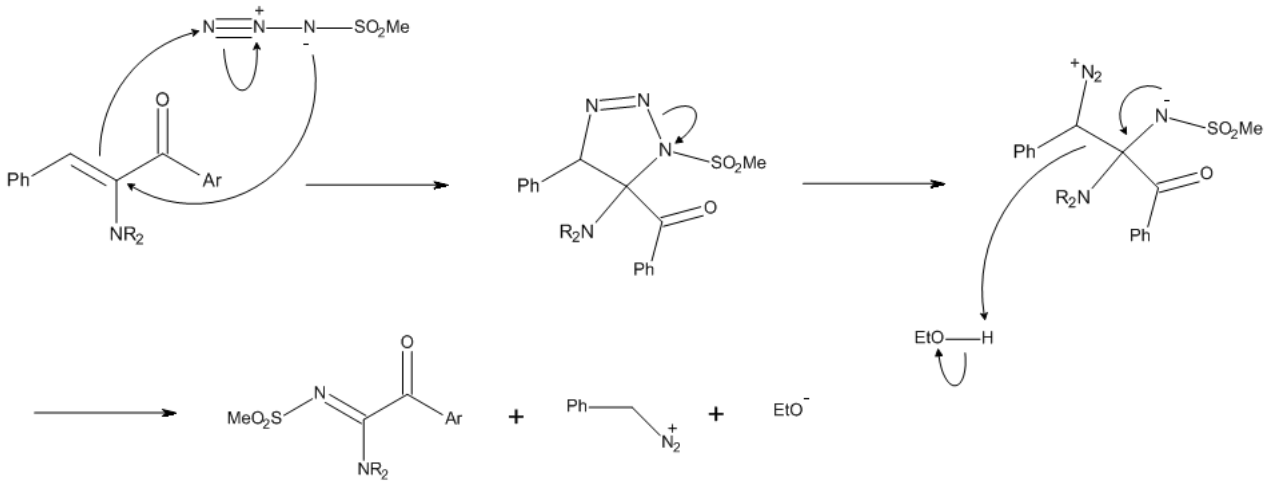
3.2.4 The Synthesis of 2-Dialkylamino-N-methanesulfonyl Arylketoamidines



Scheme 3.33

Fortunately, to counter the unreliable and unworkable enamine step discussed previously, the N-methanesulfonyl amidine synthesis was often very simple and highly practical. The enamine starting material could be taken as a crude mixture and successfully reacted with methanesulfonyl azide to form the amidine in good yields after a simple purification. Due to this high reliability, it was assumed that all reactions that failed at this stage were probably unsuccessful at the previous enamine stage. So convenient was this reaction that occasionally the products could be purified by simple recrystallisation from ethanol.

Methanesulfonyl azide was prepared in solution by reaction of sodium azide with methanesulfonyl chloride[119]. Reaction with the enamine proceeds as shown below in Scheme 3.34 to yield the desired N-methanesulfonyl ketoamidines.



Scheme 3.34 – Reaction mechanism for synthesis of amidines from corresponding enamines.

The reaction mechanism initiates with the 1,3-dipolar cycloaddition of the azide across the dipolarophilic C=N bond of the enamine. This yields an unstable 1,2,3-triazoline which, following a spontaneous cycloreversion, yields the desired amidine product with phenyldiazomethane and ethoxide[120,121]. The range of amidines and yields are summarised in Table 3.12. The individual reactions are discussed below.

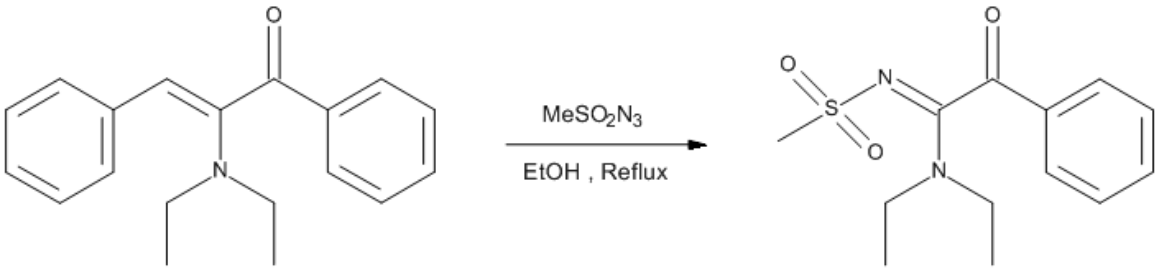
Entry	Arene	Amine	Product	Yield (%)
1	Ph	Et_2	**(106)**	57
2	Ph	Pr_2	**(107)**	48
3	Ph	Piperidinyl	**(108)**	17
4	4-MeOPh	Pr_2	**(109)**	55
5	4-MeOPh	Piperidinyl	**(110)**	24
6	4-MeOPh	Morpholinyl	**(111)**	3
7	4-ClPh	Et_2	**(112)**	42
8	4-ClPh	Pr_2	**(113)**	67
9	4-ClPh	Piperidinyl	**(114)**	44
10	4-MePh	Et_2	**(115)**	20
11	4-MePh	Piperidinyl	**(116)**	42

Table 3.12

NMR spectroscopy and mass spectrometry proved significant analytical techniques for structural determination of the amidine series. Though carried out, analysis by FT-IR spectroscopy was not commented upon due to the significance of other analytical data.

Lack of observation of any amidine product suggested that the nitro derivative dibromo compound **(97)** (entry 7 in Table 3.11) was not successfully converted to the enamine. This derivative was not pursued further.

3.2.4.1 Synthesis of N,N-diethyl-N'-methylsulfonyl-2-oxo-2-phenyl-acetamidine



(94) **(106)**

Scheme 3.35

Analysis of the product by ^{1}H NMR spectroscopy revealed some interesting features. Firstly the success of the reaction was inferred by the presence of the singlet integrating as three protons at δ2.97 which must account for protons *a*.

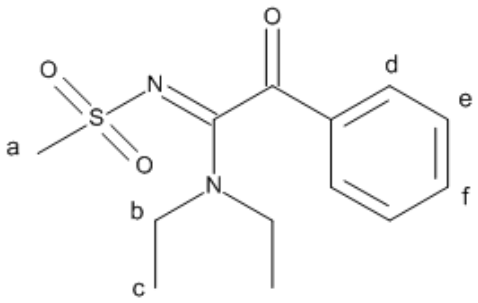


Figure 3.35

The phenyl protons *d, e,* and *f* are present as the expected doublet, doublet of doublets and triplet at δ7.90, δ7.65 and δ7.53 respectively. However, the most interesting feature of the NMR spectrum is the nature of the N-ethyl groups. Protons *c* resonate as two well established triplets (δ1.09 and δ1.34), rather than one. This suggests the terminal methyl group of protons are distinct and non-equivalent.

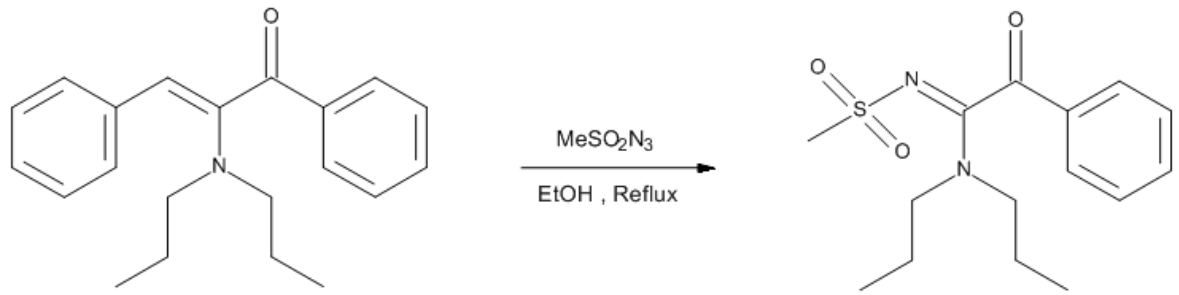
A similar situation is observed with the methylene protons *b* which resonate as distinct signals also. Interestingly, these protons resonate as 3 signals. These signals consist of an apparent quintet at

δ3.15 which integrates as two protons and as two multiplets at δ3.46-3.59 and δ3.67-3.83 which each integrate as one proton.

Analysis of the molecule by ^{13}C NMR spectroscopy seems to confirm the above structure. The amine methyl carbons are visible at δ11.92 and δ13.69 and the methylene carbons at δ42.67 and δ44.24. The methanesulfonyl carbon is observed at δ42.58. Other crucial signals present in the spectrum are the amidine carbon and ketone carbon at δ161.94 and δ192.57, respectively.

The molecular structure of this compound was confirmed by HRMS which delivered an accurate mass of 305.0930 for the $[M+Na]^+$ ion comparing well with the expected 305.0928.

3.2.4.2 Synthesis of N'-methylsulfonyl-2-oxo-2-phenyl-N,N-dipropyl-acetamidine



(95) **(107)**

Scheme 3.36

The dipropyl derivative amidine **(107)** was synthesised in the same manner as the above, by refluxing the crude enamine in ethanol with methanesulfonyl azide, in 48% yield.

The dipropylamino section of this molecule led to much anticipation in terms of what we would potentially observe by ^1H NMR spectroscopy, given the peculiarities of the diethylamino analogue **(106)**. The ^1H NMR spectrum is exactly as expected for the remainder of the molecule. In the ^1H NMR spectrum, the diagnostic methanesulfonyl protons are observed as a singlet at δ2.97 and the triplet-doublet of doublets-doublet system for the phenyl protons at δ7.53, δ7.75 and δ7.90. The most interesting feature is the dipropylamine group. The two terminal methyl groups (protons *d*) are once again unique and are observed as triplets at δ0.72 and δ1.02. The protons of the methylene groups (protons *c*) resonate as two multiplets at δ1.40-1.65 and δ1.72-1.88. One set of methylene protons *b*

resonates as an apparent quartet-type signal, somewhat masked by the strong methanesulfonyl singlet. The methylene protons of the remaining methylene each resonate as individual signals at δ3.33-3.44 and δ3.62-3.76, which again shows inequivalency.

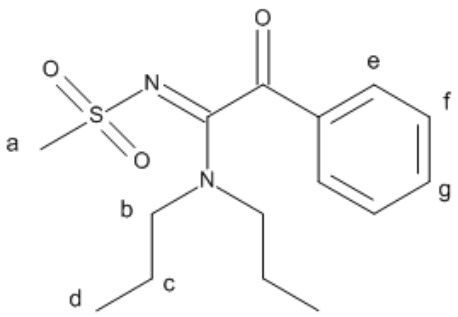
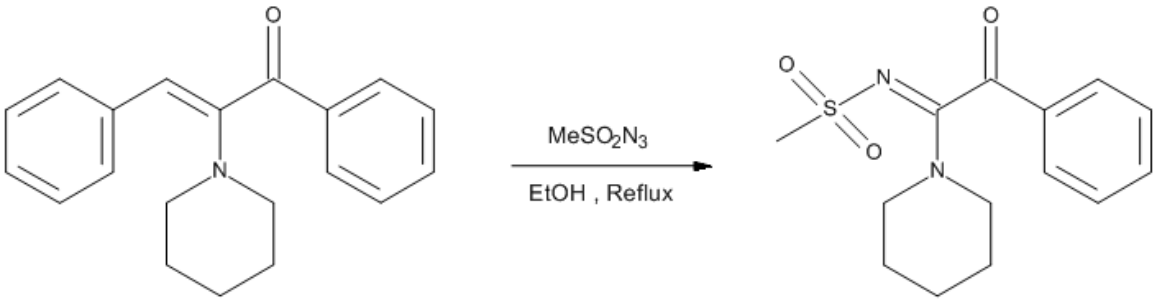


Figure 3.36

The ^{13}C NMR spectrum supports the structure well and as before, illustrates the non-equivalent nature of the amine strands. The terminal methyl carbons are observed at δ10.87 and δ11.45, the β-methylene carbons at δ19.87 and δ21.67 and finally the α-methylene carbons at δ49.64 and δ51.38. The diagnostic methanesulfonyl carbon signal is observed at δ42.57.

The HRMS spectrum confirms this molecular structure. The theoretical mass for the $[M+Na]^+$ ion was determined to be 333.1243, which compared well with the measured accurate mass of 333.1241.

3.2.4.3 Synthesis of N-[2-oxo-2-phenyl-1-(piperidyl)ethylidene] methanesulfonamide



(96) **(108)**

Scheme 3.37

The phenyl amidine derivative featuring the piperidinyl substituent was synthesised in 17% yield, which suggests that the previous enamine step may not have worked well; the bulky and more rigid nature of the piperidine unit may possibly offer some explanation.

The ^{1}H NMR spectrum shows a broad multiplet at δ1.35-1.56 integrating as two protons for the γ-methylene protons *d*. Protons *c* of the β-methylene units resonate at δ1.65-1.80. The protons of methylenes *b* appear at very different shifts, as multiplets at δ3.11-3.29 and δ3.78-3.92. This suggests that the α-methylene groups either side of the piperidine heterocycle are different.

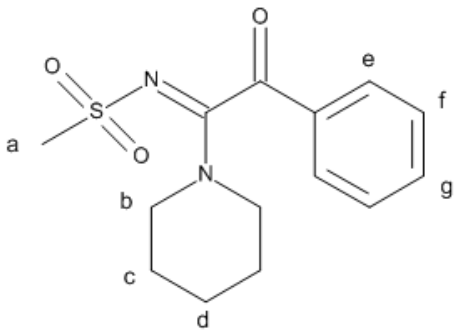


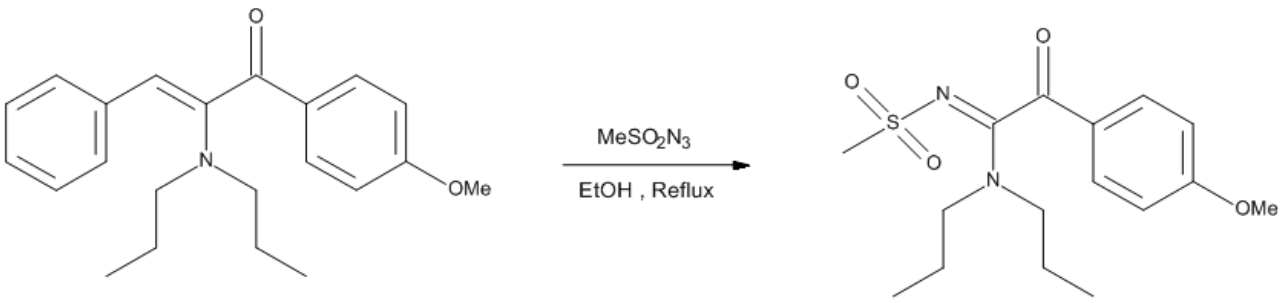
Figure 3.37

Additionally, a singlet at δ2.98 indicates the presence of the methanesulfonyl group. The phenyl protons are observed in the typical region in the expected pattern.

The ^{13}C NMR spectrum shows the presence of the γ-methylene carbon at δ23.87, the two β-methylene carbons at δ25.27 and δ26.03 and finally the two α-methylene carbons at δ45.90 and δ48.84. The methanesulfonyl carbon is present at δ42.61.

The molecular structure was fully confirmed by HRMS which, for the calculated $[M+Na]^+$ ion of 317.0930, delivered an accurate mass for of 317.0922.

3.2.4.4 Synthesis of 2-(4-methoxyphenyl)-N'-methylsulfonyl-2-oxo-N,N-dipropyl-acetamidine



(98) **(109)**

Scheme 3.38

The first of the 4-methoxyphenyl derivative enamines **(98)**, was successfully converted to the amidine product **(109)** in a moderate 55% yield.

The ^{1}H NMR spectrum is consistent with the previous dipropyl amidine.

The ^{13}C NMR spectrum is fully consistent with what one would expect and the structure was confirmed by HRMS with an accurate mass for the $[M+Na]^+$ ion of 363.1348, correlating well with the theoretical mass of 363.1349.

3.2.4.5 Synthesis of N-[2-(4-methoxyphenyl)-2-oxo-1-(1-piperidyl)ethylidene] methanesulfonamide

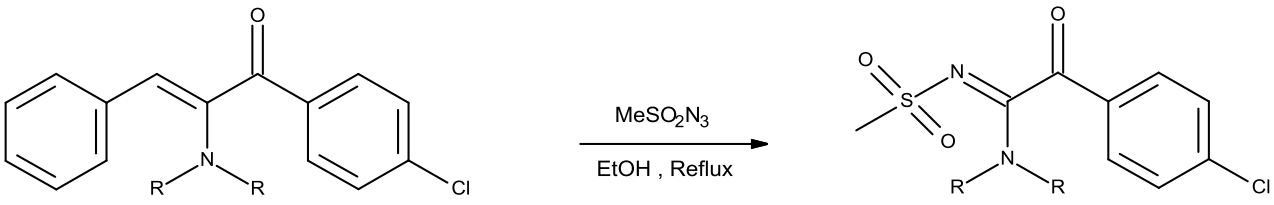
(99) **(110)**

Scheme 3.39

The 4-methoxyphenyl/piperidine amidine **(110)** was successfully synthesised, though in low yield of 24%. Lower yields were consistently observed with piperidinyl derivatives throughout this project.

The ^{1}H NMR spectrum was consistent with the expected structure. The ^{13}C NMR spectrum and HRMS confirmed the structural assignment.

3.2.4.6 Synthesis of 2-(4-chlorophenyl)-methylsulfonyl-2-oxo-acetamidines



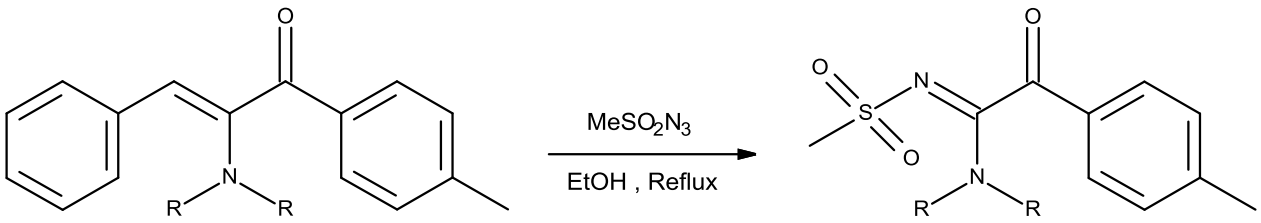
(101-103)

(112) R = Et, 42%
(113) R = Pr, 67%
(114) R = -$(CH_2)_5$-, 44%

Scheme 3.40

The 4-chlorophenyl amidines **(112-114)** were synthesised effectively in 42-67% yield, giving fully consistent spectroscopic data.

3.2.4.7 Synthesis of methylsulfonyl-2-oxo-2-(p-tolyl)acetamidines



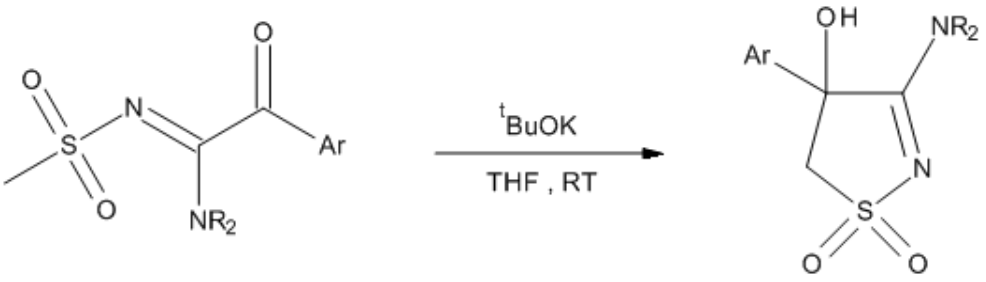
(104-105)

(115) R = Et, 20%
(116) R = -$(CH_2)_5$-, 42%

Scheme 3.41

The tolyl/diethylamine amidine system **(115)** and corresponding piperidinyl system **(116)** were successfully synthesised yields of 20% and 42% respectively. Both gave fully consistent spectroscopic data.

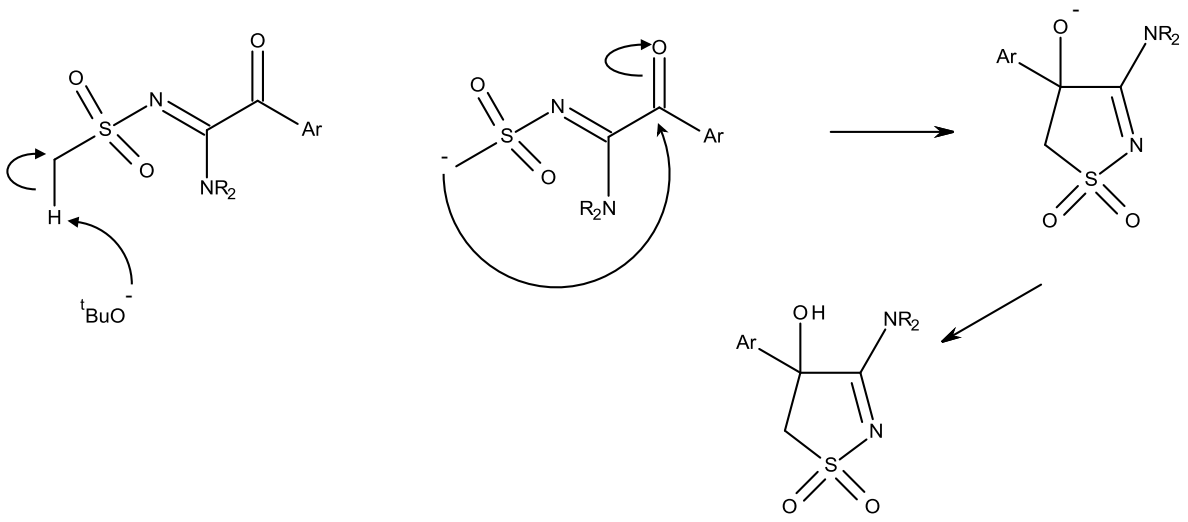
3.2.5 The Synthesis of 3-Dialkylamino-4-hydroxy-4-aryl-isothiazoline-1,1-dioxides



Scheme 3.42

The cyclisation of the methanesulfonyl amidine to the 3-amino-4-hydroxy-4-aryl isothiazoline-1,1-dioxide was achieved by treatment with one equivalent of potassium *tert*-butoxide in dry THF at room temperature[79] in mostly good to excellent yields throughout.

The key diagnostic feature of this cyclisation is the conversion of the carbonyl group to a tertiary alcohol due to nucleophilic attack by the methanesulfonyl carbon which becomes the isothiazoline 5-position methylene, as shown in Scheme 3.43.



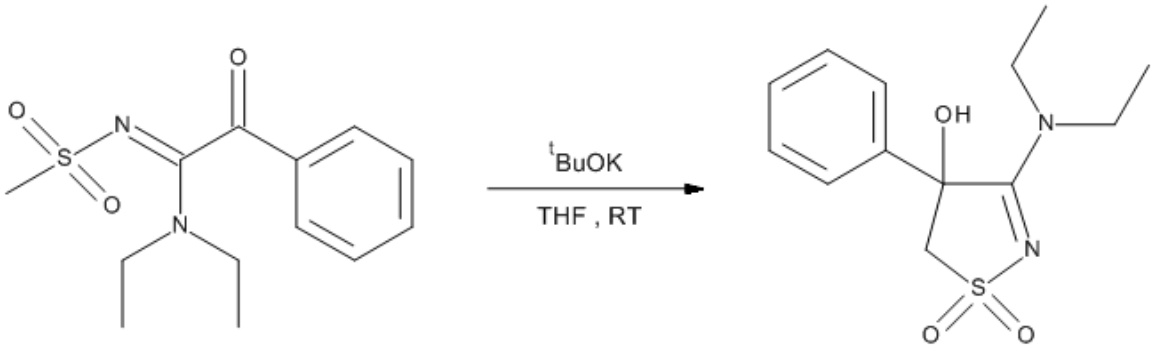
Scheme 3.43 – Reaction mechanism for base mediated cyclisation of amidine to isothiazoline.

The reaction mechanism proceeds with the deprotonation of the methanesulfonyl group by BuO^- yielding the corresponding methanesulfonyl carbanion which triggers the nucleophilic attack of the carbonyl followed by protonation of the isothiazoline oxide to yield the 4-hydroxyisothiazoline compound[79]. The compounds shown in Table 3.13 were synthesised via this reaction and some of the details of their characterisation are given below.

Entry	Arene	Amine	Product	Yield (%)
1	Ph	Et_2	**(117)**	81
2	Ph	Pr_2	**(118)**	96
3	Ph	Piperidinyl	**(119)**	87
4	4-MeOPh	Pr_2	**(120)**	99
5	4-MeOPh	Piperidinyl	**(121)**	60
6	4-MeOPh	Morpholinyl	**(122)**	-
7	4-ClPh	Et_2	**(123)**	87
8	4-ClPh	Pr_2	**(124)**	76
9	4-ClPh	Piperidinyl	**(125)**	-
10	4-MePh	Et_2	**(126)**	77
11	4-MePh	Piperidinyl	**(127)**	42

Table 3.13

3.2.5.1 Synthesis of 3-(Diethylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



(106) **(117)**

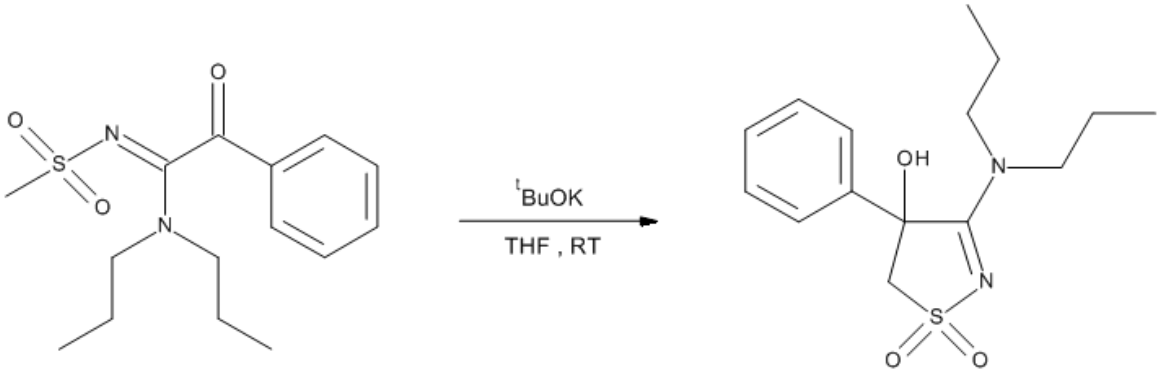
Scheme 3.44

The 3-diethylamino-5-hydroxy-5-phenyl isothiazoline derivative **(117)** was successfully synthesised via reaction with ^{t}BuOK in THF in 81% yield.

Confirmation of the structure of the above compound was achieved by NMR spectroscopy. The diagnostic features of the spectrum are the disappearance of the methanesulfonyl singlet of **(106)** and the appearance of a broad singlet representing the OH proton at δ5.44. The new methylene protons are represented by two doublets at δ3.67 and δ3.91, coupled with a frequency of J=14.2Hz. This splitting shows the protons of this α-sulfonylmethylene group are non-equivalent due to the adjacent chiral centre. The terminal methyl groups resonate as two triplets at δ0.74 and δ1.24. The diethylamine methylene groups remain non-equivalent and now resonate as two sets of two overlapping doublets of quartets at δ3.27 and δ3.48.

The ^{13}C NMR spectrum is perfectly as expected, with the loss of the carbonyl carbon and methanesulfonyl carbon signals. The structure was confirmed by HRMS which presented an accurate mass for the $[M+Na]^{+}$ ion of 305.0923. The theoretical mass figure of this ion was determined to be 305.0930.

3.2.5.2 Synthesis of 3-(Dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



(107) **(118)**

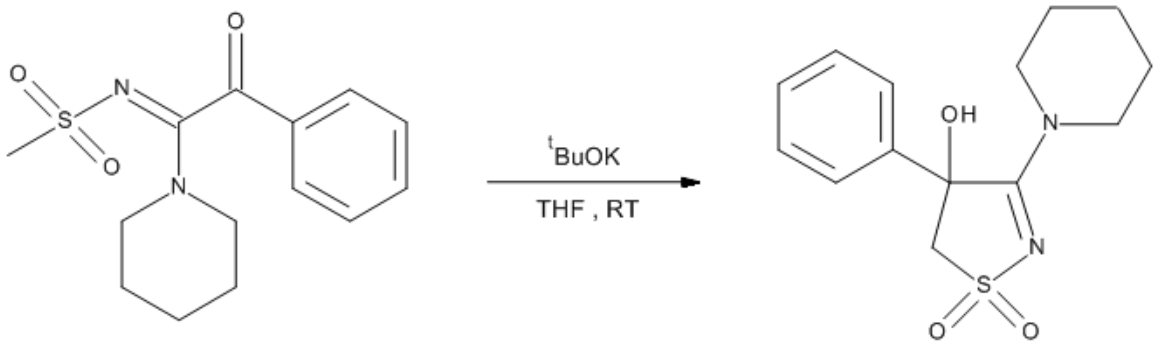
Scheme 3.45

Amidine **(107)** reacted well with potassium *tert*-butoxide to form the cyclised product **(118)** in 96% yield.

The structure of the product was confirmed by ^{1}H NMR spectroscopy. Each proton of the α-sulfonylmethylene group resonated as a doublet, one at δ3.66 and the other at δ3.95. The hydroxyl proton is observed as a singlet at δ5.69. The terminal methyl protons follow the usual pattern; all four β-methylene protons now each resonate each as separate multiplets at δ0.77-0.87, δ1.38-1.52, δ1.56-1.69 and δ1.70-1.83. The α-methylene protons show complex splitting patterns resulting in two signals at δ3.16 and δ3.36.

The structure was fully consistent with the observed ^{13}C NMR spectrum and HRMS, with the accurate mass for the $[M+Na]^{+}$ ion determined to be 333.1240. The theoretical mass figure of this ion was determined to be 333.1243.

3.2.5.3 Synthesis of 3-(Dipropylamino)-1,1-dioxo-4-phenyl-5H-isothiazol-4-ol



Scheme 3.46

(108) **(119)**

Piperidine-isothiazoline **(119)** was synthesised in a yield of 87%.

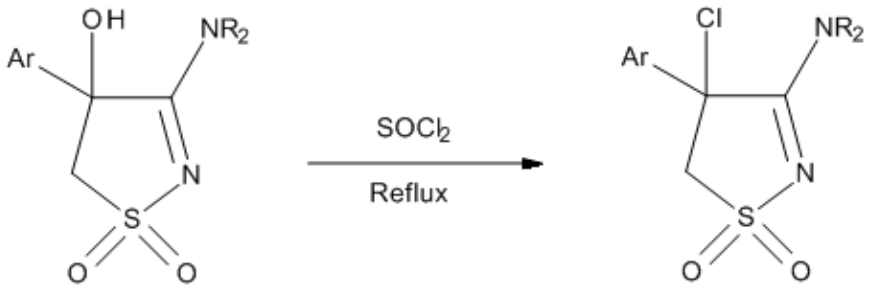
The structure of compound **(119)** was assigned by ^{1}H NMR spectroscopy which showed the α-sulfonylmethylene protons as two expected doublets at δ3.66 and δ3.90. The hydroxyl proton is visible as the broad stretch at approximately δ6.36. The piperidine protons are observed as several multiplets resonating at δ0.84-0.97 and δ1.29-1.42 for the γ-methylene protons and δ1.45-1.72 for four β-methylene protons and one α-methylene proton. Two of the remaining three α-methylene protons can be observed as a pair of multiplets at δ3.34, with the last of these protons masked by the α-sulfonylmethylene doublet at approximately δ3.66.

The ^{13}C NMR spectrum is in accordance with this structure, showing five CH_2 signals for the piperidine ring.

3.2.5.4 Synthesis of Remaining Isothiazol-4-ols

Most of the remaining isothiazoles **(120-122, 123,124, 126,127)** in Table 3.14 were synthesised in the same manner and all gave fully consistent spectroscopic data and were obtained in the yields shown. Morpholinyl and piperidinyl derivative Isothiazoles **(122)** and **(125)** were not observed. Given the variety of the series, these derivatives were not pursued further.

3.2.6 The Synthesis of 3-Dialkylamino-4-chloro-4-aryl-isothiazoline-1,1-dioxides



Scheme 3.47

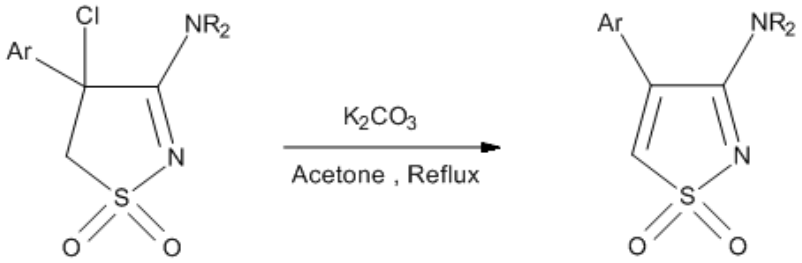
The 4-hydroxylisothiazolines were converted to the 4-chloroisothiazolines in order provide a more reliable opportunity to generate the fully unsaturated isothiazoles. The installation of chlorine at the 4-position provides a sensible, mild route to the fully unsaturated heterocycle due to easy elimination of HCl. The chlorination was achieved by treatment with excess thionyl chloride under reflux conditions. The compounds synthesised by this method are shown in Table 3.14, below. It is notable that the first few reactions attempted gave some of the (desired) elimination products, the synthesis of which is done deliberately in the next step.

Entry	Arene	Amine	Chlorinated Product	Yield	Dehydrochlorinated Product	Yield
1	Ph	Et_2	**(128)**	56	**(137)**	31
2	Ph	Pr_2	**(129)**	55	**(138)**	5
3	Ph	Piperidinyl	**(130)**	33	**(139)**	4
4	4-MeOPh	Pr_2	**(131)**	97	-	-
5	4-MeOPh	Piperidinyl	**(132)**	89	-	-
6	4-ClPh	Et_2	**(133)**	82	-	-
7	4-ClPh	Pr_2	**(134)**	85	-	-
8	4-MePh	Et_2	**(135)**	66	-	-
9	4-MePh	Piperidinyl	**(136)**	71	-	-

Table 3.14

All of the chlorinated products **(128-136)**, gave the expected spectroscopic analysis. The major dehydrochlorinated product **(137)** also gave the expected spectroscopic characteristics, with the loss of the chiral centre resulting in the diethyl unit becoming much simpler. Dehydrochlorinated products **(138-139)** were also observed, but as insignificant minority products. The chlorinated products showed splitting patterns in the ^{1}H NMR that were broadly similar to those observed in the alcohols and this will not be detailed further here.

3.2.7 The Synthesis of 3-Dialkylamino-4-aryl-isothiazole-1,1-dioxides



Scheme 3.48

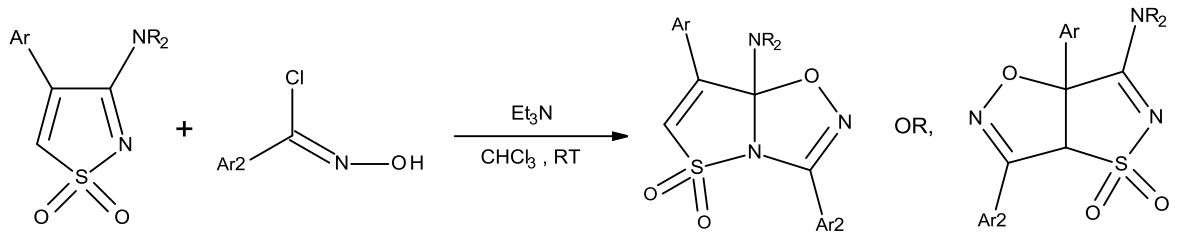
Entry	Arene	Amine	Product	Yield (%)
1	Ph	Pr_2	**(138)**	62
2	4-MeOPh	Pr_2	**(140)**	76
3	4-MeOPh	Piperidinyl	**-**	-
4	4-ClPh	Et_2	**(141)**	79
5	4-ClPh	Pr_2	**(142)**	97
6	4-MePh	Et_2	**(143)**	30
7	4-MePh	Piperidinyl	**(144)**	20

Table 3.15

This straightforward reaction gave six further examples of the 3-dialkylamino-4-aryl-isothiazole-1,1-dioxides to add to compound **(137)** (see Table 3.14). The loss of chirality in each of the products **(140-144)** and the formation of the planar fully unsaturated heterocycle simplified the ^{1}H NMR

spectra considerably, since the dialkyl chain showed equivalent alkyl groups. The new singlet in the unsaturated isothiazole-1,1-dioxide ring typically appeared around δ7.2 in the ^{1}H NMR spectrum and at δ132 in the ^{13}C NMR spectrum. The phenyl derivatives generated by spontaneous dehydrochlorinarion in the previous step were taken on by another group member. Unfortunately, the dehydrochlorination of piperidinyl derivative **(132)** was unsuccessful. This derivative was not pursued further.

3.2.8 The Synthesis of 3,6-diaryl-7-dialkylamino-isothiazolo-isoxazole-1,1-dioxides

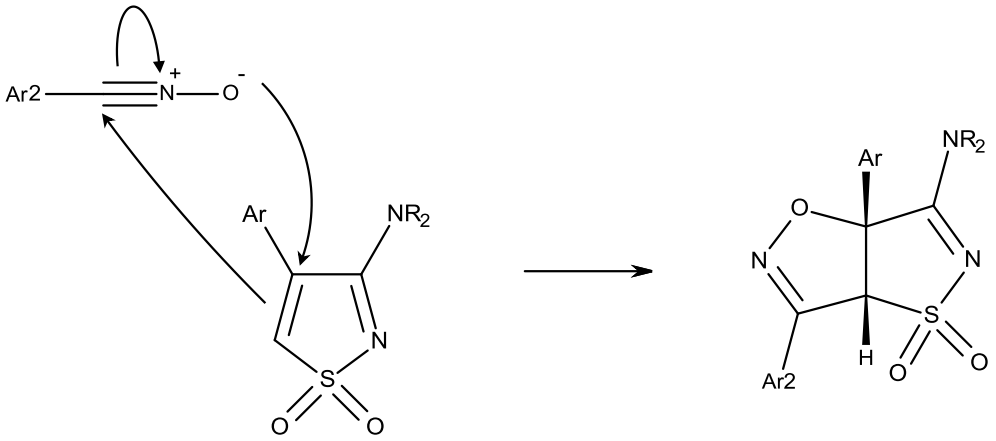


Scheme 3.49

The major motive for synthesising the isothiazole-1,1-dioxides was to explore the possibility of 1,3-dipolar cycloaddition at the imine bond of the heterocycle, thereby enabling access to isothiazolo-oxadiazoles. We have found that in all cases, cycloaddition occurs only across the alkene bond, with zero evidence of any cycloaddition across the imine bond, in either the starting material or the newly formed product.

To the best of our knowledge, only a small number of isothiazolo-isoxazole systems have been synthesised with very few investigations conducted into their anti-cancer activity[78]. Thus, a small series of these molecules were screened for anti-cancer activity. This will be described later.

The isothiazolo-isoxazoles were obtained by careful treatment of previously prepared imidoyl halides with triethylamine to generate the *in-situ* 1,3-dipolar nitrile oxide species which reacted successfully with the dipolarophilic isothiazole-1,1-dioxides across the C=C bond:



Scheme 3.50

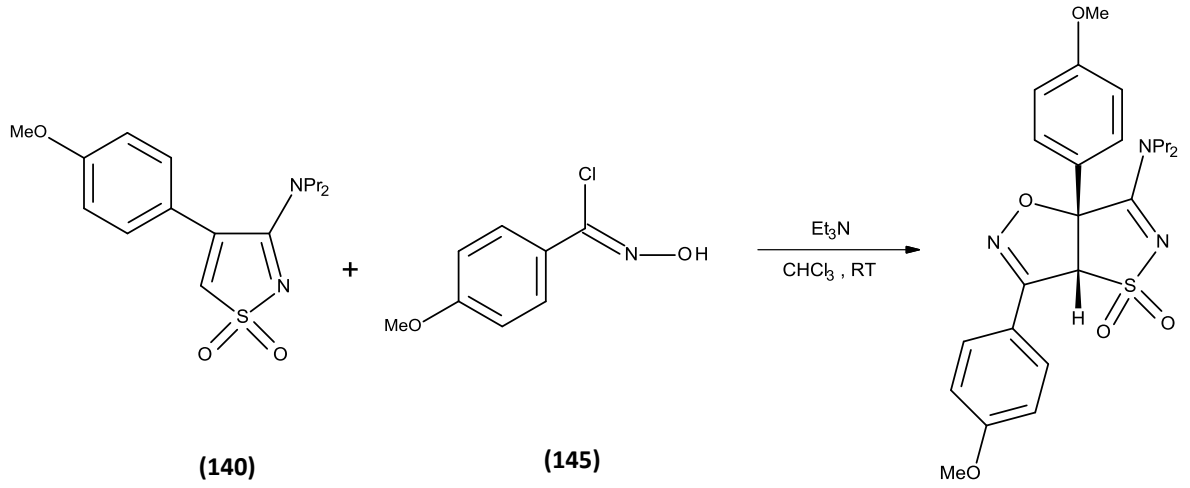
Significantly, this reaction produces two new chiral centres, located at the isothiazolo-isoxazole bridging carbon atoms. In all cases, a single diastereomer was observed.

Table 3.16 shows the range of isothiazolo-isoxazoles that were produced in this study. In this thesis, the compounds synthesised via this route focused upon substituted benzene rings meaning that isothiazoles **(137)** and **(138)** were taken on by another group member. Some of the typical spectroscopic data of these compounds is discussed below.

Entry	Isothiazole Arene	Isothiazole Amine	1,3-Dipole Arene	Product	Yield (%)
1	4-MeOPh	Pr_2	4-MeOPh	**(147)**	29
2	4-MeOPh	Pr_2	4-ClPh	**(148)**	44
3	4-ClPh	Et_2	4-ClPh	**(149)**	17
4	4-ClPh	Et_2	4-MeOPh	**(150)**	42
5	4-ClPh	Pr_2	4-MeOPh	**(151)**	25
6	4-ClPh	Pr_2	4-ClPh	**(152)**	29
7	4-MePh	Et_2	4-MeOPh	**(153)**	39
8	4-MePh	Et_2	4-ClPh	**(154)**	14
9	4-MePh	Piperidinyl	4-MeOPh	**(155)**	54
10	4-MePh	Piperidinyl	4-ClPh	**(156)**	28

Table 3.16

3.2.8.1 Synthesis of 3,6a-bis(4-methoxyphenyl)-4,4-dioxo-N,N-dipropyl-3aH-isothiazolo[5,4-d]isoxazol-6-amine



(140) **(145)** **(147)**

Scheme 3.51

The 1,3-dipolar cycloaddition of *insitu* generated 4-methoxyphenyl nitrile oxide from **(145)** with **(140)** occurred solely across the isothiazole alkene bond in 29% yield.

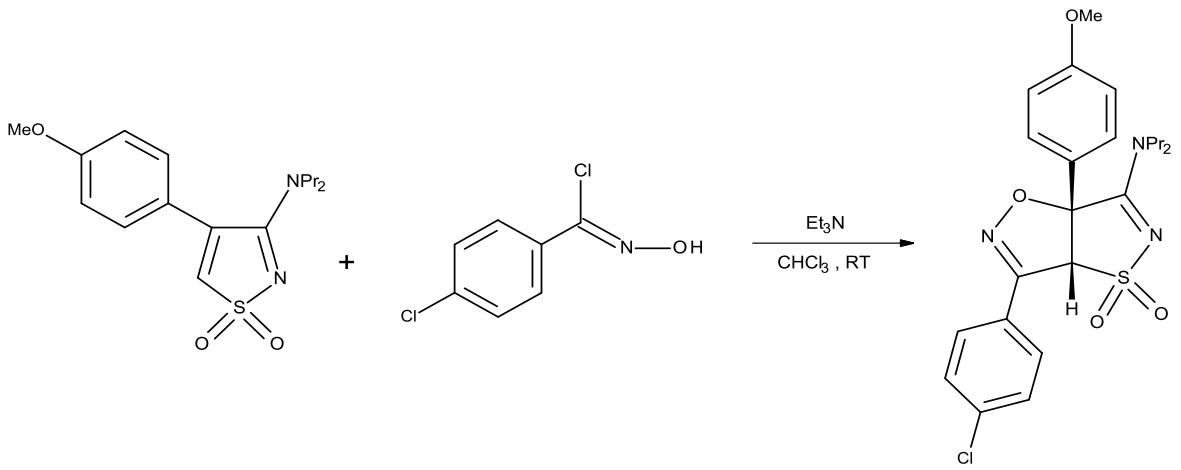
The isothiazolo-isoxazole structure was confirmed by ^{1}H NMR spectroscopy which showed the dipropylamine chains to be intact and appearing again as characteristically complex signals. The two sets of aryl methoxy protons appear very close together at δ3.827 and δ3.831. The singlet at δ5.07 is the stereocentre bridgehead proton. All aryl protons are accountable by the presence of doublets at δ6.92, δ6.97, δ7.37 and δ7.72. The absence of the isothiazole δ-proton singlet is also notable and provides clear evidence that the compound is not the isothiazolo-oxadiazole, but is indeed the isothiazolo-isoxazole.

Analysis of the HSQC spectrum shows the sulfone α-carbon stereocentre at δ79.71.

The stereochemistry of the ring junction was established as *cis*- due to the proton on the sulfone α-carbon and the protons at the *ortho* position of the bridgehead *p*-methoxyphenyl showing a signal in the NOESY spectrum. A previous worker in the group established this unequivocally by x-ray crystallography on similar adducts.

The structure was further confirmed by HRMS which indicated an accurate mass of 494.1717 for the $[M+Na]^{+}$ ion with the theoretical mass of this ion calculated to be 494.1720.

3.2.8.2 Synthesis of 3-(4-chlorophenyl)-6a-(4-methoxyphenyl)-4,4-dioxo-N,N-dipropyl-3aH-Isothiazolo[5,4-d]isoxazol-6-amine



(140) **(146)** **(148)**

Scheme 3.52

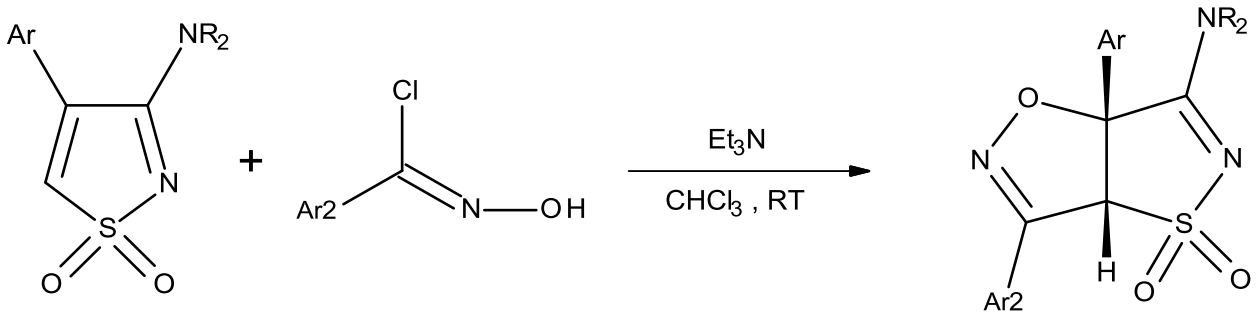
Synthesis of the bicyclic product **(148)** was achieved in 30% yield.

Confirmation was provided by ^{1}H NMR spectroscopy which showed the new bridgehead proton at δ5.06, with the methine carbon appearing at δ79.08 in the ^{13}C NMR spectrum. The spectrum was completely in accordance with that of adduct **(147)**, with the only major difference being the presence of one methoxy singlet rather than two.

Analysis by HRMS delivered an accurate mass of 498.1222 for the $[M+Na]^{+}$ ion compared with the expected figure of 498.1225.

The NOESY spectrum again showed a strong correlation between the proton on the sulfone α-carbon and the *ortho* protons on the *p*-methoxyphenyl, again inferring *cis*- stereochemistry across the ring junction.

3.2.8.3 Synthesis of Remaining Isothiazolo-isoxazoles



(149) Ar - 4-ClPh, Ar2 - 4-ClPh, R - Et_2

(150) Ar - 4-ClPh, Ar2 - 4-MeOPh, R - Et_2

(151) Ar - 4-ClPh, Ar2 - 4-MeOPh, R - Pr_2

(152) Ar - 4-ClPh, Ar2 - 4-ClPh, R - Pr_2

(153) Ar - 4-MeOPh, Ar2 - 4-MeOPh-, R - Et_2

(154) Ar - 4-MeOPh, Ar2 - 4-ClPh, R - Et_2

(155) Ar - 4-MeOPh, Ar2 - 4-MeOPh-, R - Piperidinyl

(156) Ar - 4-MeOPh, Ar2 - 4-ClPh, R - Piperidinyl

Scheme 3.53

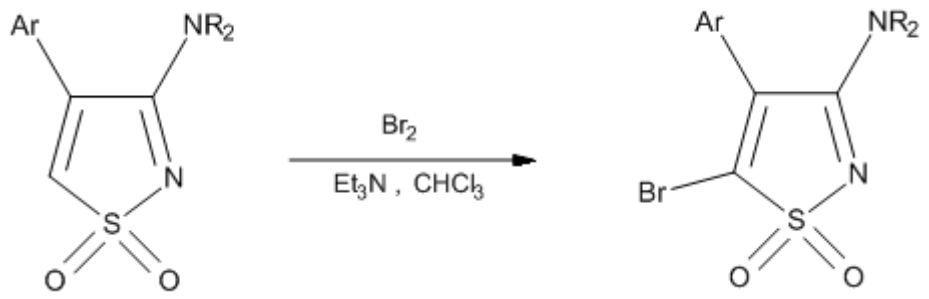
All isothiazolo-isoxazole structures were determined by ^{1}H NMR spectroscopy, the diagnostic singlet observed at approximately δ5.08 denoting the presence of the bridgehead proton, which confirmed addition across the C=C bond. All other signals and data were consistent with the assigned structures. All gave ^{1}H NMR, ^{13}C NMR, IR and HRMS data that were fully consistent with the assigned structures (see experimental section 2.2.8).

The structural details and yields of compounds **(150-156)** are detailed in Table 3.16.

The biological data from the synthesised isothiazolo-isoxazoles is discussed in section 3.2.11.

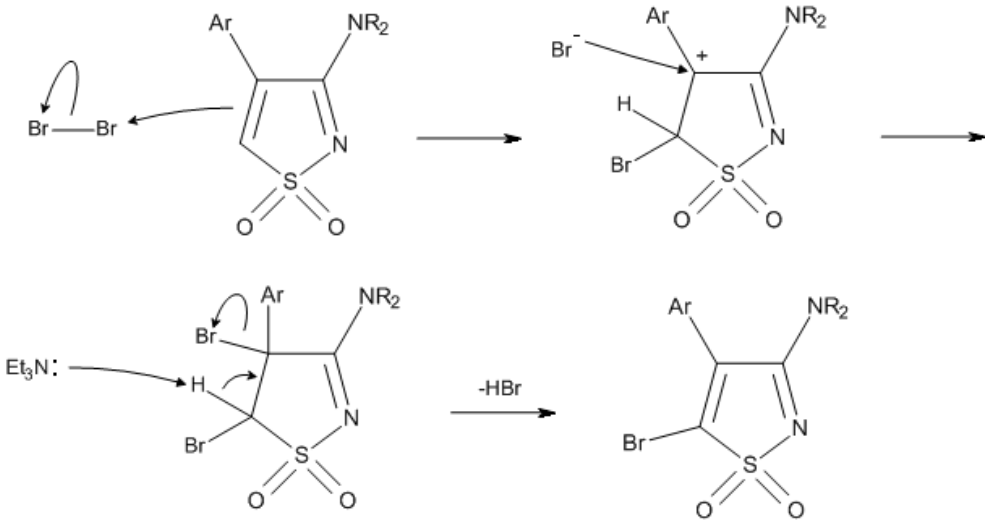
Two isothiazoles were chosen as substrates to attempt ring contraction to a β-sultam and this is discussed next.

3.2.9 The Synthesis of 3-Dialkylamino-4-aryl-5-bromo-isothiazole-1,1-dioxides



Scheme 3.54

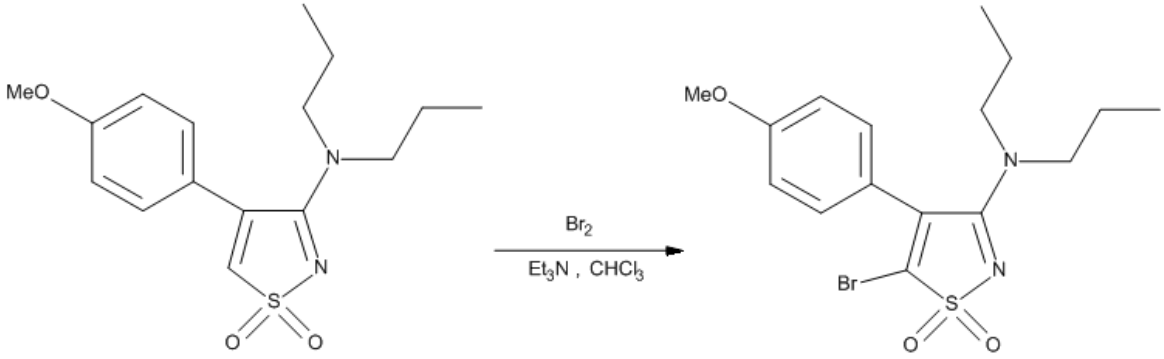
As studied above, two isothiazoles were explored as substrates for β-sultam formation. The first step in this sequence was bromination. The α-bromination of the isothiazole was achieved by treatment with one equivalent of a solution of bromine in chloroform (1M), which affords the dibrominated product. Deprotonation of the α-carbon by base then triggers β-elimination of bromide and the subsequent loss of HBr resulting in the α-brominated isothiazole-1,1-dioxide[77], as shown below.



Scheme 3.55 – Reaction mechanism for the α-bromination of isothiazole-1,1-dioxides.

The two isothiazoles selected for this study are discussed below.

3.2.9.1 Synthesis of 5-bromo-4-(4-methoxyphenyl)-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(140) **(157)**

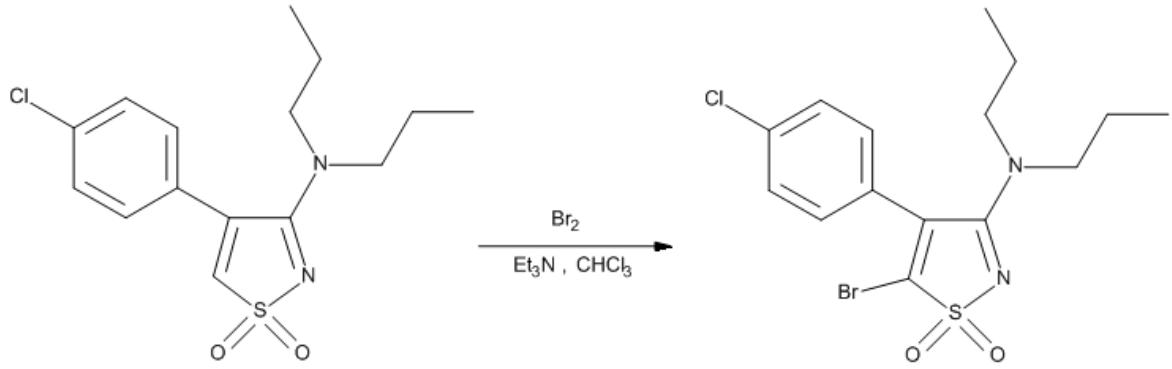
Scheme 3.56

The α-bromination of the 3-dipropylamino-4-(4-methoxyphenyl) derivative isothiazole-1,1-dioxide **(140)** was successfully achieved in 88% yield.

The ^{1}H NMR spectrum was consistent with previous spectra with the propyl chains resonating as two triplets and two sets of multiplets. Critically, the ^{1}H NMR signal representing the α-proton of **(140)** is no longer present.

The ^{13}C NMR spectrum supports the assignment and, most importantly, showed loss of the isothiazole ring CH and appearance of a new quaternary carbon. The consistent NMR data and concerns about stability meant that this compound was deemed sufficiently characterised for continuation.

3.2.9.2 Synthesis of 5-bromo-4-(4-chlorophenyl)-1,1-dioxo-N,N-dipropyl-isothiazolo-3-amine



(142) **(158)**

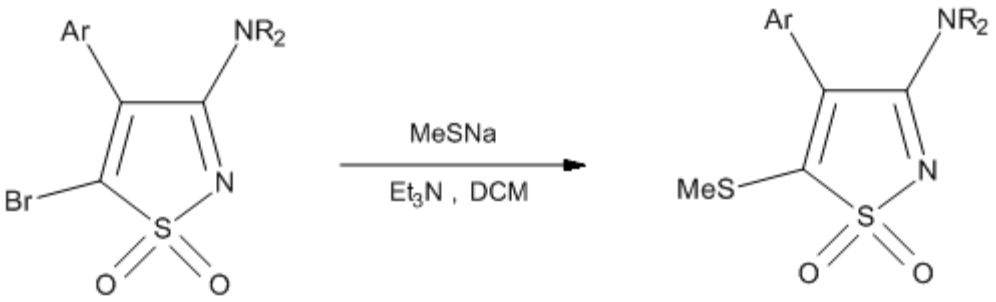
Scheme 3.57

The α-bromination of the 3-dipropylamino-4-(4-chlorophenyl) derivative **(142)** was successfully achieved in 80% yield.

Analysis by ^{1}H NMR spectroscopy is strongly supportive of the formation of compound **(158)**; the absence of the isothiazole α-proton giving the most clear indication; an assignment supported by the ^{13}C NMR spectrum. The remainder of the spectroscopic data accounts for the rest of the structure of the product with little change from the spectra of **(142)**.

The product was confirmed beyond reasonable doubt by HRMS which provided an accurate mass for the $[M+Na]^{+}$ ion of 426.9850 for the expected figure of 426.9853.

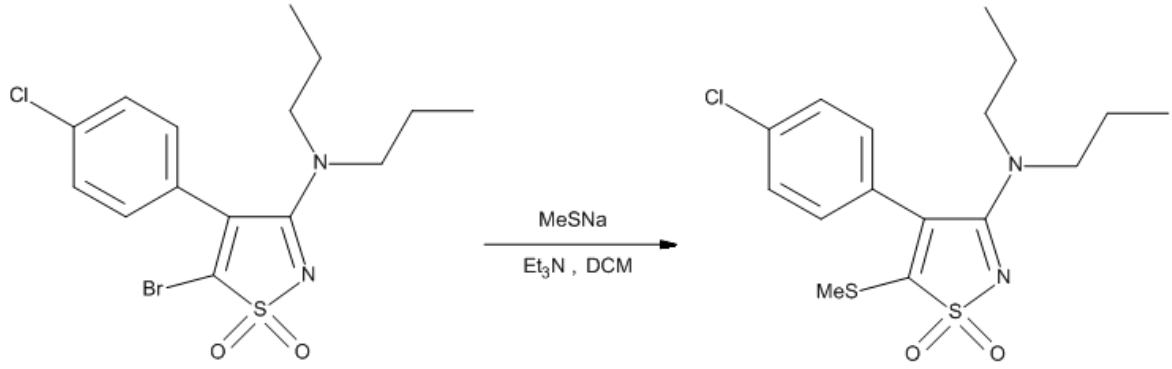
3.2.10 The Synthesis of 3-Dialkylamino-4-aryl-5-thiomethoxy-isothiazole-1,1-dioxides



Scheme 3.58

The 3-amino-4-aryl-5-methylsulfide derivatives were synthesised by simple nucleophilic displacement of bromide by thiomethoxide in the presence of triethylamine in dichloromethane. The presence of triethylamine was necessary to minimise the protonation risk of the thiomethoxide ion, thereby preserving its nucleophilicity[77].

3.2.10.1 Synthesis of 4-(4-chlorophenyl)-5-methylsulfanyl-1,1-dioxo-N,N-dipropyl-isothiazol-3-amine



(158) **Scheme 3.59** **(159)**

The synthesis of compound **(159)** was achieved successfully in 41% yield.

Analysis by ^{1}H NMR spectroscopy allowed the observation of a new singlet at δ2.78, which integrates perfectly as three protons and so confirms the methylsulfidation.

The structure of the product is confirmed further by ^{13}C NMR spectroscopy which shows the new methylsulfide signal at δ12.96.

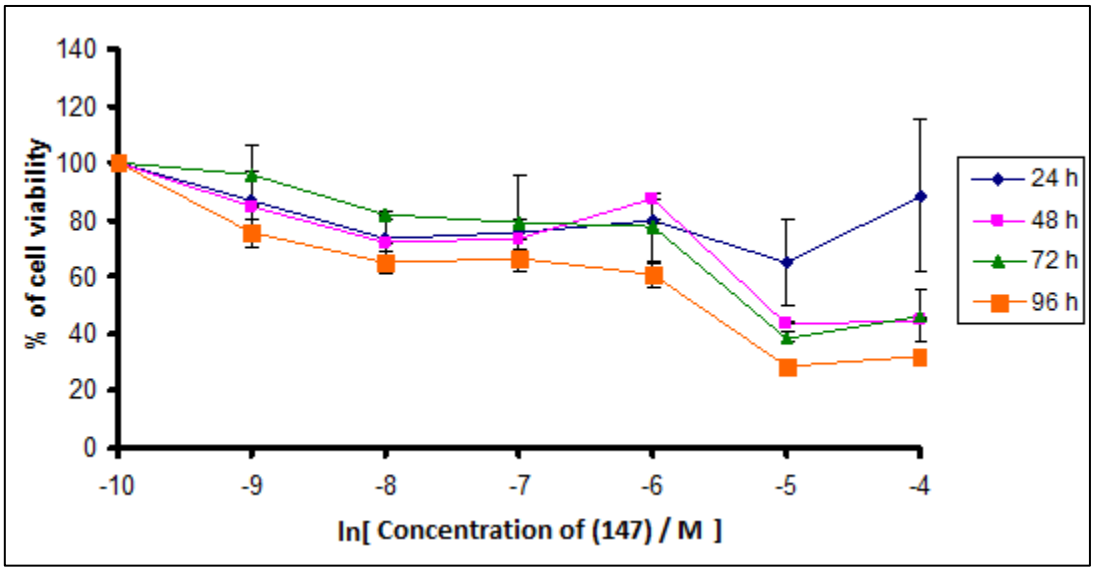
The compound was noted to be very unstable and, unfortunately, we were unable to synthesise any β-sultams. These remain a priority for future work and are described in this later section.

3.2.11 The Anti-cancer Activity of Synthesised Isothiazolo-Isoxazoles

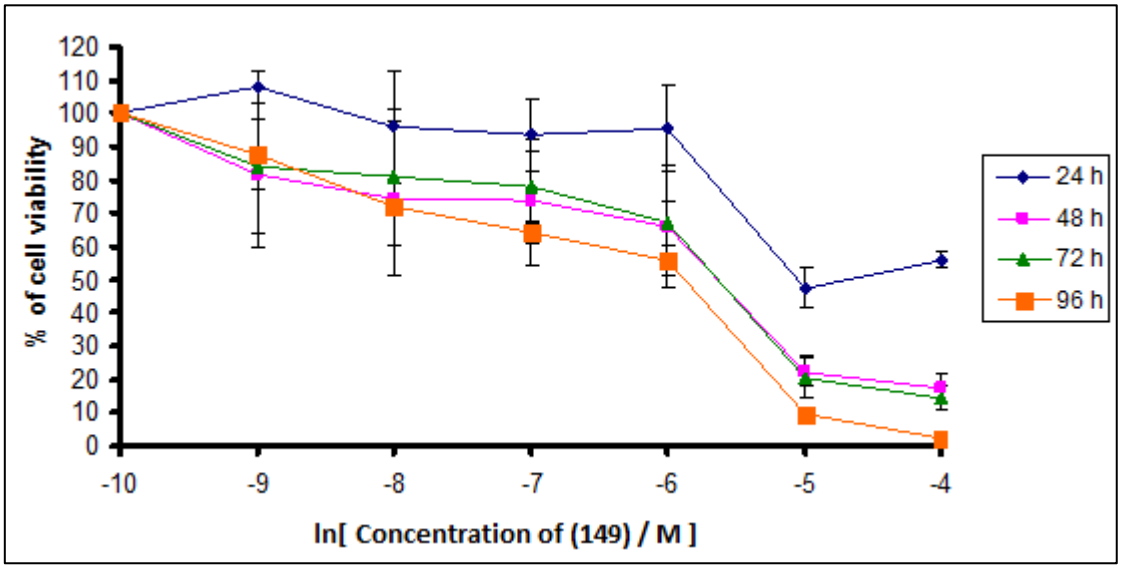
Eight of the ten synthesised isothiazolo-isoxazoles were submitted for cell proliferation studies, however only four of these **(147), (149), (151)** and **(152)** showed good ethanol solubility. The cell proliferation studies were carried out by the research group of Dr Farideh Javid at the University of Huddersfield.

MCF-7 cells, human breast (American Type Culture Collection) were grown and maintained in RPMI 1640 medium and were supplemented with 10% fetal bovine serum at 37 ^{o}C under 5% CO_2. The cells were plated in 96-well culture plates at a density of 1 x 104 cells per well and were allowed to adhere at 37 ^{o}C for 24 hours. The following day, various doses of compounds **(147), (149), (151)** and **(152)** were added to the cells and incubated for a further 24 h, 48 h, 72 h or 96 h. Following removal of the supernatant, MTT (3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) was added over 4 hours. The ability of cells to form formazan crystals by active mitochondrial respiration was determined by using a Microplate reader after dissolving the crystals in DMSO. Cytotoxicity was expressed as the relative percentage of the absorbance measured at 540nm in the control and extract-treated cells.

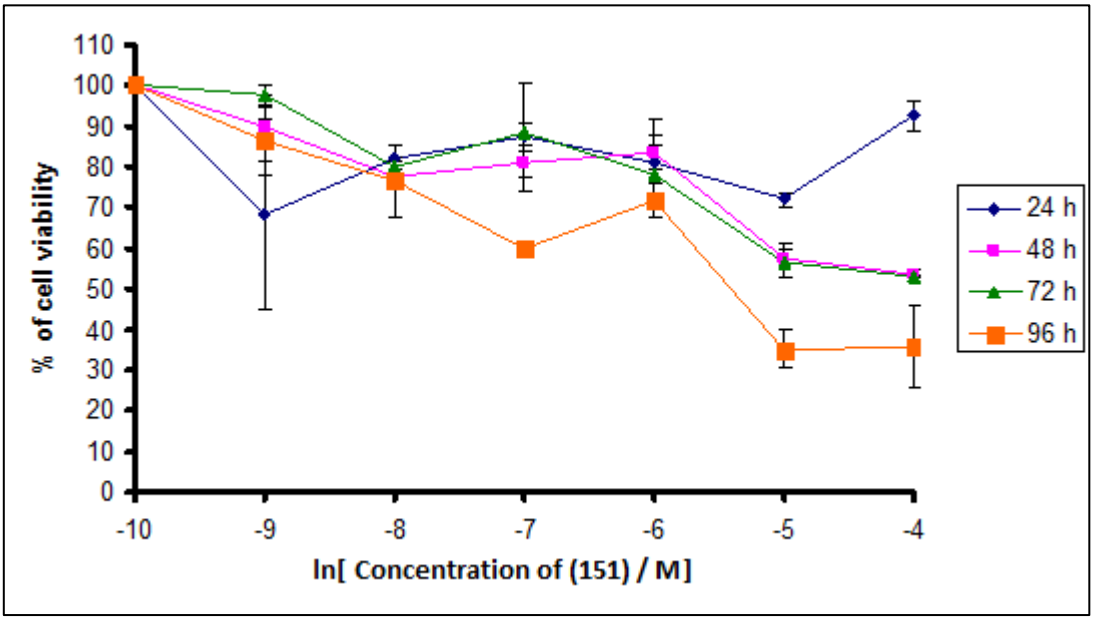
The data points in the following graphs were presented as the mean $\pm$s.e. mean of n=2, with each point representing the mean of four separate experiments of eight readings for each concentration of compound used.



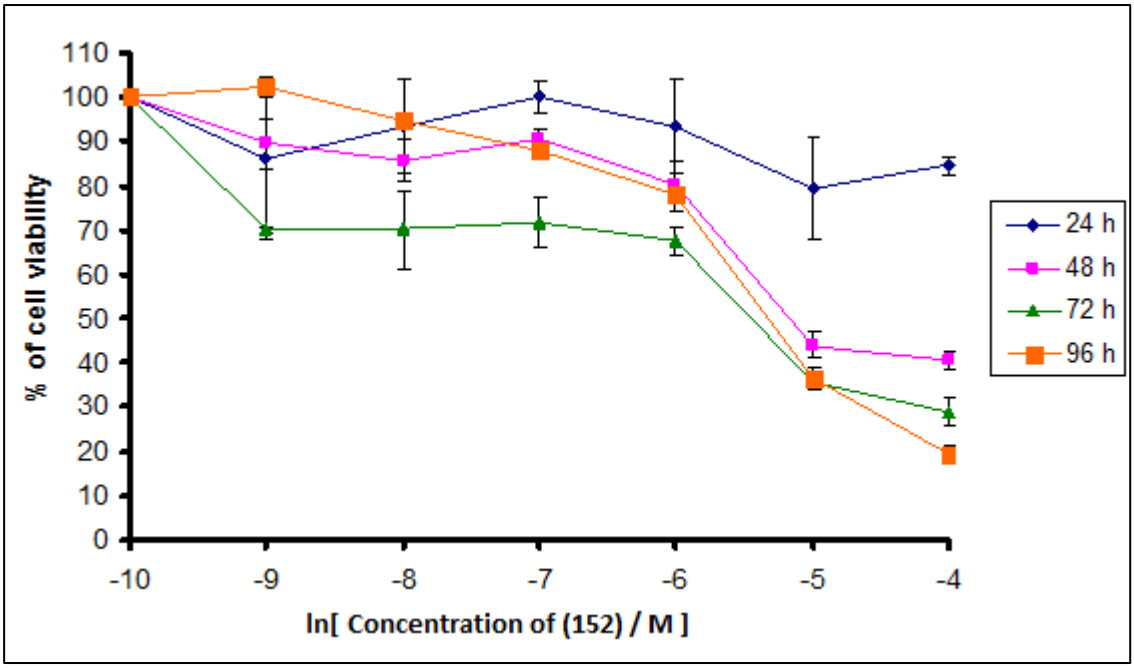
Graph 1 - The effect of **(147)** on human breast carcinoma over 24, 48, 72 and 96 hour periods (IC50 for 96 h exposure time 3.75 µM + 1.25; 72 h exposure time 6.25 µM + 1.25; 48 h exposure time 8.5 µM).



Graph 2 - The effect of **(149)** on human breast carcinoma over 24, 48, 72 and 96 hour periods (IC50 for 96 h exposure time 1.5 µM + 0.5; 72 h exposure time 3.75 µM + 1.25; 48 h exposure time 3.1 µM +2.4).



Graph 3 - The effect of **(151)** on human breast carcinoma over 24, 48, 72 and 96 hour periods (IC50 for 96 h exposure time 5.5 µM + 0.5).



Graph 4 - The effect of **(152)** on human breast carcinoma over 24, 48, 72 and 96 hour periods (IC50 for 96 h exposure time 6.5 µM + 0.5; 72 h exposure time 5.5 µM + 0.5; 48 h exposure time 8.25 µM + 0.75).

All compounds submitted for cancer cell screening showed greatest promise when exposed to cells over a 96 hour period. Compound **(149)** was the most effective, showing an IC50 of 1.5μm and total cell death at 1 x 10^{-4} M concentrations following 96 hours of cell exposure. The concentration of 1 x 10^{-5} M seems significant, with all compounds showing a sharp rise in activity at this dosage.

3.2.12 Conclusions

In conclusion, a range of hitherto unreported isothiazolo-isoxazoles have been successfully developed through a challenging, seven-step synthesis via a series of also previously unreported isothiazole-1,1-dioxides. Several of the synthesised isothiazolo-isoxazoles were tested on MCF-7 cells and shown to have promising anti-proliferation activity.

Attempts at synthesising the corresponding β-sultams were not successful and this remains a current target of our research group.

3.3 The 1,2,4-Oxadiazole Unit as Structural Feature For Asymmetric Catalysts

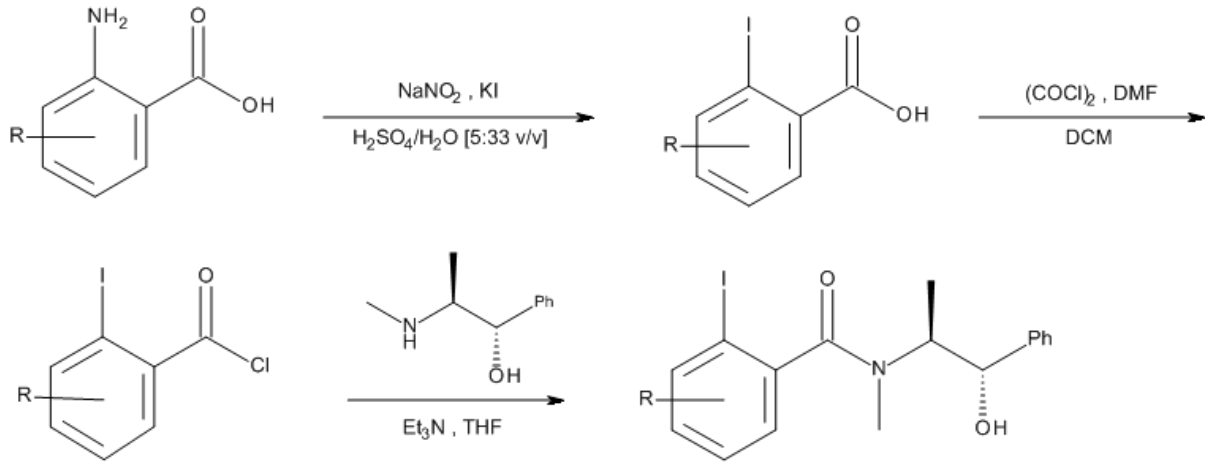
In this chapter progress towards the development of 1,2,4-oxadiazole based chiral catalysts for investigations into asymmetric catalysis will be described. These systems were developed around an aspect of this research which focussed on the discovery of hypervalent iodine catalysts. This chapter starts by describing the development of a pseudoephedrine based hypervalent iodine system and describes its use for the synthesis of lactones. On the basis of this, the chapter moves on to describe the synthesis of a potential 1,2,4-oxadiazole based chiral catalyst before describing progress towards an iodine containing analogue.

3.3.1 The Synthesis and Catalytic Activity of Pseudoephedrine based Hypervalent Iodine System

As described in the introduction, in hypervalent iodine chemistry, the iodine atom is usually in the 2-position on the arene. This, during catalysis, enables closer proximity of the chiral components of the catalyst with the substrate and in theory, offers the catalyst a better opportunity to impart its chirality by promoting a specific facial attack.

The initial chiral amine selected for this project was (1S,2S)-pseudoephedrine. This amine was selected for a number of reasons. The first was that since pseudoephedrine is a secondary amine, the product of subsequent Schotten-Baumann amide synthesis will be a fully substituted tertiary amide, reducing the likelihood of unwanted reactivity. Secondly, pseudoephedrine is relatively simple, and aside from the hydroxyl group, does not possess any reactive centres of concern. Additionally, pseudoephedrine has a strong pedigree in asymmetric synthesis, demonstrating significance as a chiral auxiliary by Myers and co-workers in 1994[122] and later in 1997, where systems including pseudoephedrine were developed further to demonstrate superiority as a chiral auxiliary in asymmetric transformations[123].

Whilst only a few substituted 2-iodobenzoic acids are commercially available, a good range of 2-aminobenzoic acid derivatives are available. Whilst the iodination of such aminoarenes involved adding another step to the synthesis, a far greater range of potential catalysts is enabled by sourcing these materials. Having selected appropriate starting materials, the synthesis of chiral iodine(I) and subsequent hypervalent iodine(III) catalysts were planned thusly:

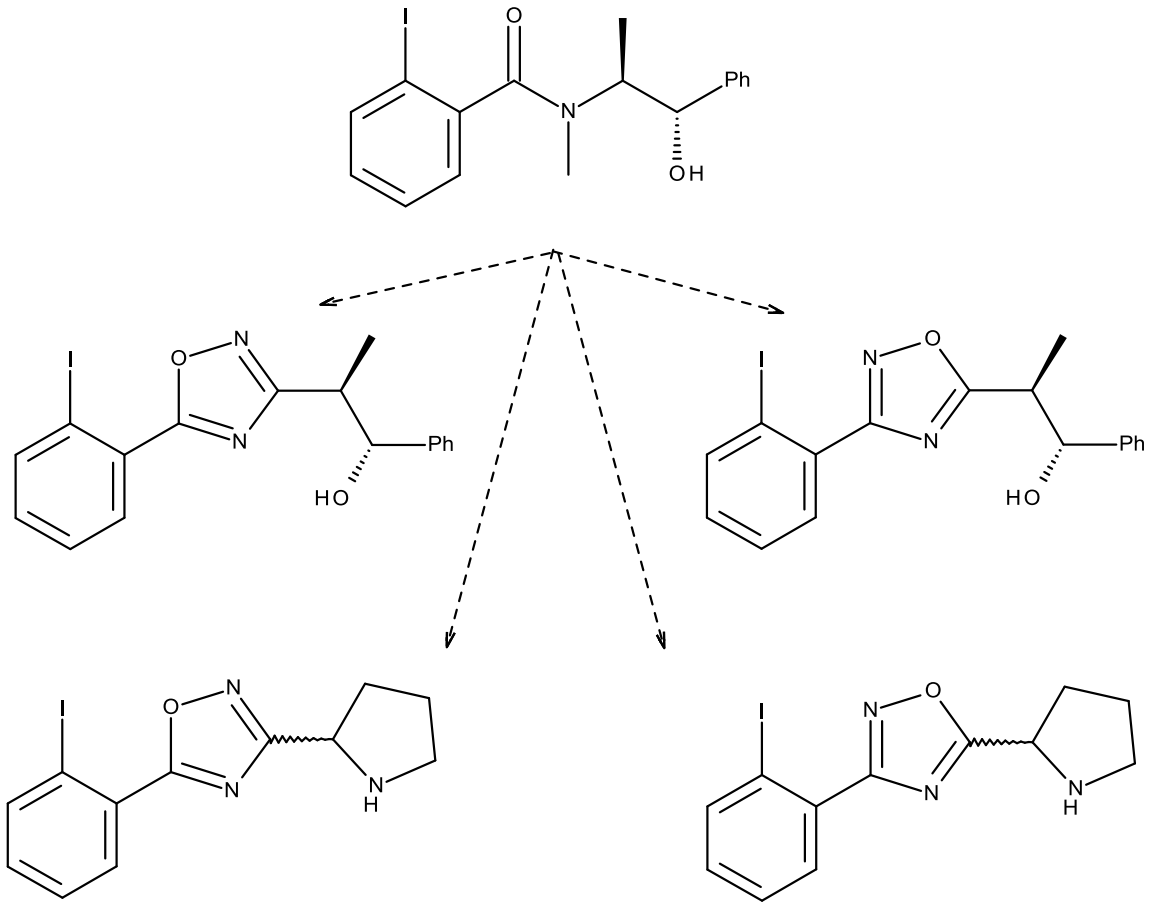


Scheme 3.60 – Target synthesis for pseudoephedrine based iodo-catalysts.

Sandmeyer reaction of the 2-aminobenzoic acid derivatives enables access to the iodinated product. Subsequent synthesis of the acid chloride from the 2-iodobenzoic acid derivative enables Schotten-Baumann coupling with (S,S)-pseudoephedrine, yielding the desired iodine(I) precatalyst.

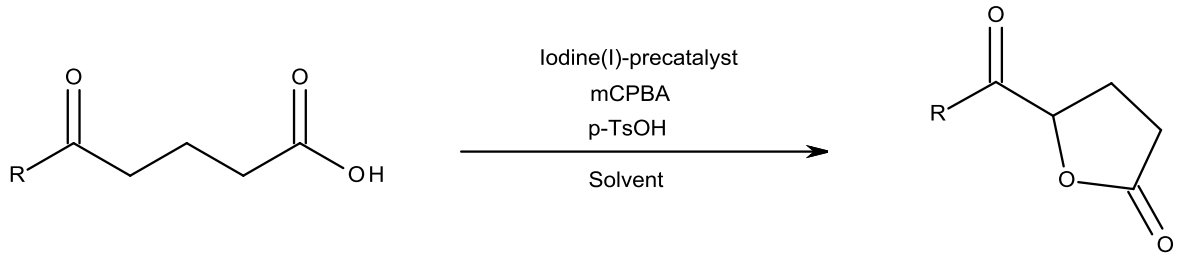
Once synthesised, it was planned that the hypervalent iodine(III) species would be generated *in-situ* in accordance with current research methods (detailed in the introduction). The oxidant selected was mCPBA, which is a proven reagent in organoiodine oxidations. The selected activating agent chosen to generate the reactive hypervalent iodine(III) species was *p*-toluenesulfonic acid.

Once the pseudoephedrine systems had been made, the idea was to produce the corresponding 1,2,4-oxadiazole systems as potential isosteres as shown in Scheme 3.61:



Scheme 3.61 – Potential array of isosteres from aryliodide-pseudoephedrine scaffold.

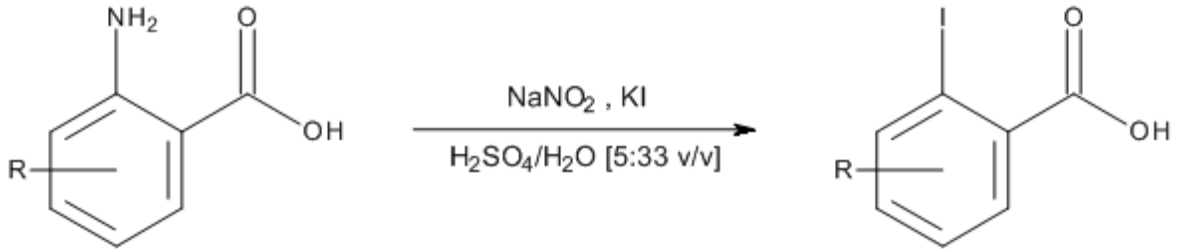
The choice of reaction for investigating these catalysts was the lactonisation reaction discussed previously:



Scheme 3.62

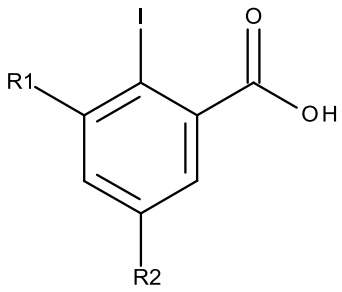
3.3.1.1 The Synthesis of Iodine(I) Precursor Materials

The iodination of the 2-aminobenzoic acid derivatives was achieved via Sandmeyer reaction.



Scheme 3.63

In strongly acidic solution, the 2-aminobenzoic acid derivatives were treated with sodium nitrite, which is protonated and dehydrated *insitu* yielding the nitrosonium ion which then reacts with the aryl primary amine yielding the diazo compound following a further dehydration. The diazo group is displaced by nucleophilic iodide and leaves as nitrogen, thereby yielding the desired 2-iodobenzoic acid derivatives as shown in Table 3.17.

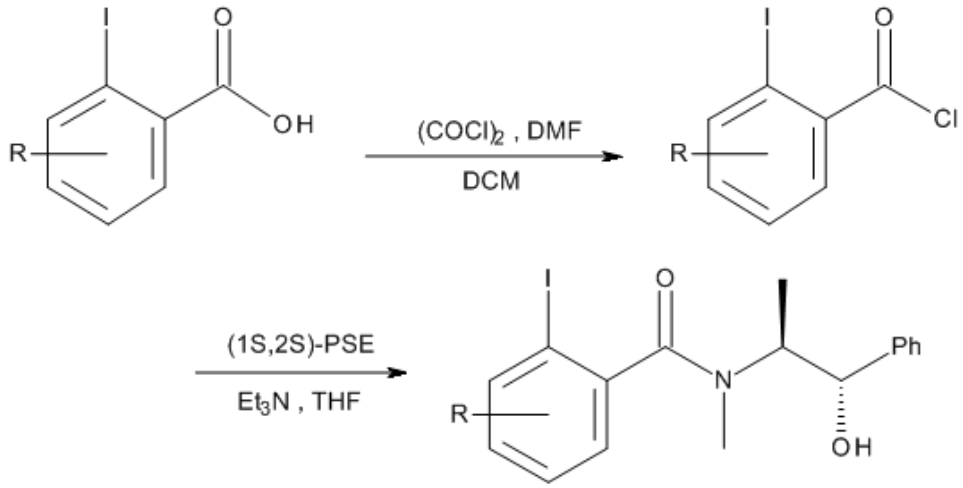


Entry	R1	R2	Product	Yield (%)
1	Me	H	**(165)**	86
2	CF_3	H	**(166)**	92
3	Me	Me	**(167)**	84
4	Me	Cl	**(168)**	91
5	Cl	H	**(169)**	86

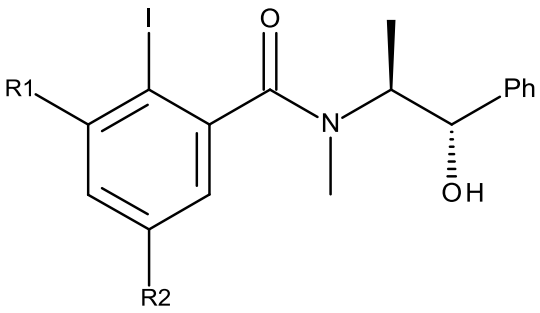
Table 3.17

3.3.1.2 The Synthesis of Chiral Iodine(I) Pre-catalysts

The 2-iodobenzoic acid derivatives were converted to the corresponding acid chlorides **(171-175)** and immediately coupled with (1S,2S)-pseudoephedrine in a standard Schotten-Baumann amide synthesis.



Scheme 3.64



Entry	R1	R2	Product	Yield (%)
1	H	H	**(176)**	52
2	Me	H	**(177)**	59
3	CF_3	H	**(178)**	65
4	Me	Cl	**(179)**	68
5	Cl	H	**(180)**	70

Table 3.18

The first iodine(I) precatalyst to be synthesised was the 2-iodophenyl derivative **(176)**. This was synthesised by chlorination of 2-iodobenzoic acid **(170)** by oxalyl chloride under catalytic DMF conditions to give the acid chloride **(171)** which was subsequent coupled by Schotten-Baumann reaction with (1S,2S)-pseudoephedrine. The product was synthesised in 52% yield.

Analysis by HRMS delivered an accurate mass for the $[M+Na]^+$ ion of 418.0289 which corresponds with the expected value of 418.0274.

Analysis by ^{1}H NMR spectroscopy suggests that this compound exists as a mixture of rotamers. This can be postulated since in the majority of cases, each ^{1}H NMR signal is partnered with a corresponding minor signal.

The synthesis of the 3-methyl-2-iodophenyl derivative **(177)** was achieved via acyl chlorination of **(165)** and subsequent coupling with (1S,2S)-pseudoephedrine in 59% yield.

The structure of this product was confirmed by HRMS which delivered an accurate mass of 432.0427 for the $[M+Na]^+$ ion, with the expected mass determined to be 432.0431.

The ^{1}H NMR spectrum shows doublets at δ0.95, δ1.12, δ1.15 and δ1.44, each of which is likely to correspond to the stereocentre methyl protons of one rotamer. Three of these signals are major and one minor (δ0.95) suggesting three rotameric forms are present. The integration ratios of these signals suggests a 3:3:3:1 relationship of rotamers. Singlets at δ2.48, δ2.49 and δ2.60 originate from the aryl methyl protons. The signal at δ2.48 is significantly stronger than those at δ2.49 and δ2.60, which are of the same intensity. This may suggest that this stronger signal is masking that of the minor rotamer. Singlets at δ2.80, δ2.86, δ3.16 and δ3.17 correspond to the N-methyl protons. The region between δ3.5 to δ5.5 is busy with signals. These are likely to originate from each of the two stereocentre CH protons. Signals at δ4.54, δ4.61, δ4.71 and δ4.88 resonate as doublets and thus correspond to the benzylic protons. Multiplets at δ3.67-3.77, δ4.24-4.34, δ4.96-5.05 and δ5.07-5.21 originate from the remaining CH proton. The rotameric effect is once again observed and in approximately the same ratio as that suggested by other signals.

The 3-trifluoromethyl derivative precatalyst **(178)** was successfully synthesised from **(166)** via the usual protocol in 65% yield.

The structure of this product is supported by ^{1}H NMR spectroscopy, which again appears to show the existence of four rotamers. Three rotamers of this compound are major, with one minor rotamer and these exist in an approximate 6:6:6:1 ratio. Four doublets at δ0.96, δ1.16, δ1.18 and δ1.47

corresponding to the stereocentre methyl protons demonstrate this ratio. Singlets at δ2.62, δ2.80, δ3.19 and δ3.21 correspond to the N-methyl protons, which demonstrate a similar ratio of rotamers.

The structure was confirmed by HRMS which delivered an accurate mass for the $[M+Na]^+$ ion of 486.0148 corresponding exactly with the calculated figure.

The 3-chloroaryl derivative precatalyst **(180)** was successfully synthesised in 70% yield.

The structure was confirmed by HRMS. For the expected value of 451.9885, determination of the accurate mass of the $[M+Na]^+$ ion delivered an exact match.

The ^1H NMR spectrum once again reveals the presence of rotamers strongly suggested by doublets at δ0.97, δ1.13, δ1.15 and δ1.45 which originate from the stereocentre methyl protons. The signal at δ0.97 is representative of the minor rotamer which appears to exist in a 6:6:6:1 ratio with the three major rotamers. The singlets at δ2.63, δ2.83, δ3.17 and δ3.20 originate from the N-methyl protons, the integrations of which suggest a similar ratio of rotameric forms. Doublets at δ4.57, δ4.73 and δ4.94 correspond to the benzylic stereocentre.

The 5-chloro-3-methyl pre-catalyst derivative **(179)** was successfully synthesised from **(168)** in 68% yield.

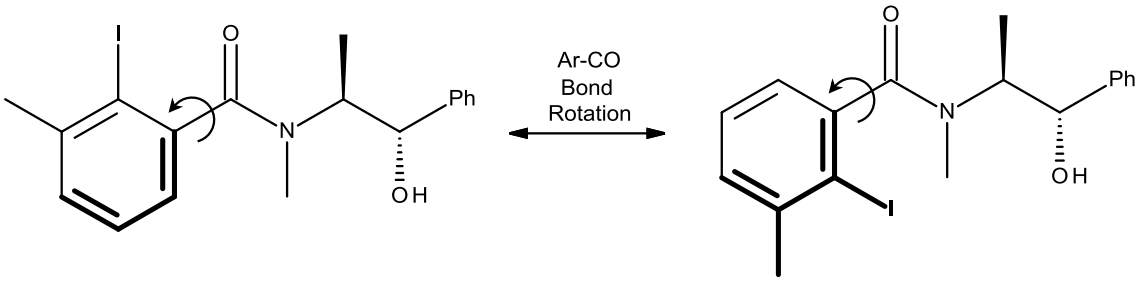
Confirmation of the product was achieved by HRMS which delivered an accurate mass of the $[M+Na]^+$ ion of 466.0041 which correlated exactly with the theoretical figure for this ion.

The ^1H NMR spectrum showed doublets at δ0.95, δ1.12, δ1.14 and δ1.38 corresponding to the methyl protons on the stereocentre and again suggests the presence of three major rotamers and one minor in a 6:6:6:1 ratio. The protons of the arene methyl group appear at δ2.41, δ2.61 and δ2.43, the latter of which features two overlapping signals. Doublets which are likely originate from the benzylic CH proton are visible at δ4.49, δ4.66 and δ4.84. The other stereocentre proton resonates as a series as of complex signals at δ3.55-3.63, δ4.24-4.38 and δ4.95-5.04.

The 3,5-dimethyl-2-iodobenzoic acid derivative **(167)** was not effectively coupled to pseudoephedrine following analysis by ^1H NMR spectroscopy. No further attempts were made to synthesise this particular derivative.

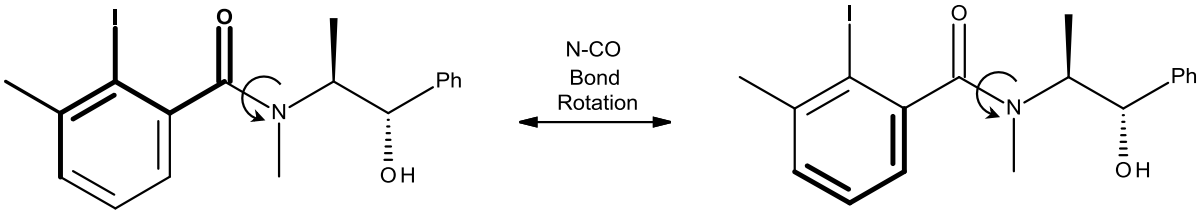
3.3.1.3 The Rotameric Nature of Pseudoephedrine Based 2-Iodoaryl Precatalysts

As seen from analysis by ^{1}H NMR spectroscopy, the pseudoephedrine based catalysts synthesised in this project exist as up to four rotamers, some in greater prevalence than others. Reviewing the literature, it has been seen previously with tertiary aromatic amides, even with a small degree of steric constraint from substitution about the arene, that two rotational conformers about the arene-carbonyl bond are possible[124]. Taking **(177)** as an example catalyst (Scheme 3.65), the two potential aryl-carbonyl rotamers are shown below:



Scheme 3.65 – Ar-CO bond rotation with dihedral angle of 90°.

It has also been observed that for less hindered tertiary aryl amides, that rotation about the carbonyl-nitrogen bond is possible[124], as shown in Scheme 3.66.



Scheme 3.66 – N-CO bond rotation with dihedral angle of 90°.

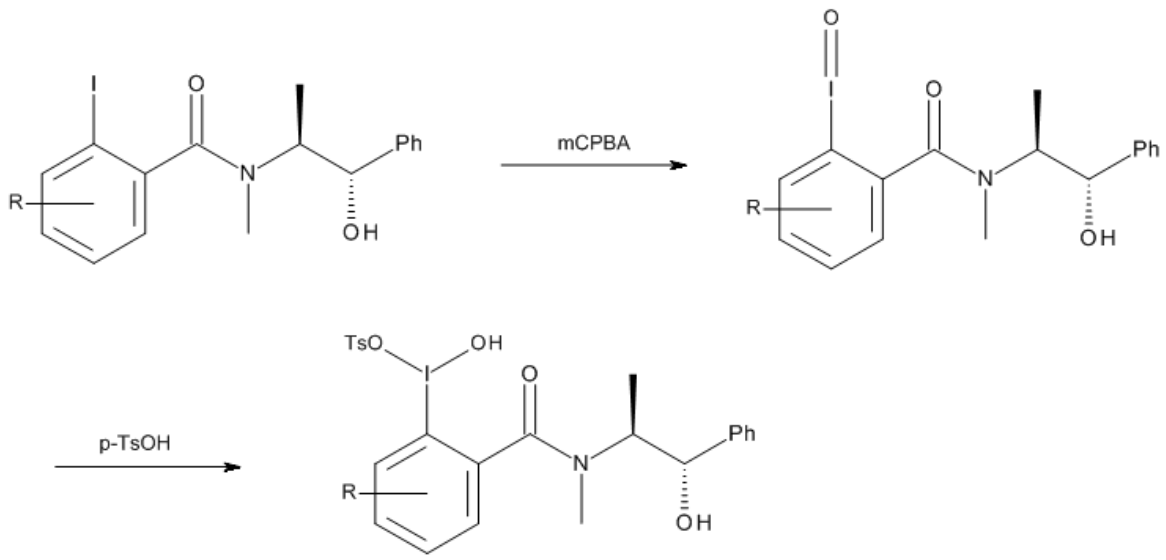
Given the rotation about the Ar-CO bond and the rotation about the N-CO bond, the pseudoephedrine compounds synthesised can exist in up to four rotational conformers. This is concurrent with much of the ^{1}H NMR analysis, which has suggested the presence of four rotamers, often with one as a minor component and the remaining three in approximately the same ratio as

major conformers. The observation of rotamers was less significant with catalyst **(176)**. The lack of aryl substitution with this catalyst reduces the number of potential rotamers to two as was observed by ^{1}H NMR analysis.

3.3.1.4 The Catalytic Activity of Pseudoephedrine Based 2-Iodoaryl Precatalysts

As described in the introduction, reactive hypervalent iodine(III) reagents are usually synthesised by firstly oxidising the iodide to the iodosyl iodine(III) compound, followed by the addition of an organic acid such as AcOH or TFA to create the active iodine(III) species. Both of these steps are often conducted *in-situ*. In order to make this species catalytic, the presence of a co-oxidant is required to re-oxidise the reacted organoiodine back to iodine(III).

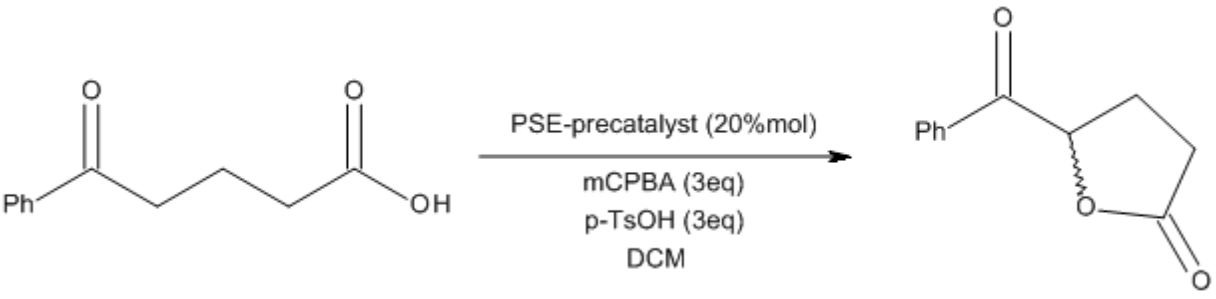
The oxidant selected for the generation of the hypervalent iodine(III) catalysts was mCPBA and the acid additive selected was *p*-toluenesulfonic acid.



Scheme 3.67

3.3.1.5 Synthesis of 5-Benzoyltetrahydrofuran-2-one

As described in the introduction, there are a wealth of potential asymmetric reactions in which hypervalent iodine catalysts can be screened. Given the poor results obtained by Wirth and co-workers with the lactonisation reaction first examined by Moriarty in 1990[101] and also the distinct lack of asymmetric induction reported from other HVI research groups, this reaction provides the perfect screening reaction.



(181)

Scheme 3.68

The lactonisation of 5-oxo-5-phenylpentanoic acid to the tetrahydrofuranone **(181)** was successfully achieved with all described PSE catalysts, in 58-72% yield. The catalysts were screened in 20%mol concentrations. A high excess of mCPBA and *p*-TsOH was used to ensure reproduction of the reactive iodine(III) species. In all cases the catalyst was retrievable, post-reaction.

The structure of the product is strongly suggested by ^{1}H NMR spectroscopy which shows the two sets of tetrahydrofuranone CH_2 protons as a complex multiplet at δ2.41-2.63. The stereocentre proton is observable as a complex signal at δ5.78-5.84. The protons of the mono-substituted benzene ring are observable in the expected pattern at δ7.52, δ7.64 and δ7.95-8.01.

The structure was further confirmed by ^{13}C NMR spectroscopy which clearly showed the tetrahydrofuranone CH_2 carbons at δ25.37 and δ27.21. The stereocentre carbon resonates as a signal at δ78.66 with the four aromatic carbons at δ129.16, δ129.42, δ133.93 and δ134.70. The compound contains two carbonyl carbons at δ194.72 and δ176.69.

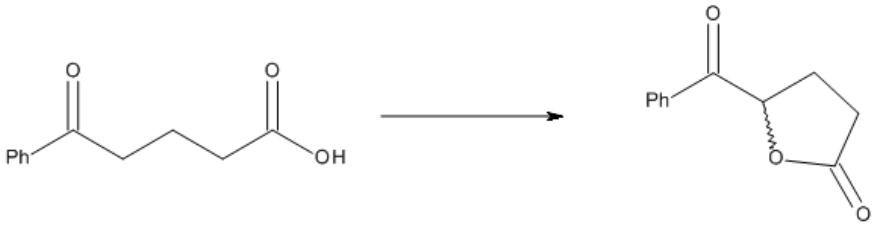
The structure of the cyclised product is fully confirmed by HRMS which delivered an accurate mass of the $[M+Na]^+$ ion of 213.0516 with the theoretical figure determined to be 213.0522.

This data is consistent with literature reports[101].

3.3.1.6 Asymmetric Induction by (1S,2S)-Pseudoephedrine Based Hypervalent Iodine(III) Catalysts

The purified lactone enantiomers were separated by HPLC analysis using a Hewlett-Packard Series 1050 chromatogram with a Chiralpak I-B column. Conditions for separation were 85% hexane:15% IPA solvent system, with a flow rate of 1ml/min.

The results of asymmetric induction by the (1S,2S)-pseudoephedrine based hypervalent iodine(III) catalysts are tabulated below:



Entry	Catalyst	Yield (%)	e.e (%)
1	**(176)**	66	14
2	**(177)**	70	53
3	**(178)**	58	7
4	**(179)**	72	48
5	**(180)**	67	29

Table 3.19

Pleasingly all catalysts induced asymmetry in the lactonisation reaction. Catalysts **(177)** and **(179)** performed most notably, delivering good e.e's of 53% and 48%, respectively, greater than any reported in the literature for this reaction.

The most apparent observation when considering the critical structural features of the catalysts **(177)** and **(179)** is the apparent necessity of the methyl group at the 3-position of the iodoarene. Without this group the catalyst performs less well, delivering an e.e of just 14%.

Upon the introduction of a chlorine atom at the 5-position **(179)**, retaining the methyl group at the 3-position, the activity of the catalyst is slightly reduced giving an e.e. of 48%.

Following the promising results obtained with catalyst **(177)**, a solvent screen was conducted.

Entry	Solvent	Yield (%)	e.e (%)
1	DCM	70	53
2	$CHCl_3$	42	36
3	1,2,-DCE	48	49
4	TFE	50	32
5	MeCN	83	27
6	EtOAc	-	-
7	Et_2O	20	36
8	IPA	-	-
9	MeOH	-	-
10	PhMe	27	44
11	C_6H_{14}	12	6

Table 3.20 – Results of solvent screen with catalyst **(177)**.

Whilst the results of the solvent screen were interesting, unfortunately no improvement in enantiomeric excess was observed, with the original DCM solvent proving to be the most suitable, although DCE and toluene also proved promising.

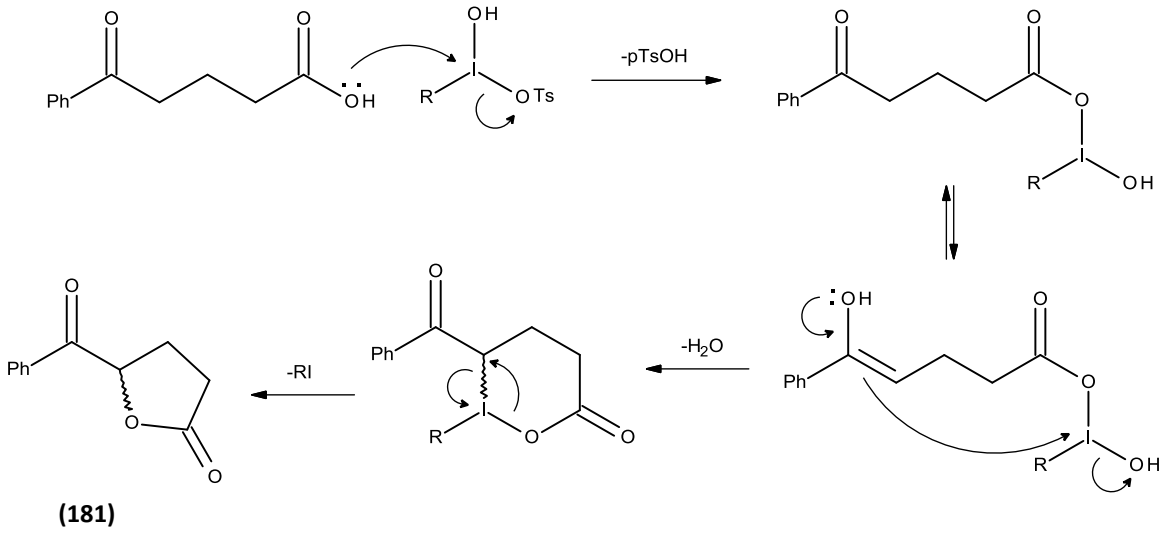
Following the determination that DCM was the most effective solvent for inducing selectivity in this reaction using compound **(177)** as catalyst, a brief temperature screening was conducted. No improvement in enantiomeric excess was observed.

Entry	Temperature (^{o}C)	Yield (%)	e.e (%)
1	0	16	49
2	25	70	53
3	40	56	40

Table 3.21 – Results of temperature screen for **(177)** in DCM.

A catalyst loading screen was not conducted due to time constraints.

A plausible mechanism by which the synthesised hypervalent iodine(III) compound catalyses the lactonisation is shown:



(181)

R = Aryl-PSE scaffold

Scheme 3.69

Substitution of tosylate from the nucleophilic attack of the carboxylic oxygen of the substrate at the hypervalent iodine(III) centre results in the generation of the acylated iodane and the net loss of toluenesulfonic acid. Cyclisation by further nucleophilic attack of the acylated iodane centre from the enol functionality of the substrate prompts the elimination of a molecule of water and the generation of a 6-membered iodoxanone intermediate. Reductive elimination of the catalyst and subsequent ring contraction generates the tetrahydrofuranone, lactonised product **(181)**.

It is imaginable that during the enantiodetermining, cyclisation step, the pseudoephedrine scaffold may successfully hinder attack of the iodane from the enol at one face more so than the other. Bond rotation about the iodine-arene bond enables the pseudoephedrine scaffold to partially block one face over the other. However, it is very difficult to suggest reasons how the 3-methyl group contributes so significantly to preferential attack of one face of the iodane over the other, possibly implying its influence may be electronic and not steric.

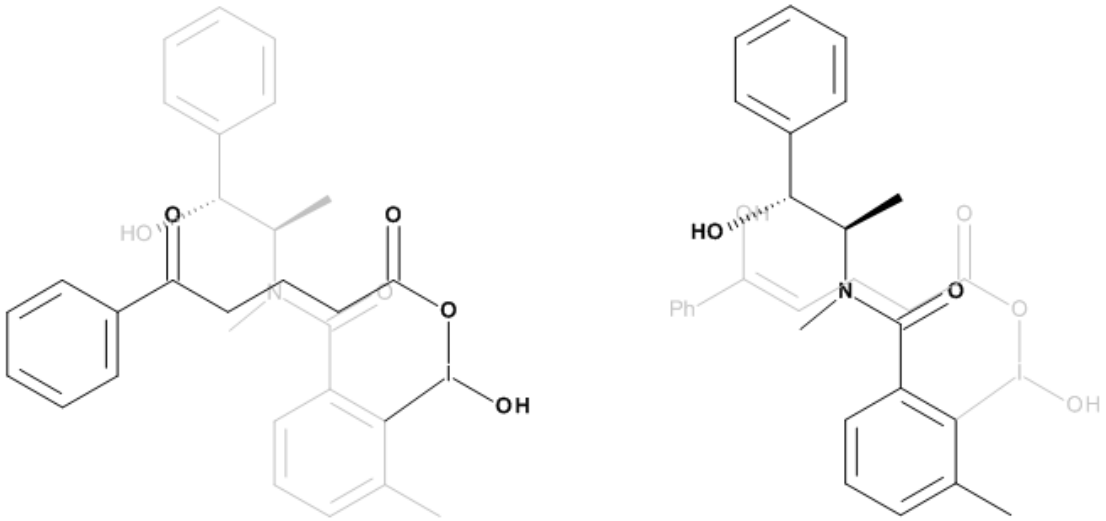


Figure 3.38 – Diagram illustrating the steric results of iodine-arene bond rotation.

In summary, it has been demonstrated that a range of iodoarenes featuring the chiral scaffold of (1S,2S)-pseudoephedrine induce promising asymmetry in the lactonisation of 5-oxo-5-phenylpentanoic acids.

3.3.2 The Synthesis and Catalytic Activity of L-Proline Based Chiral 1,2,4-Oxadiazole Systems

The target of this part of the project was to synthesise a potential catalytic system featuring the 1,2,4-oxadiazole as a structural feature. L-Proline was selected as the unit with which to provide the system with chirality. L-Proline was also selected since it has been the subject of much research as a catalyst by virtue of its versatility to act as an acid, base and nucleophile[89].

The initial target of this project was an L-proline-1,2,4-oxadiazole–pyridine type system, as shown below; chosen by virtue of our interesting results with ligands based on this motif. Ultimately, our aim was to replace the pyridine ring with an ortho-iodo substituted aryl ring.

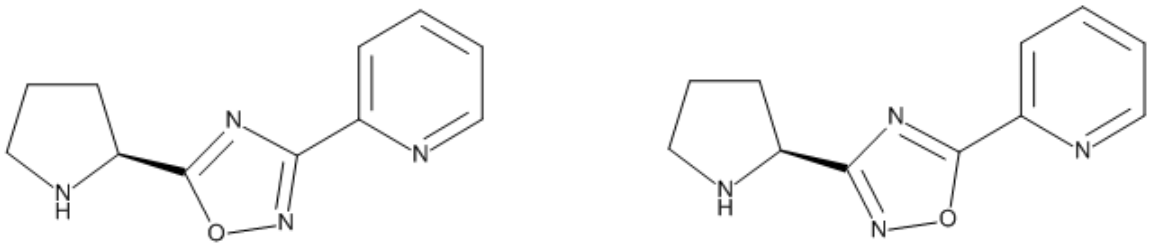


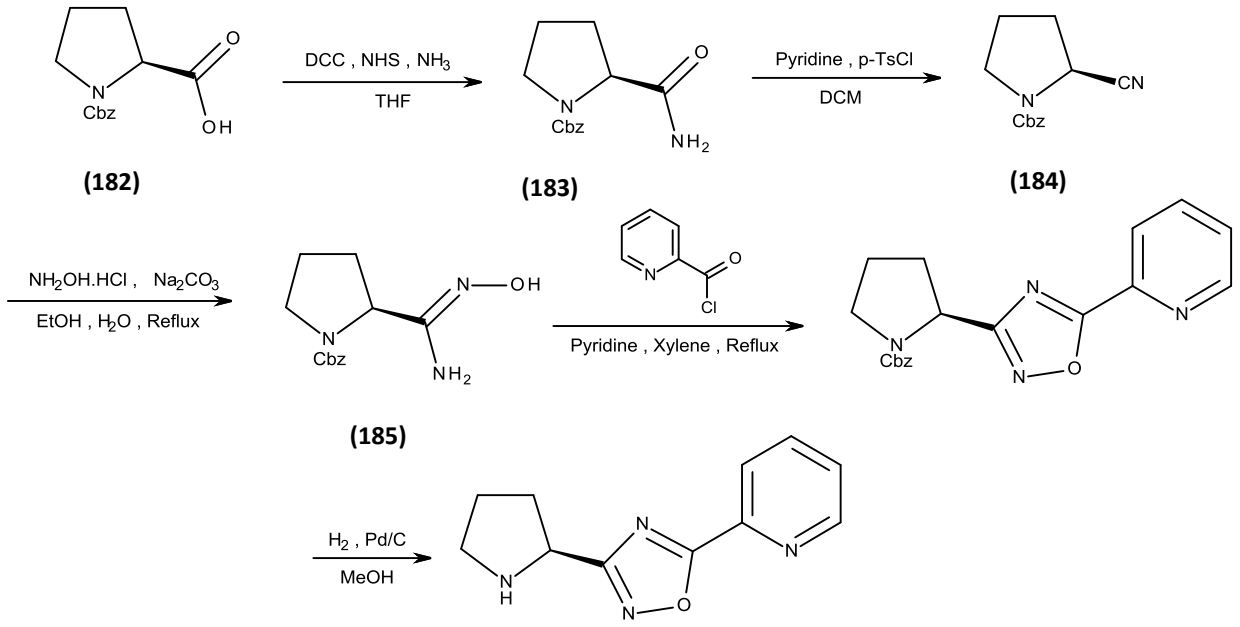
Figure 3.39 – Early potential 1,2,4-oxadiazole catalyst targets.

Four routes to the compounds shown in Figure 3.39 were explored and these are discussed below.

3.3.2.1 Route One; Via Reaction of Cbz-Protected-L-Proline Amidoximes with Pyridine Acid Chlorides

In order to prevent unwanted reactivity towards the acid chloride, it was necessary to select an N-protected L-proline. The first of these to be explored was Cbz-L-proline.

All previous syntheses of 1,2,4-oxadiazoles to this point had been achieved via the acid chloride/amidoxime reaction route. Thus, this route was deemed a sensible initial focus and is detailed below:



(182) **(183)** **(184)** **(185)**

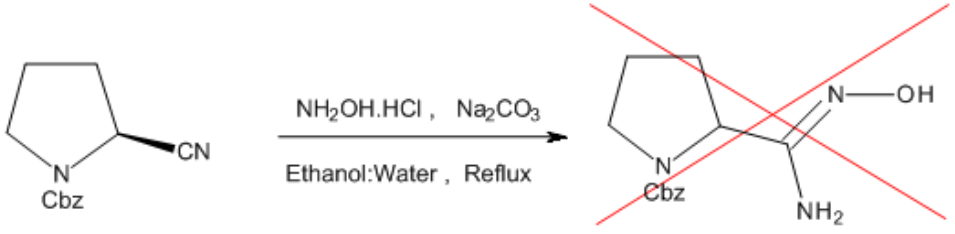
Scheme 3.70

The conversion of carboxylic acid **(182)** to primary amide **(183)** was achieved in 49% yield by N,N'-dicyclohexylcarbodiimide coupling of ammonia. Activation of the DCC was achieved using an excess of N-hydroxysuccinimide, as reported by Ley[117].

The conversion of the primary amide **(183)** to nitrile **(184)** was achieved via reaction with *p*-toluenesulfonyl chloride in the presence of pyridine in 48% yield.

Analysis by NMR spectroscopy showed a product that was consistent with that reported by Ley[117].

Efforts to synthesise the amidoxime **(185)** using the classic hydroxylamine method, were not successful and subsequently this route towards the desired system was abandoned.

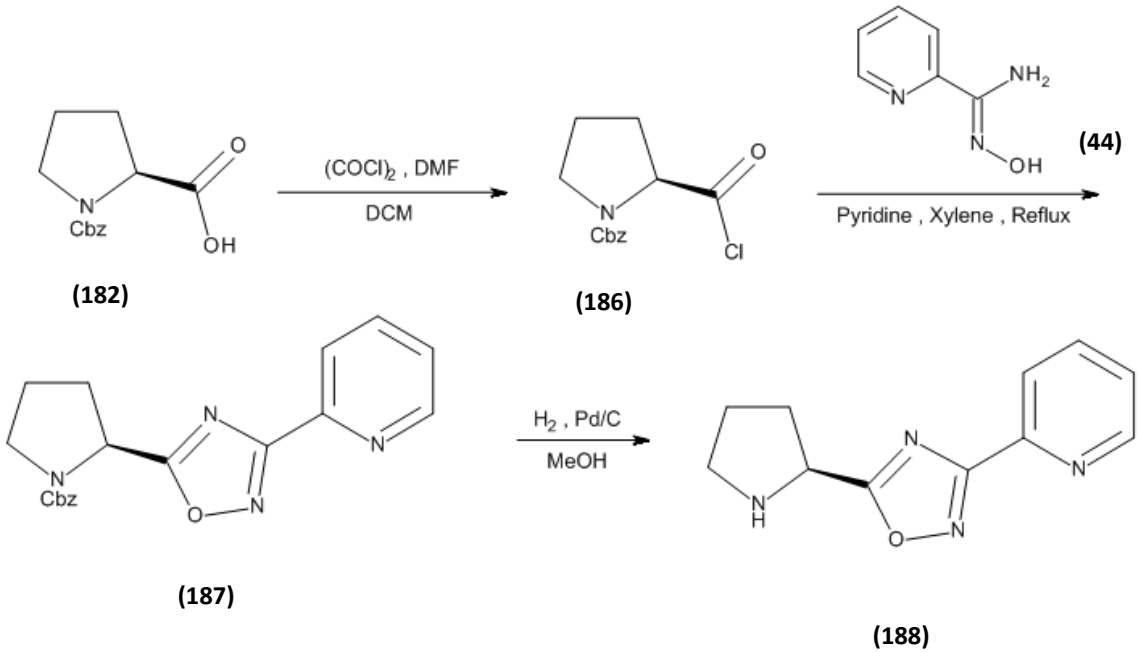


(184) **(185)**

Scheme 3.71

3.3.2.2 Route Two; Via Reaction of the Cbz-Protected-L-Proline Acid Chloride with Pyridine Amidoxime

The second route towards the synthesis of an L-proline-1,2,4-oxadiazole system involved reversing the acid chloride/amidoxime conditions, as shown below:



Scheme 3.72

The Cbz-protected protected system **(187)** was successfully synthesised in 55% yield. This was achieved through conversion of Cbz-L-proline **(182)** to the corresponding pyrrolidine-2-carbonyl chloride **(186)** by chlorination with $(COCl)_2$ in the presence of catalytic DMF and subsequent coupling with pyridine-2-amidoxime **(44)** in the presence of pyridine in refluxing xylene.

The structure of the product was confirmed by NMR spectroscopy, the ^{1}H NMR spectrum of which shows the six pyrrolidine CH_2 protons as the multiplet at δ1.99-2.51 integrating as four protons, and the two multiplets at δ3.55-3.71 and δ3.76-3.86, each integrating as one proton for those adjacent to the pyrrolidine nitrogen. A signal at δ5.12 accounts for the Cbz group CH_2 protons and adjacent to this signal at δ5.29 is an apparent doublet of doublets of doublets representing the stereocentre proton. All of the aromatic protons were present in the expected regions, with the complexity of the peaks suggesting that the compound exists as a mixture of rotamers.

The ^{13}C NMR spectrum is particularly interesting since each signal appears to be doubled, or shadowed, by an almost identical signal. Assuming each of these pairs of signals corresponds to one

carbon atom, the spectrum is fully consistent with that which one would expect for this structure, but that it is present in two major rotameric forms.

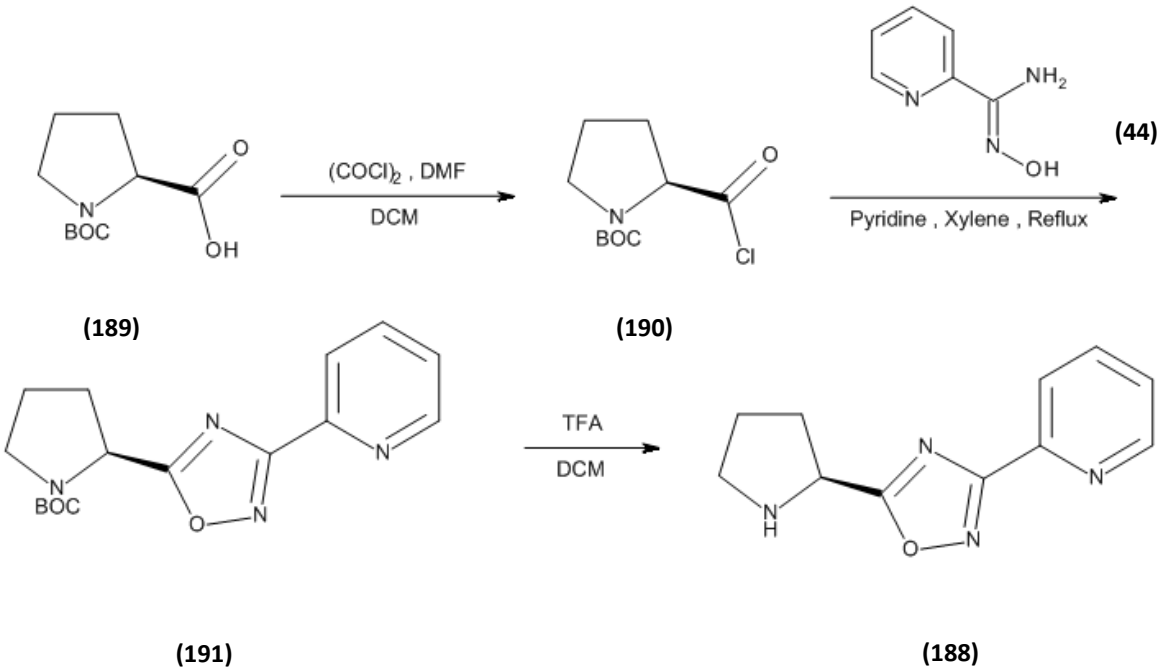
This structure was confirmed by HRMS which delivered an accurate mass of 373.1271 for the $[M+Na]^+$ ion, correlating well with the calculated value of 373.1266.

The N-Cbz deprotection to **(188)** was attempted under standard catalytic hydrogenation conditions. This reaction was not successful despite several attempts under a variety of conditions (including an attempted HBr reaction). In all cases, the hydrogenation led to the destruction of the 1,2,4-oxadiazole ring with analysis by TLC showing many spots. Attempts to purify the crude products by column chromatography were hindered with many of the spots too close and too dilute to permit effective separation. However, persistent purification did enable separation of one particular spot which on all occasions appeared to be the more major of the many products.

The ^{1}H NMR data suggests that both the pyridine and pyrrolidine units are intact, with loss of the Cbz group also apparent, with the broad signal at δ6.76 likely denoting the presence of the pyrrolidine NH proton. A C-H at δ5.23 integrates as one proton and may indicate the CH on the chiral centre. The ^{13}C NMR spectrum was not consistent with the expected structure. This, together with the very low yield and literature evidence that the 1,2,4-oxadiazole ring may have been reduced under these conditions, meant that this route was not explored further.

3.3.2.3 Route Three; Via Reaction of Boc-Protected-L-Proline Acid Chloride with Pyridine Amidoxime

The third attempt at synthesising the desired compounds involved a switch in starting material from Cbz-L-proline to Boc-L-proline since it was envisaged that Boc removal would be less problematic than removing Cbz from such systems, since hydrogenation could be avoided.



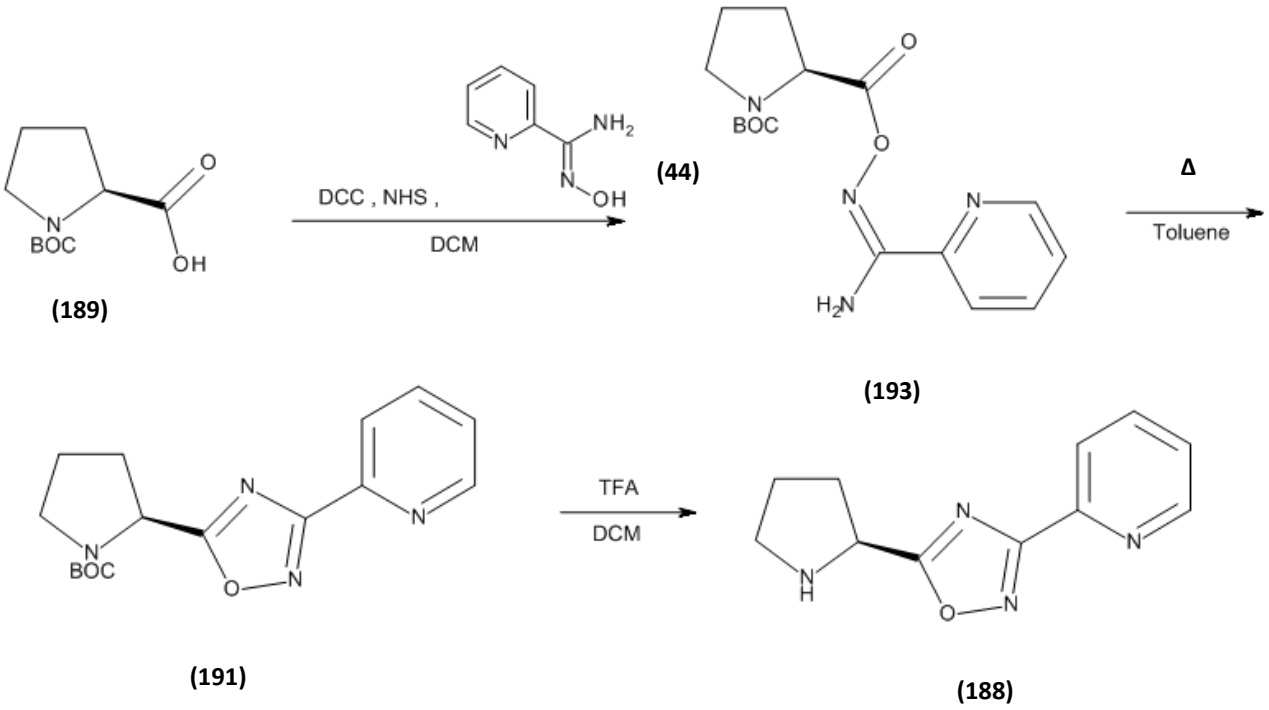
Scheme 3.73

The acid chloride **(190)** was synthesised with predictable simplicity. However, reaction in refluxing xylene with pyridine-2-amidoxime **(44)** resulted in an unworkable mixture upon cooling to room temperature. Having attempted to work-up the mixture with various washes and extraction, no sensible or identifiable amount of product was isolated.

These practical problems led to attempts with alternative solvents such as toluene. However, the same, intractable mixture was observed, and rendered this an unfeasible synthesis to pursue further.

3.3.2.4 Route Four; Via DCC Mediated Coupling Reaction of Boc-Protected-L-Proline with Pyridine Amidoximes

Following the difficulties with acid chloride-amidoxime couplings involving these compounds, it seemed sensible to pursue alternative coupling conditions. The most attractive initially was via the DCC/NHS conditions, which had proven successful in coupling N-Cbz-L-proline to ammonia, discussed earlier, and shown below in Scheme 3.74:



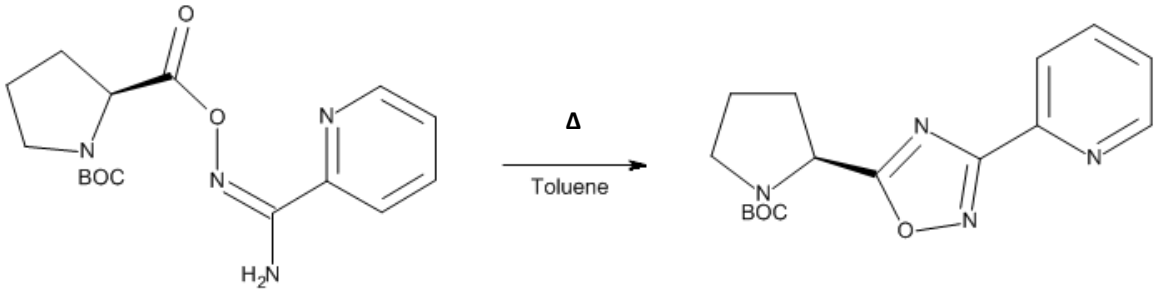
(189) **(193)** **(191)** **(188)**

Scheme 3.74

DCC mediated coupling of N-boc-L-proline **(189)** to pyridine-2-amidoxime **(44)** was achieved in DCM at room temperature using NHS as activating agent.

Analysis by ^{1}H NMR spectroscopy showed evidence for the *O*-acylated compound **(193)**. The presence of the Boc protons was confirmed by strong signals at δ1.38 and δ1.44, rather than just one signal. The NH_2 protons were observed as a broad singlet at δ6.45. The remainder of the spectrum observed was in accordance with previous similar structures in this sub-chapter. The strong evidence for this structure by ^{1}H NMR spectroscopy was deemed sufficient to proceed to ring closure.

3.3.2.4.1 Synthesis of 5-[(2S)-N-boc-pyrrolidin-2-yl]-3-(2-pyridyl)-1,2,4-oxadiazole



(193) **(191)**

Scheme 3.75

Cyclodehydration of the *O*-acylated intermediate **(193)** was successfully achieved by using toluene at reflux in 82% yield over the two steps.

Confirmation of the ring-closed structure **(191)** was determined largely by NMR spectroscopy, the ^{1}H spectrum of which shows loss of the broad singlet at δ6.45, previously corresponding to the NH_2 protons. The pyridyl and pyrrolidinyl protons remain intact with a moderate shift downfield. The Boc protecting group remains intact also. The highly complex nature of many of the signals suggests that this compound, like the pseudoephedrine and Cbz-protected analogues, exists as a mixture of rotamers.

The ^{13}C NMR spectrum showed the presence of the Boc carbonyl at δ181.47. The spectrum also showed the presence of seven aromatic carbons. Interestingly, duplication of signals is observed with the majority of those present in this spectrum, confirming the presence of two rotamers.

The structure of the cyclodehydrated product **(191)** was confirmed by HRMS which delivered a measured value of 339.1429 with the theoretical mass of this ion calculated to be 339.1428.

3.3.2.4.2 Synthesis of 3-(2-pyridyl)-5-[(2S)-pyrrolidin-2-yl]-1,2,4-oxadiazole

(191) **(188)**

Scheme 3.76

The removal of the Boc-protecting group from the pyrrolidine unit of **(191)** was successfully achieved by treatment with trifluoroacetic acid in dichloromethane. The free pyrrolidine-oxadiazole-pyridine system **(188)** was synthesised in 83% yield.

As per the usual trend with all of the proline-oxadiazole-pyridine systems discussed previously, the reaction did not proceed with immediate success. The removal of Boc protecting groups via treatment with TFA is well documented in the literature with the use of low concentration dilutions in DCM popular, with 1:1 mixtures the general upper limit. Treatment of the above Boc-protected system with 1:1 DCM:TFA resulted in destruction of the 1,2,4-oxadiazole. Following efforts to remove the Boc protecting group in many other concentrations of TFA:DCM systems, deprotection in good yield (83%) was finally achieved with a 20:1 DCM:TFA system.

Analysis by ^{1}H NMR spectroscopy reveals the disappearance of all signals corresponding to the Boc group protons and the appearance of a broad signal at δ8.80-10.20 corresponding to the pyrrolidine freebase NH proton. Following removal of the Boc protecting group, all signals of the spectrum simplify, from highly complex multiplets to more defined signals. This confirms that previous structures with pyrrolidine N-protection in place existed as two rotameric forms, causing complexity of the ^{1}H NMR spectrum.

The ^{13}C NMR spectrum also provides strong support for the desired structure, although a high aromatic carbon signal at δ182.79 provided a little cause for concern.

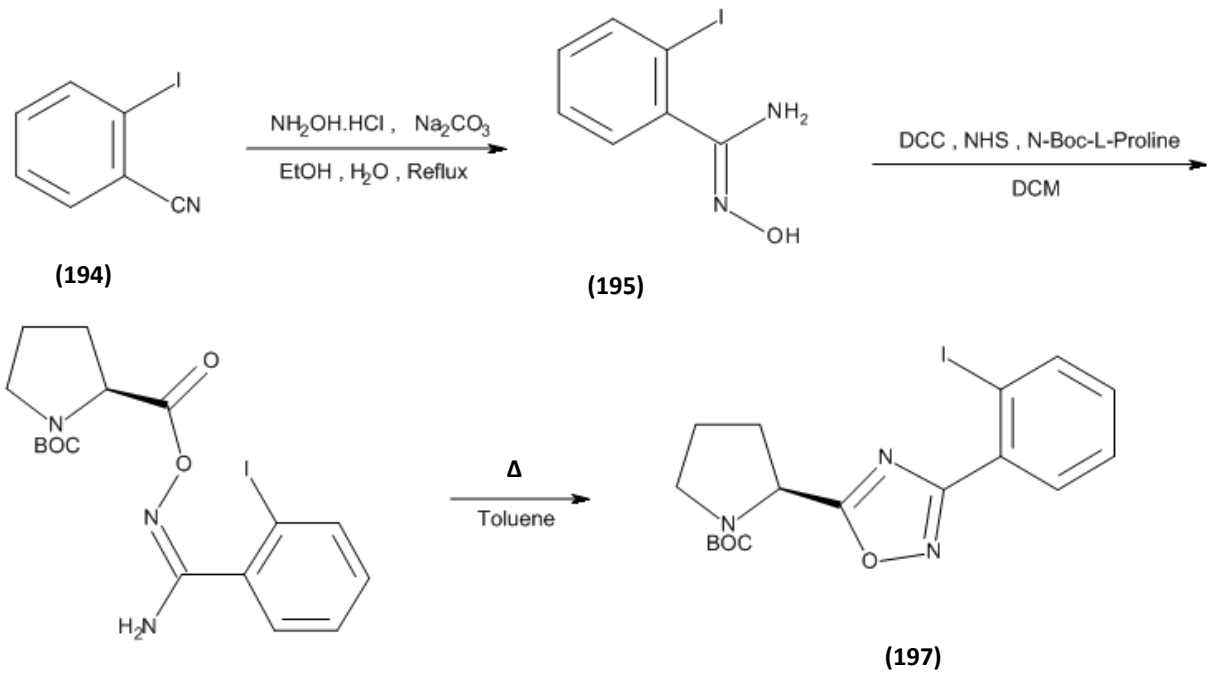
Fortunately the structure was later fully confirmed by HRMS which determined the accurate mass of the $[M+Na]^{+}$ ion to be 239.0906 for the expected figure of 239.0903.

3.3.2.5 The Catalytic Activity of L-Proline Enriched, Chiral 1,2,4-Oxadiazole Systems

Due to the unexpected difficulties encountered during the synthesis of L-proline based 1,2,4-oxadiazole-pyridine compound **(188)**, there was insufficient time to explore the use of compound **(188)** as a ligand in asymmetric synthesis and this aspect of the work was taken up by another group member. The remaining time in this PhD project was dedicated to an initial exploration into producing the ortho-iodoaryl analogue of compound **(188)**.

3.3.3 The Attempted Synthesis of a Chiral, L-Proline, Iodo-containing 1,2,4-Oxadiazole Derivative

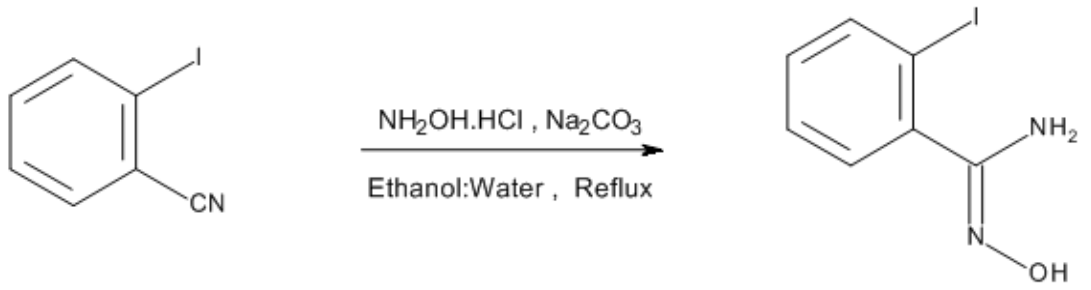
Having synthesised a catalyst featuring the proline-oxadiazole unit, it was decided to modify the compound to include some iodide character (Scheme 3.77). This could enable the development of an *in-situ* hypervalent iodine system, which could be modified to behave in an asymmetric catalytic manner due to the inherent chirality from the proline unit. It was intended that this system could then be screened in the furanone synthesis discussed previously in this chapter and described above in the chapter aims.



(194) **(195)** **(196)** **(197)**

Scheme 3.77

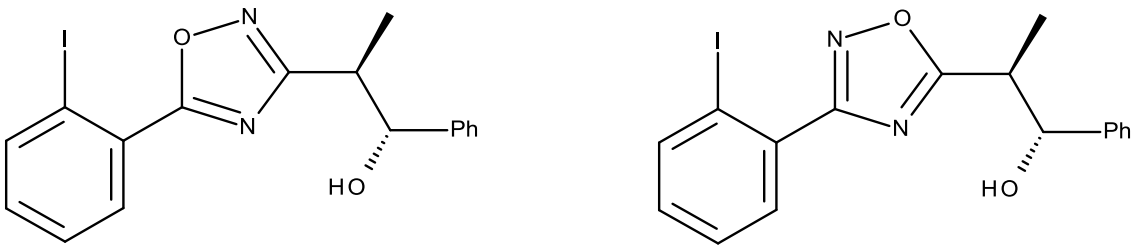
3.3.3.1 Synthesis of N'-Hydroxy-2-iodo-benzamidine



(194) **(195)**

Scheme 3.78

Conversion of the nitrile to the amidoxime was achieved as described previously. All attempts to couple it to N-Boc-L-proline were unsuccessful. This compound remains the target of future work that will be undertaken by another group member. A second target will be to incorporate the pseudoephedrine unit into the system, as such a system (as described previously), showed some success. These systems are shown below:



(198) **(199)**

Figure 3.40 – Target iodoaryl pseudoephedrine based 1,2,4-oxadiazole systems.

It was hoped that these systems may offer the advantage of a simplified system that would not have the complications presented by rotamers observed with pseudoephedrine systems derived from aryl amides, described above. Further ideas for future work in this area are described in the relevant section.

3.3.4 Conclusions

In conclusion for this section, a range of iodoaryl-pseudoephedrine pre-catalytic systems were successfully synthesised. The oxidation of the iodine to the iodine(III) system and the catalytic regeneration of these systems was observed. The asymmetric catalytic activity of the oxidised hypervalent iodine(III) derivative was assessed through screening via a lactonisation reaction, the lactone product of which bears one stereocentre. Although modest enantioselectivities were observed, an e.e. of 53% suggests such 2-iodoaryl-pseudoephedrine species possess good potential in the asymmetric catalysis of oxidative ring formation reactions. Unfortunately, the opportunity to develop a 1,2,4-oxadiazole analogue was not possible due to time constraints. This, however, is now the focus of other students within our research group.

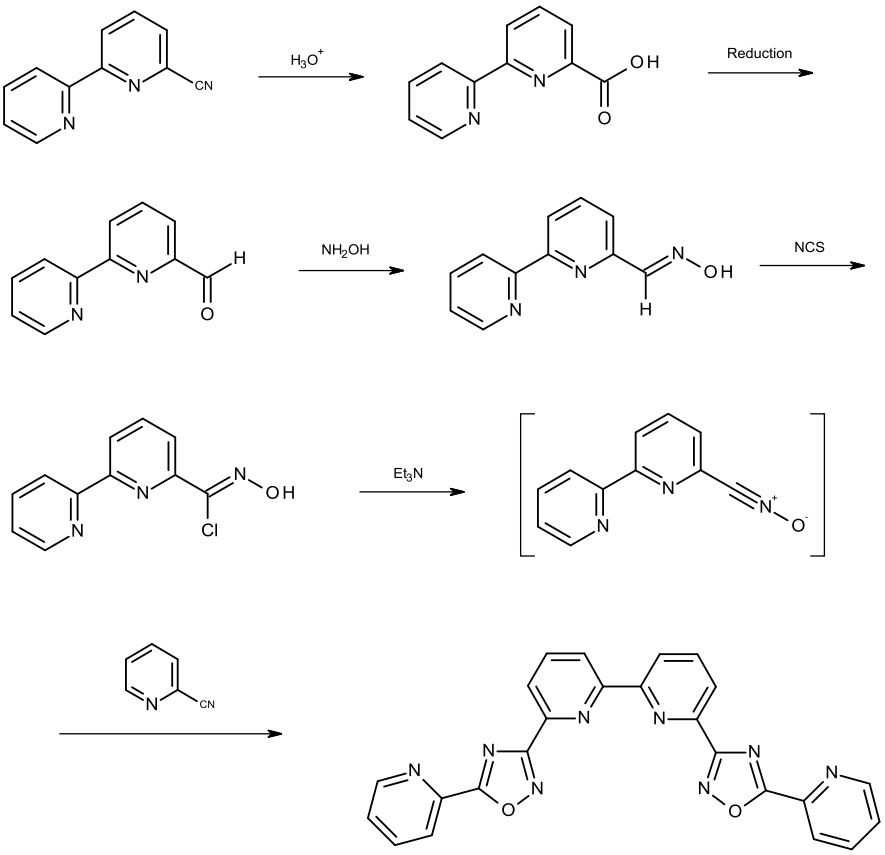
The synthesis of an L-proline-based, 1,2,4-oxadiazole system has also been achieved. Though opportunity to screen this compound and synthesise derivatives was not possible, the wealth of opportunity for such compounds is such that this is also now the focus of a colleague within our research group.

IV Future Work

This section aims to briefly consider any potential future work or interesting ideas that may have arisen from the work described in this thesis.

The examination of the supramolecular potential of the 1,2,4-oxadiazole in ligand systems proved to be a highly successful venture. In an extension from this success, many interesting ideas can be proposed.

One of the most interesting pieces of potential future work is the synthesis of 1,2,4-oxadiazole containing ligand systems by 1,3-dipolar cycloaddition. Whilst synthesis via the amidoxime method was reliable, products were only formed in low yields. Therefore it would be very interesting to examine the corresponding 1,3-dipolar cycloaddition synthesis in a bid to boost these low yields. Additionally, the 1,3-dipolar cycloaddition of nitrile oxides to nitriles opens up the possibility of some previously inaccessible ligands, for example, a pyridine-oxadiazole-bipyridine-oxadiazole-pyridine ligand **(200)**, analogous with Rice's thiazole ligand **(26)**. This is shown in Scheme 4.1. The synthesis of this ligand was not possible by the amidoxime method due to the lack of success observed with the synthesis of the bipyridine-2,2'-diamidoxime **(51)**. Synthesis via the 1,3-dipolar cycloaddition method could enable the synthesis of this ligand, since the bipyridine-dinitrile would suffice as a precursor.



Scheme 4.1

Stepping away from the 1,2,4-oxadiazole and on to similar heterocycles, it has been discovered that to the best of our knowledge, no supramolecular advances have been made using 1,2,4-thiadiazole containing ligands. Given the only structural difference between the 1,2,4-oxadiazole and the 1,2,4-thiadiazole is the chalcogen switch, it would be very interesting to attempt the synthesis and crystallisation of some metal-organic ligand complexes featuring this heterocycle. In a further chalcogen switch, it has been noted that no published supramolecular work exists featuring selenium heterocyclic ligands. This could also be a very interesting piece of future work.

Moving onto the medicinal chemistry of the isothiazolo-isoxazoles, it was unfortunate that opportunities to synthesise the corresponding β-sultams were not forthcoming. This was due to time constraints caused by the successes observed with the isothiazolo-isoxazole analogues which

demanded most of the research attention. The synthesis of these β-sultams and investigation into their biological activity remains at the forefront of the group's research in this area.

An additional and interesting potential piece of future work concerns the reactivity of the isothiazolo-isoxazoles. The bridgehead proton is likely to be acidic due to its α-sulfonyl position. Extension of these biologically active bicyclic compounds may be possible by investigating the chemistry at this position.

There is much scope for further development of the catalytic systems described in this thesis. First and foremost, our group plan to screen the proline-oxadiazole catalyst **(187)** and, providing results show some promise, synthesise a range of derivatives and optimise the reactivity. Additionally, the synthesis of an iodide derivative of this proline-oxadiazole as a pre-hypervalent iodine catalyst remains a priority, followed by screening of this catalyst on the lactonisation reaction described earlier. Finally, it should be possible to synthesise 1,2,4-oxadiazole analogues of the pseudoephedrine hypervalent iodine catalysts in a bid to examine the impact of this heterocycle on the catalytic potential.

V References

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