1-Azetines, 1,2-Thiazetin-1,1-dioxides and Isothiazol-1,1-dioxides as Building Blocks in Heterocyclic Synthesis: the Attempted Synthesis of Bicyclic *β*-Sultams

Arnaud Pitard

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

University of Huddersfield
Department of Chemical and Biological Sciences

April 2009

I would like to dedicate this thesis to my mother Christiane Pitard, my father Bernard Pitard and my brother Laurent Pitard with my deep appreciation for their love, support and patience for all those many years of studies. This thesis is also dedicated to my best friend Fabrice Huger for his invaluable friendship and support.

Contents

Acknowledgements

Firstly, I would like to express my deep gratitude to my director of studies, Dr Karl Hemming, for his excellent supervision, guidance, critical advice and support during the course of my research and for trusting me and giving me the opportunity to work with him. His kindness allowed me to work in a friendly and relaxed environment, and his generosity gave me the chance to share his knowledge and have fascinating discussions, which expanded my own understanding of chemistry.

I would like to thank the university technical staff, especially Graham Charnock and Ibrahim George for their great availability, commitment and kindness, Dr Neil McLay for running NMR and mass spectrometry experiments and Dr Linsay Harding for performing mass spectroscopic analyses at the early stage of this PhD.

I would like to thank Dr Craig Rice for interesting discussions and his usefull advice in the laboratory, especially on crystallisation techniques, and for running the XRD experiments and providing and solving the crystallographic data.

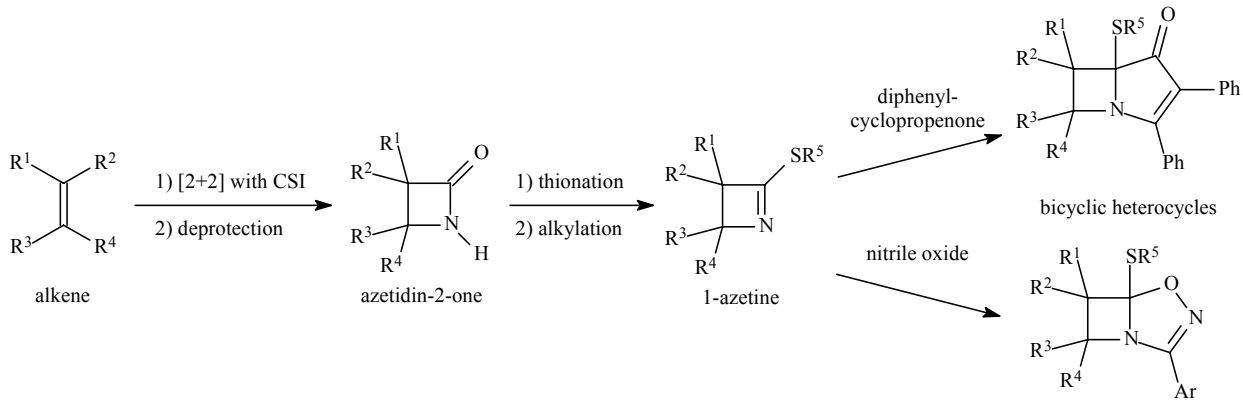
I would like to show gratitude to Dr Mathew Stirling and Dr Nick Powles (IPOS) to have allowed me to use their GC and HPLC, and attend their interesting course on process chemistry development.

Finally, special thanks must be made for my fellow colleagues Chris Chambers, Martina Whitehead and Maq for their support and encouragement during the good and the bad times.

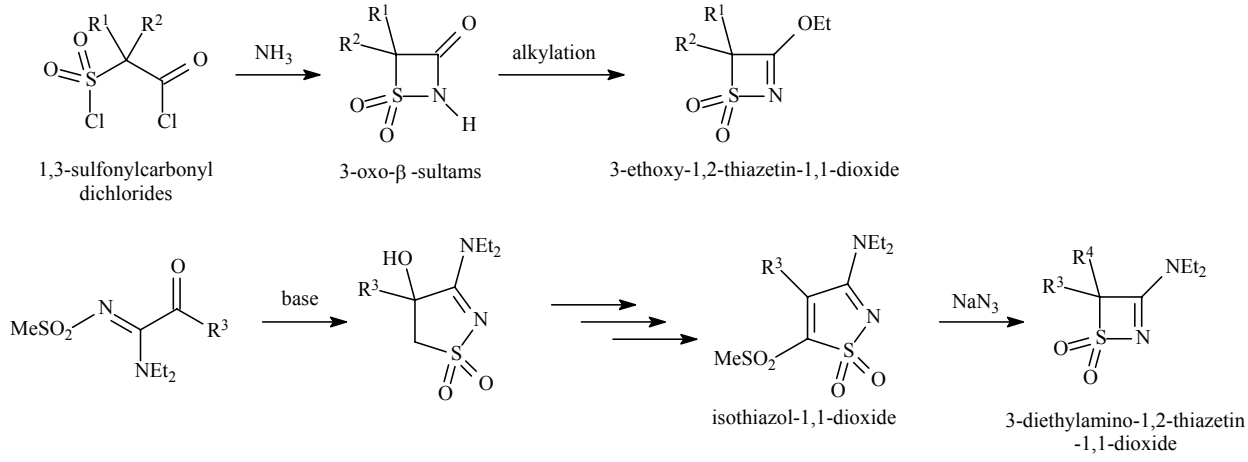
Abstract

This thesis is concerned with the synthesis of *β*-sultams and the development of new routes for the synthesis of bicyclic versions of these molecules as potential anti-bacterials. The synthesis of 1-azetines, 1,2-thiazetin-1,1-dioxides and isothiazol-1,1-dioxides as precursors of bicyclic heterocycles is described.

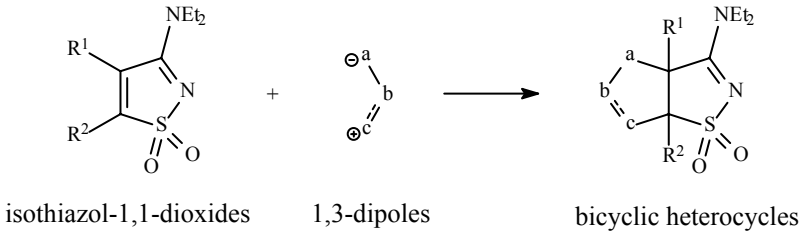
1-Azetines were synthesised from azetidin-2-ones prepared *via* the [2+2] cycloaddition of alkenes with *N*-chlorosulfonyl isocyanate (CSI). They reacted with diphenylcyclopropenone or nitrile oxides to afford bicyclic systems whose reactivity was explored and afforded a range of heterocycles such as 1,2,4-oxadiazoles, pyridines or pyrimidines *via* novel reaction pathways.



The synthesis of 1,2-thiazetin-1,1-dioxide through two routes will be discussed: the alkylation of 3-oxo-*β*-sultams to afford 3-ethoxy-1,2-thiazetin-1,1-dioxides, and the ring contraction of an isothiazol-1,1-dioxide to afford a 3-diethylamino-1,2-thiazetin-1,1-dioxide. The reactivity of these 1,2-thiazetin-1,1-dioxides towards diphenylcyclopropenone, 1,3-dipoles and dienes was studied and is fully described.



In the course of chemistry mentioned above, a series of isothiazol-1,1-dioxides was synthesised. Their reaction with 1,3-dipoles to yield the corresponding bicyclic heterocycles is described.



Abbreviations

Ac	acyl
ACN	acetonitrile
AIBN	azobisisobutyronitrile
ala	alanine
aq.	aqueous
Ar	aryl
b	broad (NMR)
bd	broad doublet
Bn	benzyl
Boc	butyloxycarbonyl
b.p.	boiling point
br	broad (IR)
bs	broad singlet
CSI	*N*-chlorosulfonyl isocyanate
conc.	concentrated
d	days, doublet (NMR)
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement through polarization transfer
DMAD	dimethylacetylene dicarboxylate
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DPP	diphenylcyclopropenone
dq	doublet of quartets
dt	doublet of triplets
ee	enantiomeric excess
eq.	equivalent(s)
EWG	electron-withdrawing group
FMO	frontier molecular orbital
glu	glutamic acid
h	hour(s)
HMBC	heteronuclear multiple bond connectivity
HMDO	hexamethyldisiloxane
HMDST	hexamethyldisilathiane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
LDA	lithium diisopropylamide
lit.	literature
LPS	lipopolysaccharide
LUMO	lowest unoccupied molecular orbital
lys	lysine
m	medium (IR), multiplet (NMR)
***m*-CPBA**	*meta*-chloroperbenzoic acid
min	minute(s)
Moc	methoxycarbonyl
m.p.	melting point
Ms	mesylate
MS	mass spectrometry
MW	molecular weight
NAG	*N*-acetylglucosamine
NAM	*N*-acetylmuramic acid
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile

PE	petroleum ether
PFP	pentafluorophenyl
Ph	phenyl
ppm	parts per million
q	quartet
RCM	ring closing metathesis
RT	room temperature
s	strong (IR), singlet (NMR)
SAMP	(S)-1-amino-2-methoxymethyl-pyrrolidine
t	triplet
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilane
TBDPS	*tert*-butyldiphenylsilane
td	triplet of doublets
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl
TSA	transition state analogues
tt	triplet of triplets
UV	ultraviolet
vs	very strong (IR)
w	weak (IR)
XRD	X-ray diffraction

CHAPTER 1

INTRODUCTION

1 Introduction

1.1 Biological and chemical background

This project is concerned with the synthesis of *β*-lactams and *β*-sultams and the development of new routes for the synthesis of bicyclic versions of these molecules as potential anti-bacterial agents. To understand how *β*-lactams kill bacteria requires a little knowledge of how a bacterial cell wall is formed and why bacteria need cell walls.

1.1.1 Role and structure of bacterial cell walls

Structurally, bacterial cells consist of:

- A cell membrane, which is usually surrounded by a cell wall and sometimes by an additional outer layer.
- An internal cytoplasm with ribosomes, a nuclear region, and in some cases granules and/or vesicles.
- A variety of external structures, such as capsules, flagella, and pili.

The rigid cell wall lies outside the cell membrane in nearly all bacteria. It performs two important functions. First, it helps to maintain the characteristic shape of the cell. The cell membrane is the osmotic barrier that allows the retention of nutrients and the exclusion of other compounds. Second, it prevents the cell from bursting by allowing it to withstand a range of harsh conditions such as various temperatures, pH and osmotic pressure. For example, Gram-positive and Gram-negative bacteria have internal osmotic pressures which are 10 to 30 times and 3 to 5 times the external osmotic pressure, respectively. The robust structure of the bacterial wall of both Gram-positive and Gram-negative species is due to the cross linking of linear polysaccharide chains by short segments of peptides called peptidoglycan (Figure1.1).

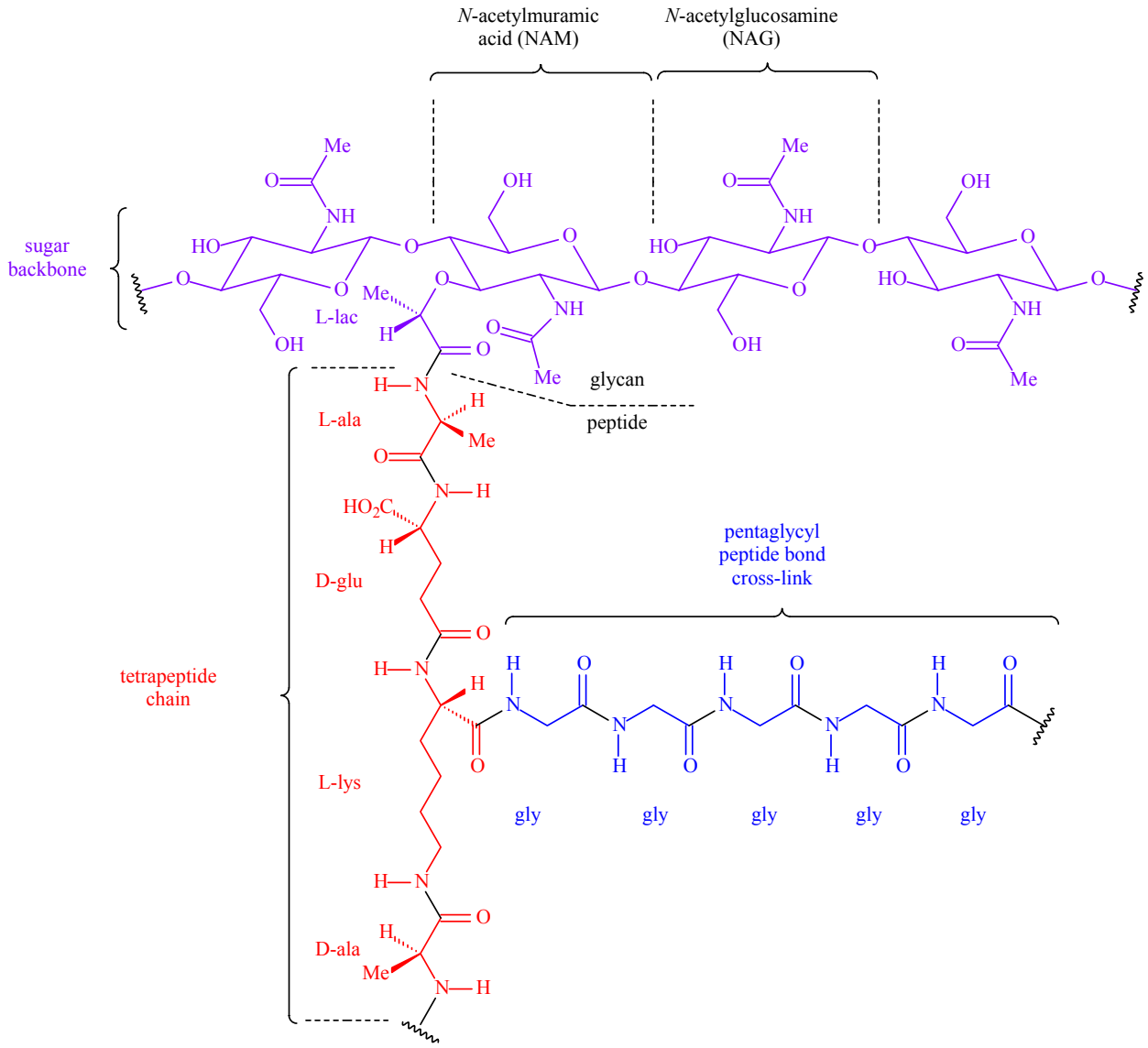


Figure 1.1 Molecular structure of the peptidoglycan unit for the Gram-positive bacterium *Staphylococcus aureus*[1]

1.1.1.1 Peptidoglycan

Peptidoglycan is the single most important component of the bacterial cell wall. It is a polymer so large that it can be thought of as one immense, covalently linked molecule. It forms a supporting net around a bacterium that resembles the multiple layers of chain-link fence (Figure 1.2).

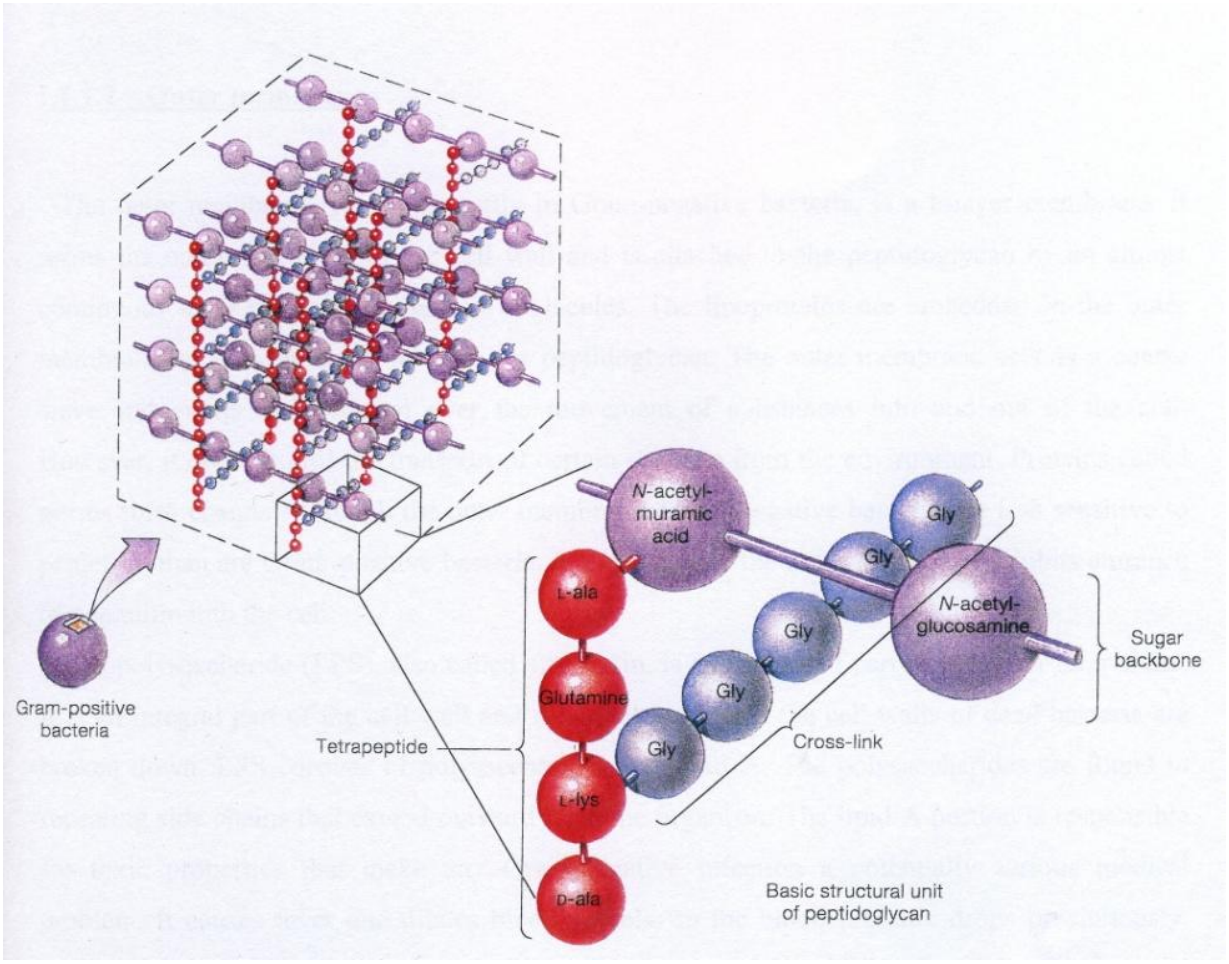


Figure 1.2 Three-dimensional view of peptidoglycan for the Gram-positive bacterium *Staphylococcus aureus*[1]

Gram-positive cells may have as many as forty such layers. In the peptidoglycan polymer, molecules of *N*-acetylglucosamine (NAG) alternate with molecules of *N*-acetylmuramic acid (NAM) to form the sugar backbone. These molecules are cross-linked by tetrapeptides, chains of four amino acids, which are also cross-linked by a peptide chain, the whole forming a massive network. Different organisms can have different amino acids in the tetrapeptide chain, as well as different cross-links.

1.1.1.2 Outer membrane

The outer membrane, found primarily in Gram-negative bacteria, is a bilayer membrane. It forms the outermost layer of the cell wall and is attached to the peptidoglycan by an almost continuous layer of small lipoprotein molecules. The lipoproteins are embedded in the outer membrane and covalently bonded to the peptidoglycan. The outer membrane acts as a coarse sieve and exerts little control over the movement of substances into and out of the cell. However, it does control the transport of certain proteins from the environment. Proteins called porins form channels through the outer membrane. Gram-negative bacteria are less sensitive to penicillin than are Gram-positive bacteria, in part because the outer membrane inhibits entrance of penicillin into the cell.

Lipopolysaccharide (LPS), also called endotoxin, is an important part of the outer membrane. It is an integral part of the cell wall and is not released until the cell walls of dead bacteria are broken down. LPS consists of polysaccharides and lipid A. The polysaccharides are found in repeating side chains that extend outward from the organism. The lipid A portion is responsible for toxic properties that make any Gram-negative infection a potentially serious medical problem. It causes fever and dilates blood vessels, so the blood pressure drops precipitously. Because bacteria release endotoxin mainly when they are dying, killing them may increase the concentration of this very toxic substance. Thus, antibiotics given late in an infection may cause a worsening of symptoms, or even death of the patient.

1.1.1.3 Periplasmic space

Another distinguishing characteristic of many bacteria is the presence of a gap between the cell membrane and the cell wall. In Gram-negative bacteria this gap is called the periplasmic space. It represents a very active area of cell metabolism. This space contains not only the cell wall peptidoglycan but also many digestive enzymes and transport proteins that destroy potentially harmful substances and transport metabolites into the bacterial cytoplasm, respectively. The periplasm consists of the peptidoglycan, protein constituents, and metabolites found in the periplasmic space.

Periplasmic spaces are rarely observed in Gram-positive bacteria. However, such bacteria must accomplish many of the same metabolic and transport functions that Gram-negative bacteria do. At present most Gram-positive bacteria are thought to have only periplasms (not

periplasmic spaces) where metabolic digestion occurs and new cell wall peptidoglycan is attached. The periplasm in Gram-positive cells is thus part of the cell.

1.1.2 Distinguishing bacteria by cell walls

1.1.2.1 Gram-positive bacteria

The cell wall in Gram-positive bacteria has a relatively thick layer of peptidoglycan, 20 to 80 nm across. The peptidoglycan layer is closely attached to the outer surface of the cell membrane. Chemical analysis shows that 60 to 90% of the cell wall of a Gram-positive bacterium is peptidoglycan. Most Gram-positive cell walls contain very little protein. If peptidoglycan is digested from their cell walls, Gram-positive bacteria become protoplasts, or cells with a cell membrane but no cell wall. Protoplasts shrivel or burst unless they are kept in an isotonic solution, i.e. a solution that has the same pressure as that inside the cell.

Gram-positive bacteria lack both an outer membrane and a periplasmic space (Figure 1.3).

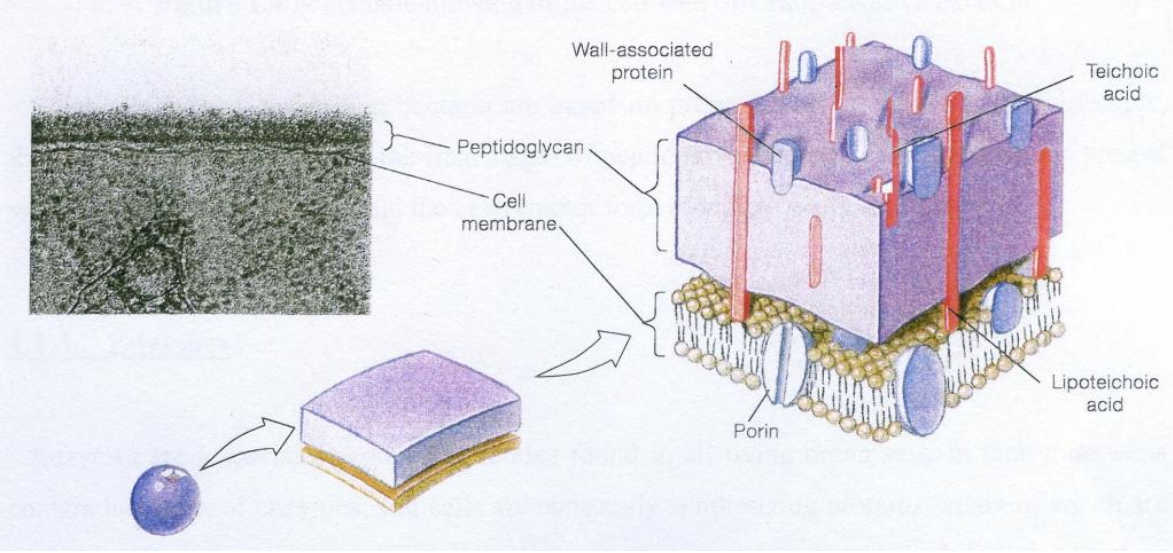


Figure 1.3 Schematic drawing of the cell wall of Gram-positive bacteria[1]

1.1.2.2 Gram-negative bacteria

The cell wall of a Gram-negative bacterium is thinner but more complex than that of a Gram-positive bacterium. Only 10 to 20% of the cell wall is peptidoglycan; the remainder consists of various polysaccharides, proteins, and lipids. The cell wall contains an outer membrane, which

constitutes the outer surface of the wall, leaving only a very narrow periplasmic space (Figure 1.4). Toxins and enzymes remain in the periplasmic space in sufficient concentrations to help destroy substances that might harm the bacterium, but they do not harm the organism that produced them.

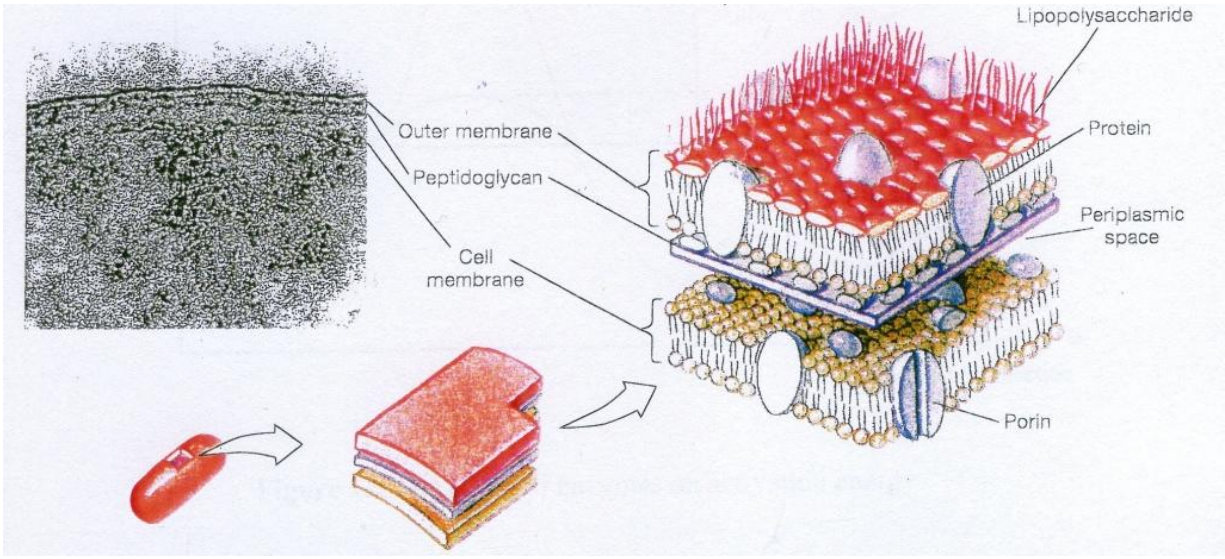


Figure 1.4 Schematic drawing of the cell wall of Gram-negative bacteria[1]

Some methods of controlling bacteria are based on properties of the cell wall. For example, the antibiotic penicillin blocks the final stages of peptidoglycan synthesis. If penicillin is present when bacterial cells are dividing, the cells cannot form complete walls, and they die.

1.1.3 Enzymes

Enzymes are a special category of proteins found in all living organisms. In fact, most cells contain hundreds of enzymes, and cells are constantly synthesising proteins, many of which are enzymes. Enzymes act as catalysts by speeding up reactions to as much as a million times the uncatalysed rate, where the latter is ordinarily not sufficient to sustain life.

In general, chemical reactions that release energy can occur without input of energy from the surroundings. Nevertheless, such reactions often occur at unmeasurably low rates because the molecules lack the energy to start the reaction. The energy required to start such a reaction is called activation energy (Figure 1.5). Activation energy can be thought of as a hurdle over which energy must be raised to get a reaction started.

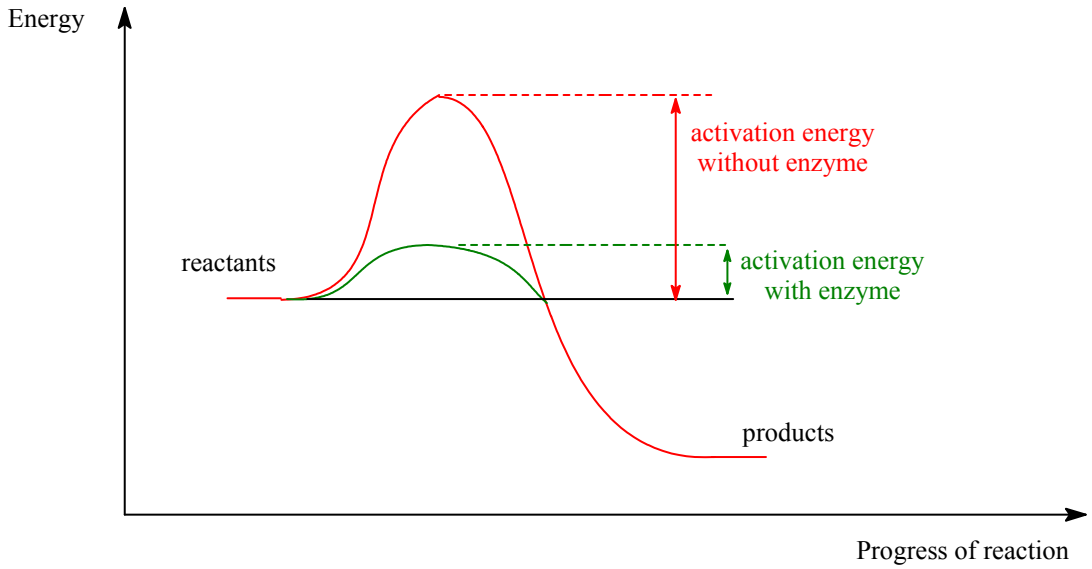


Figure 1.5 The effect of enzymes on activation energy

A common way to activate a reaction is to raise the temperature. But such a raise in temperature could be enough to denature proteins. Reactions can occur through different transition states and intermediates. Enzymes can modify the transition states or the intermediates of reactions to lower the activation energy so reactions can occur at mild temperatures in living cells.

Enzymes also provide a surface on which reactions take place. Each enzyme has a certain area on its surface called the active site, a binding site. The binding site for a polypeptide consists of a series of subsites across the surface of the enzyme. The interaction between the substrate and the enzyme can be described following the Schrechter and Berger nomenclature[2] (Figure 1.6). The amino acid residues are numbered according to their position with respect to the amide bond that is being cleaved. The section to the right of the scissile bond is called the prime side and to the left is the non-prime side. It is considered that residues of the substrate or inhibitor P (for peptide) bind to enzyme subsites S of the active site.

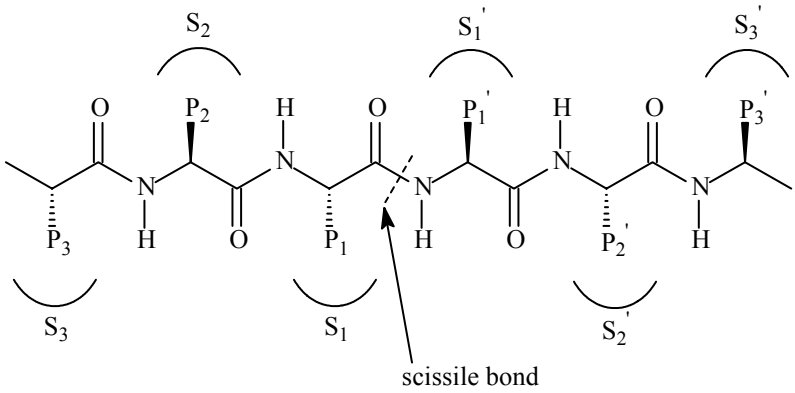


Figure 1.6 Schrechter and Berger nomenclature

The active site is the region at which the enzyme forms a loose association with the substrate (Figure 1.7). Like all molecules, a substrate molecule has kinetic energy, and it collides with various molecules within a cell. When it collides with the active site of an enzyme, an enzyme-substrate complex forms. As a result of binding to the enzyme, some of the chemical bonds in the substrate are weakened. The substrate then undergoes chemical change, the product(s) are formed, and the enzyme detaches.

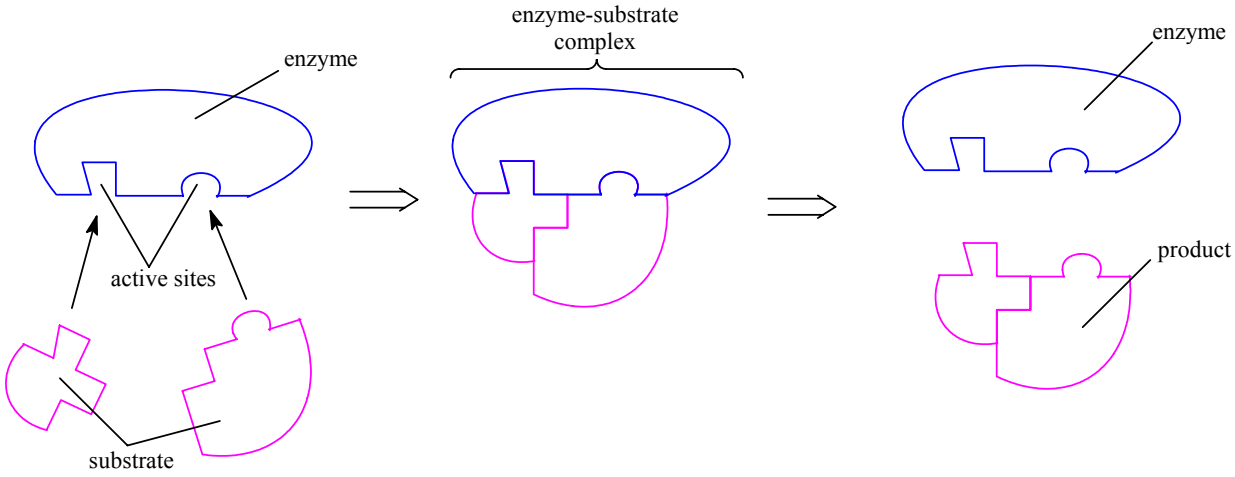


Figure 1.7 Interaction between enzyme and substrate

Enzymes generally have a high degree of specificity; they catalyse only one type of reaction, and most act on only one particular substrate. The shape of an enzyme, especially the shape and electrical charges at its active site, accounts for its specificity. When an enzyme acts on more than one substrate, it usually acts on substrates with the same functional group or the same kind

of chemical bonds. For example, proteolytic enzymes act on different proteins but always act on the peptide bonds in those proteins.

1.1.4 Enzyme inhibition

No organism can afford to allow continual maximum activity of all its enzymes. Not only is this a waste of materials and energy, but it also may allow harmful quantities of compounds to accumulate, while others are lacking. Therefore, there must be ways to inhibit enzyme activity in order to slow or even stop its rate.

1.1.4.1 Competitive inhibition

A molecule similar in structure to a substrate can sometimes bind to an enzyme's active site even though the molecule is unable to react. This non-substrate molecule is said to act as a competitive inhibitor of the reaction because it competes with the substrate for the active site (Figure 1.8). When the inhibitor binds to an active site, it prevents the substrate from binding and thereby inhibits the reaction.

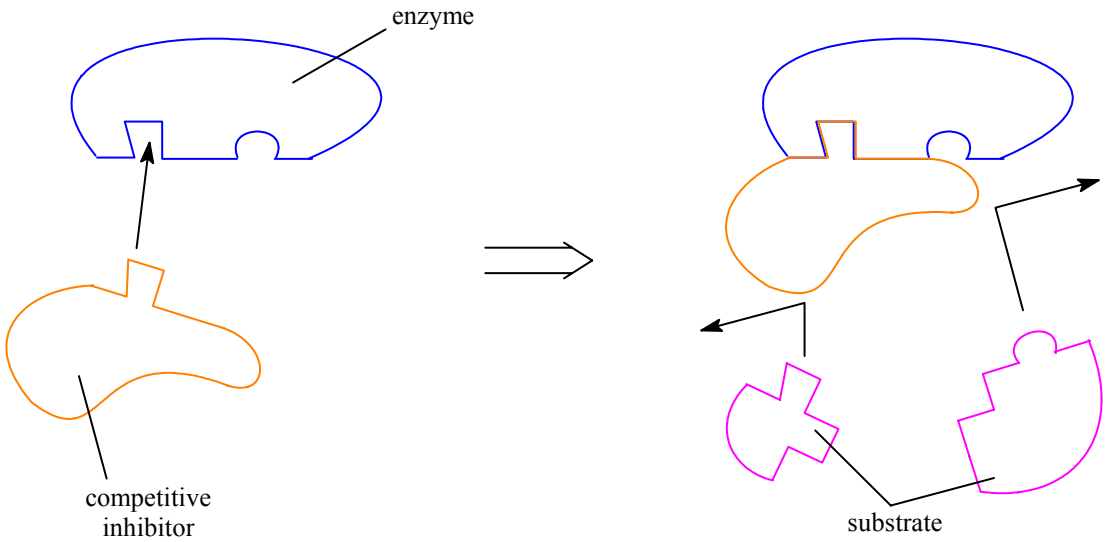


Figure 1.8 Competitive inhibition of enzymes

The competitive inhibitors are probably the most common type of enzyme inhibitors that act as drugs. They bind non-covalently to the enzyme and often resemble the geometry and structure of the substrate, the product or the transition state. Because the attachment of such a competitive inhibitor is normally reversible (Figure 1.9), the degree of inhibition depends on the relative concentrations of substrate (S) and inhibitor (I). When the concentration of the substrate (S) is high and that of the inhibitor (I) is low, only a few enzyme inhibitor complexes (EI) are formed and a lot of active sites of the enzyme remain available to form the enzyme substrate complexes (ES), and the rate of the reaction is only slightly reduced. In the contrary case, a lot of enzyme inhibitor complexes (EI) are formed and only few active sites of the enzyme remain available for the substrate, and the rate of the reaction is greatly reduced. So, reversible competitive inhibition can be overcome by high substrate concentrations.

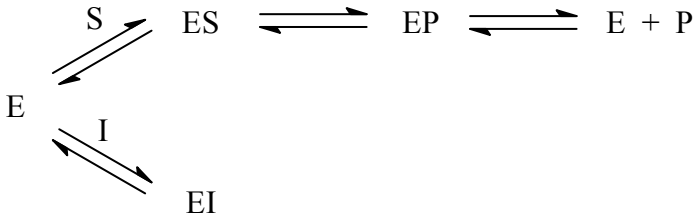


Figure 1.9 Reversible competitive inhibition of enzymes

Transition State Analogues

One category of reversible competitive inhibitors is transition state analogues (TSA). As discussed above, the use of an enzyme, as that of any other catalyst in general, is to modify the transition state of the reaction to lower its activation energy. Hence, the enzyme must probably have the ability to alter the substrate in a way that it will have a greater affinity for it in its transition state than for the substrate itself in its ground state. This approach was originally advanced by Pauling,[3] and it has been suggested that one way to inhibit enzymes is to design and synthesise compounds which would mimic the transition state.[4] TSA inhibitors are, thus, stable molecules that are designed to resemble the substrate's structure in its transition state in order to bind tighter to the enzyme than the substrate. They have to be similar to the transition state in several ways, for example, the geometry and the charge on the molecule have to be similar to that in the transition state structure.

1.1.4.2 Non-competitive inhibition

Some non-competitive inhibitors can form a non-covalent complex with both the free enzyme (E) to form an enzyme inhibitor complex (EI) (Figure 1.10, pathway 1) and the enzyme substrate complex (ES) to form an enzyme substrate inhibitor (ESI), which then expels the substrate (Figure 1.10, pathway 2).

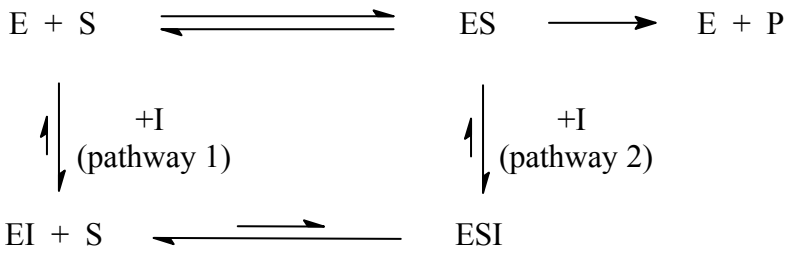


Figure 1.10 Non-competitive inhibition

To do so, they attach to the enzyme at an allosteric site, which is a site other than the active site (Figure 1.11). Such inhibitors distort the tertiary protein structure and alter the shape of the active site. Any enzyme molecule thus affected no longer can bind substrates, so it cannot catalyse a reaction.

As mentioned above, the non-competitive inhibitor can interact with the enzyme substrate complex by altering the shape of the active site and forcing the substrate to be expelled from the active site, thus preventing the enzyme from catalysing the reaction (Figure 1.12).

Although some non-competitive inhibitors bind reversibly, others bind irreversibly and permanently inactivate enzyme molecules, thereby greatly decreasing the reaction rate. In non-competitive inhibition, increasing the substrate concentration does not increase the reaction rate as it does in competitive inhibition, because the inhibitor and the substrate bind to two different sites of the enzyme, *i.e.* they do not compete for the same kind of interactions with the enzyme. Thus, the substrate cannot displace the inhibitor and non-competitive inhibition cannot be overcome by high substrate concentrations.

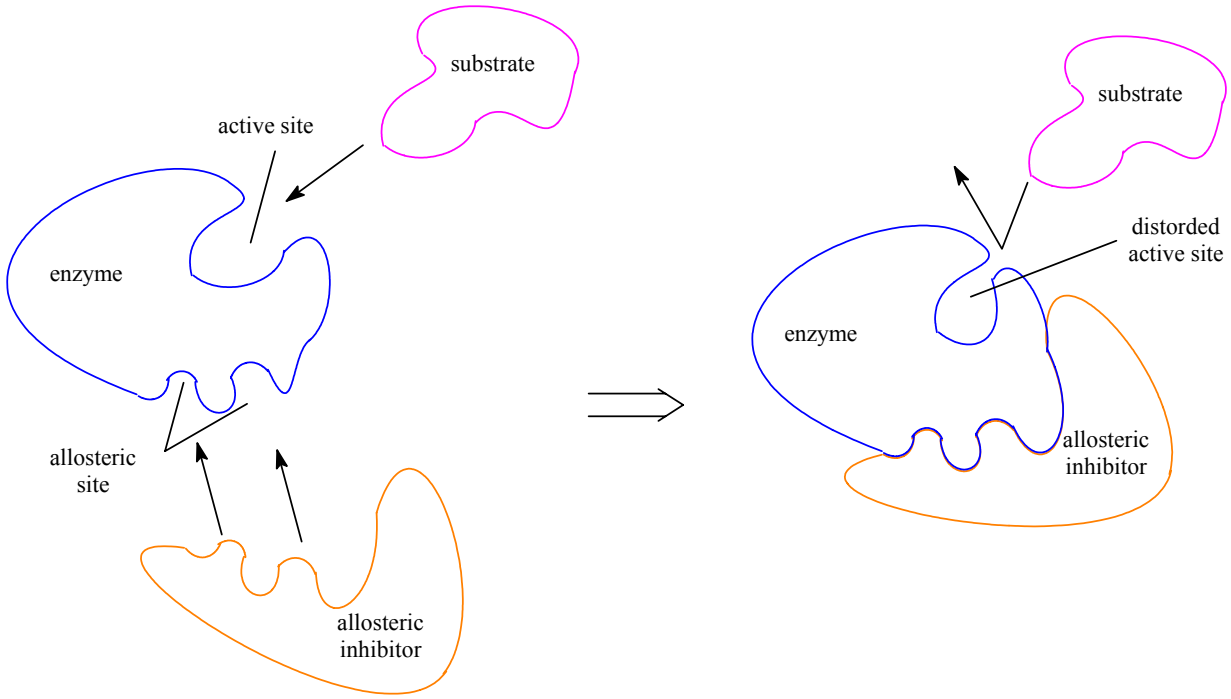


Figure 1.11 Interaction of the allosteric inhibitor with the enzyme (pathway 1)

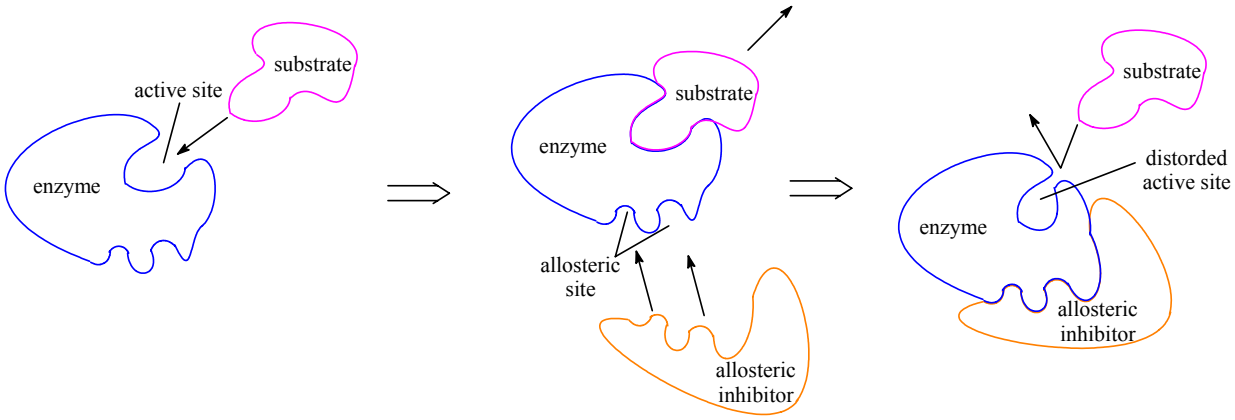


Figure 1.12 Interaction of the allosteric inhibitor with the enzyme substrate complex (pathway 2)

1.1.5 Mode of action of *β*-lactam antibiotics

To understand how *β*-lactam antibiotics kill bacteria requires some knowledge about the biosynthesis of the peptidoglycan, which is a huge polymer (Figure 1.1) and is the most important component of the cell wall, as discussed in section 1.1.1.

1.1.5.1 Biosynthesis of peptidoglycan

To synthesise in the extracellular space a polymer larger than themselves, bacteria use a clever way which involves three steps:[5]

- Building activated precursors inside the cell.
- Exporting them *via* a membrane–soluble carrier.
- Assembling the translocated pieces with the help of membrane-bound enzymes.

The first intracellular step of the process results in the formation of the *N*-acetylglucosamine (NAG) and the *N*-acetylmumaryl-pentapeptide (NAM-pentapeptide) units, which will constitute the glycan backbone. The pentapeptide is attached to the carboxyl group on the NAM residues (Figures 1.1 and 1.2) and has the sequence L-ala-D-glu-L-lys-D-ala-D-ala, *i.e.* it contains one additional terminal D-alanine residue compared to the tetrapeptide chain in the mature peptidoglycan. The length and nature of the peptide cross-links vary with bacteria, the L-lys residue may be replaced by *meso*-diaminopimelic acid, another amino carrying residue, which attaches the different peptide cross-links to each other.

The second step involves the transfer of the *N*-acetylmumaryl-pentapeptide and *N*-acetylglucosamine on the carrier, and secondary modification of the peptide. The disaccharide-peptide unit is then translocated across the cytoplasmic membrane.

The third and final step in the process takes place in the extracellular space and consists of two dinstinct reactions: a transglycosylation, which lengthens the saccharidic strands to form the sugar backbone of the polymer, and a transpeptidation, which closes the peptide cross-link and strengthens the rigidity of the cell wall. Both reactions are catalysed by membrane-bound enzymes. The enzyme responsible for the catalysis of the latter reaction is a DD-transpeptidase. Cross-linking occurs by displacing the terminal D-alanine residue of *N*-acetylmumaryl-pentapeptide with the free amino group (RNH_2) of L-lysine or *meso*-diaminopimelic acid on an adjacent peptide (Figure 1.13).

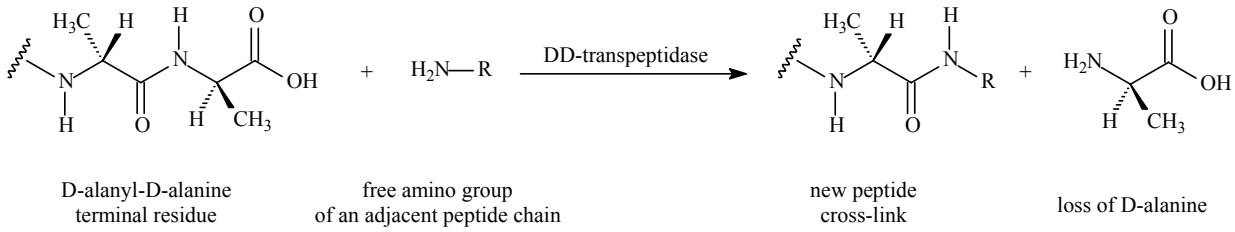


Figure 1.13 Cross-linkage of peptide chains by DD-transpeptidase

The extent of cross-linking varies with bacterial species, and the uncross-linked sections (D-ala-D-ala terminal residues) may be removed by carboxypeptidase action[5,6] (Figure 1.14). The reason for this is that peptidoglycan is continuously remodelled to allow cell growth and division, and thus new growing sites must be created by making new aminated acceptor group available.

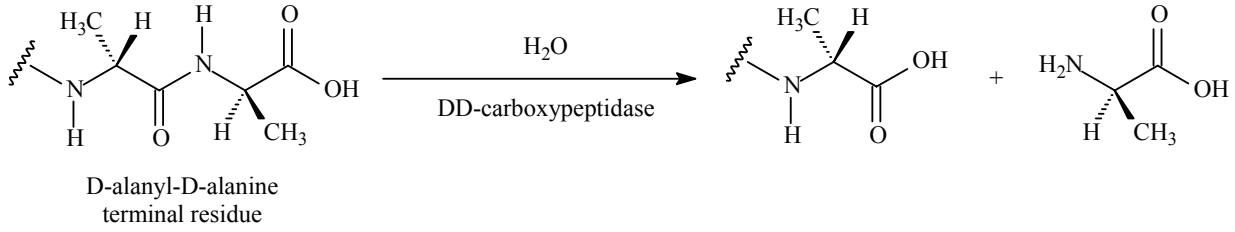
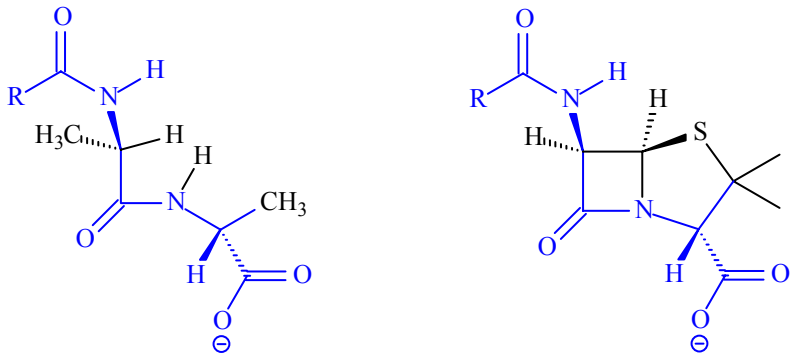


Figure 1.14 Creation of new growing sites by DD-carboxypeptidase activity

Hence, it is easy to understand that inhibition of both catalytic processes results in the formation of a defective peptidoglycan, which induces the formation of a fragile cell wall leading eventually to the death of the cell.

1.1.5.2 Interaction of penicillins with DD-transpeptidase and DD-carboxypeptidase

Both enzymes, DD-transpeptidase and DD-carboxypeptidase, were found to be the target of penicillins and were first thought[7] to be inactivated by them through an acylation process. Penicillins act as structural analogues of the D-alanyl-D-alanine terminal residue of the *N*-acetylmumaryl-pentapeptide (Figure 1.15).



N-acylated D-alanyl-D-alanine 3*S*, 5*R*, 6*R*-penicillin

Figure 1.15 Structural analogy between *N*-acylated D-alanyl-D-alanine and 3*S*, 5*R*, 6*R*-penicillin

It was also suggested[8] that the transpeptidation was a two step process involving an acyl-enzyme intermediate formed by displacement of the terminal D-alanine using a serine hydroxyl group on the enzyme (Figure 1.16a). The acyl-D-alanyl residue was then transferred from this ester intermediate to the free amino group of an adjacent peptide. It was proposed that penicillin may be an active site-directed inhibitor capable of acylating bacterial transpeptidases (Figure 1.16b). The transpeptidation pathway involving the attack of a hydroxyl group and the formation of an acyl-enzyme intermediate is now universally known.[5,9] At that time the cell death was predicted to be directly related to the inhibition of the transpeptidation. It is now known to be indirect because disruption of cell wall biosynthesis is thought to activate peptidoglycan hydrolases that hydrolyse the cell wall causing lysis.[6,10]

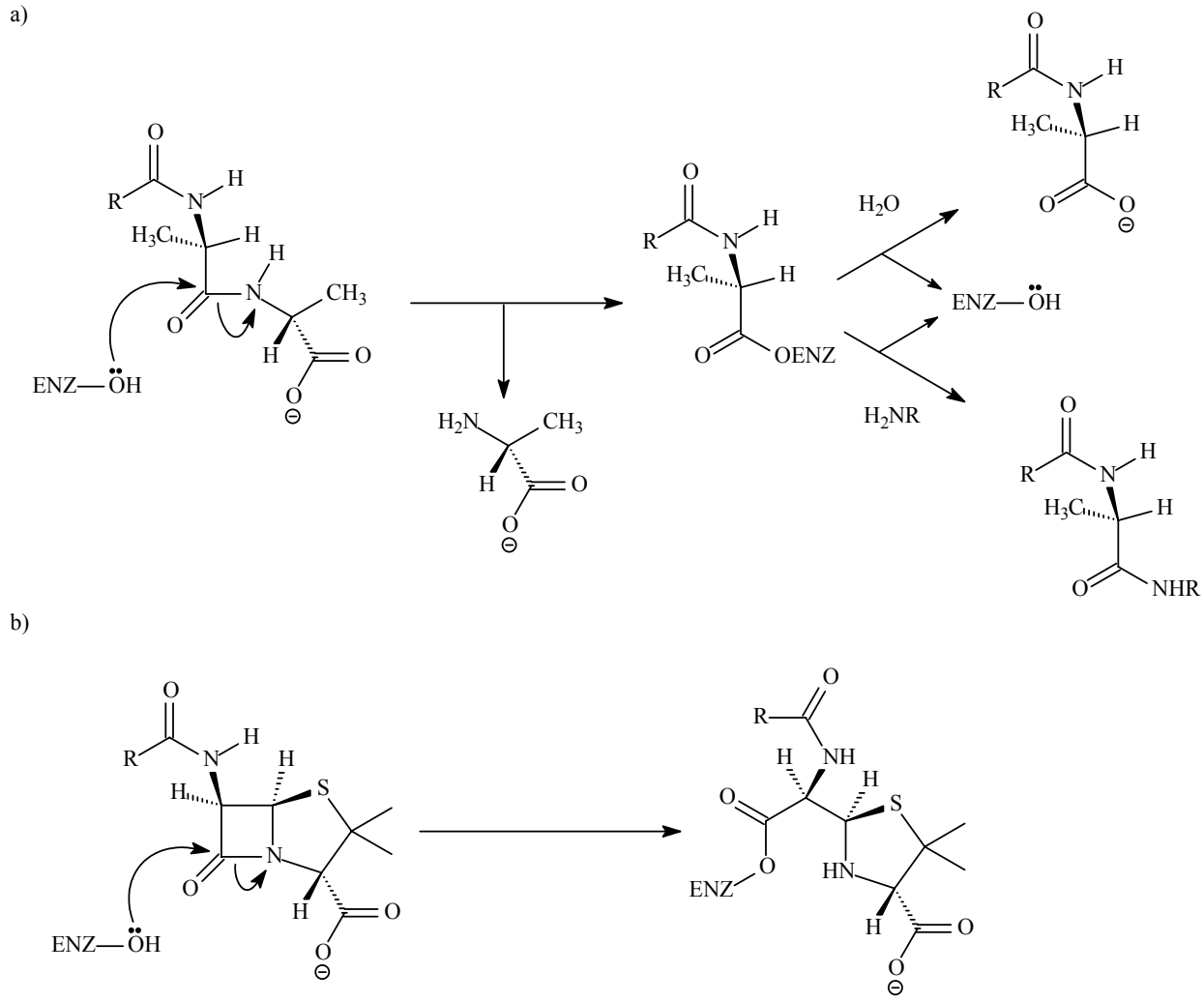


Figure 1.16 The transpeptidation and hydrolysis reactions of *N*-acylated D-alanyl-D-alanine catalysed by serine enzymes (a) compared with a *β*-lactam antibiotic's reaction with serine enzymes (b)

1.1.5.3 The "active serine" model of interaction with *β*-lactams

A kinetic analysis demonstrated that the interaction obeyed a three-step model[5] (Figure 1.17), where E is the enzyme, I the inhibitor (antibiotic), EI a non-covalent complex, EI^* a covalent acyl-enzyme complex and P(s) the inactive product(s) of degradation of the antibiotic.

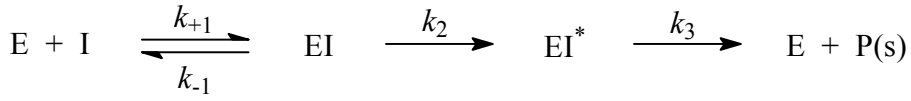


Figure 1.17 Model of interaction between the enzyme and the antibiotic

Efficient inactivation of the enzyme depends on a rapid and nearly quantitative accumulation of the EI* complex, which is the result both of its stability (low k_3), and of its rapid formation (generally due to high k_2 values).

The enzyme group involved in the formation of the acyl-enzyme was identified as a serine side chain[9] in the *Streptomyces* R61 DD-peptidase (Figure 1.18), and the same result has now been obtained with all penicillin-sensitive DD-peptidases.[5]

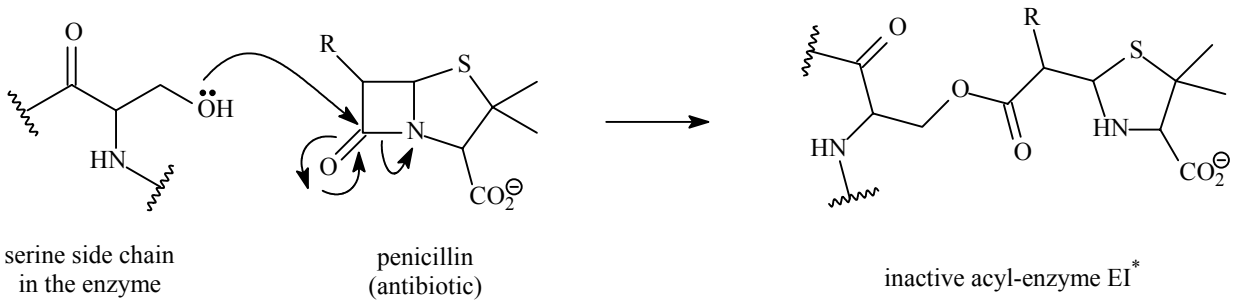


Figure 1.18 Structure of the inactive acyl-enzyme intermediate EI* formed when penicillins react with a penicillin-sensitive enzyme

1.1.5.4 Resistance to *β*-lactam antibiotics

Antibiotics are substances that can be produced by micro organisms and which can either kill or hinder the growth of other micro organisms, as discussed above. In the early stages, the penicillin antibiotics were effective against all types of infections caused by Gram-positive bacteria (*e.g.* skin infections, wound infections, septicaemia, pneumonia, strep throat and many more). Many bacteria are now resistant to most types of antibiotics, and therefore the antibiotics are becoming less and less effective against infections.

Resistance to *β*-lactam antibiotics occurs by four major mechanisms:[11]

- Production of inactivating enzymes *e.g. β*-lactamases
- Alteration in penicillin binding proteins[12]
- Efflux *via* specific drug pumps[13]
- Impaired entry into the bacterial cell *e.g.* Gram-negative bacteria decrease permeability due to the presence of an outer membrane.

Among the Gram-negative bacteria, the most important mechanism is the production of *β*-lactamases, and there are over 470 *β*-lactamases known at present.[14] The resistance to antibiotics is causing a major problem and now efforts are being made to overcome this issue, *i.e.* improving infection control, using drugs more appropriately and developing new antibiotics. It is the latter that our work is focussing on by designing and synthesising novel potential inhibitors of the enzymes which are the target for *β*-lactam antibiotics, the DD-transpeptidase as well as those responsible for the resistance, the *β*-lactamases.

The *β*-lactamase enzyme binds to the antibiotic in a similar fashion to the transpeptidase, both forming acyl-enzyme intermediates with their substrates (Figure 1.19). However, *β*-lactamase has the ability to hydrolyse the intermediate, thus destroying the antibiotic and regenerating the enzyme (Figure 1.19b). With the antibiotic having been destroyed, the transpeptidase is no longer inhibited and the cell wall biosynthesis of the bacteria can be achieved, leading to resistance.

One way to overcome the resistance of some bacteria to *β*-lactam antibiotics is to inhibit the *β*-lactamase enzyme, which is the cause of the resistance. For example, the use of mechanism based inactivators such as clavulanate (**1**), sulbactam (**2**) or tazobactam (**3**) (Figure 1.20), together with a penicillin, is a common therapy. The role of the inactivators is to preserve the antibacterial activity of the penicillin by inactivating the *β*-lactamase.

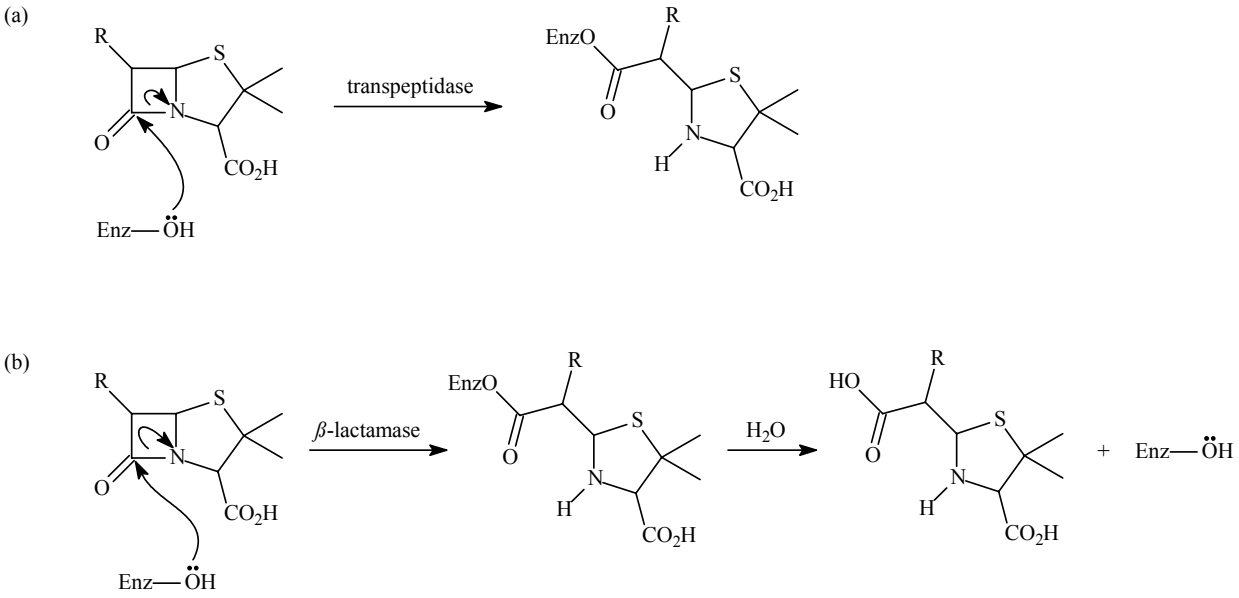
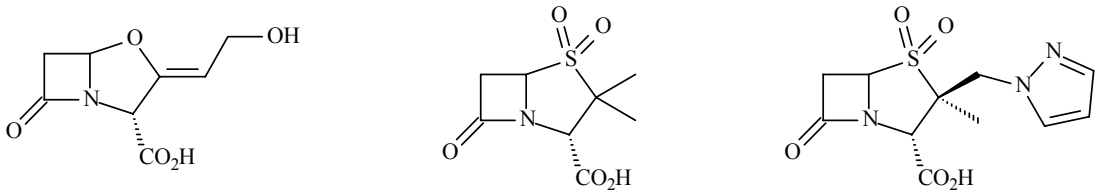


Figure 1.19 Inhibition of transpeptidase by penicillin (a) and trapping of penicillin by *β*-lactamase (b)

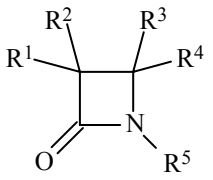


(**1**) (**2**) (**3**)

Figure 1.20 Series of mechanism based inactivators

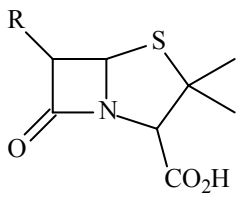
1.1.6 Physico-chemical properties and reactivity of *β*-lactams

The first *β*-lactam was synthesised by Staudinger in 1907.[15] *β*-lactams (**4**) are four-membered cyclic amide derivatives of *β*-aminopropionic acid.

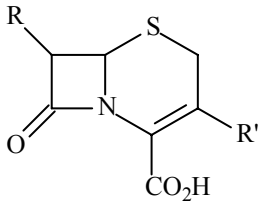


(**4**)

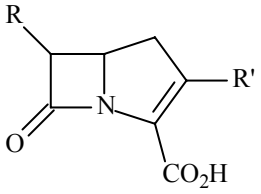
The realisation of the importance of the *β*-lactam ring came with the discovery of the structure of penicillin.[16] To this day, the *β*-lactam antibiotics are the most commonly prescribed drugs for bacterial infections. Examples of *β*-lactam antibiotics are the penicillins (**5**), cephalosporins (**6**), carbapenems (**7**), nocardicins (**8**) and the monobactams (**9**).



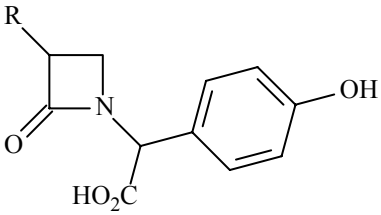
(**5**)



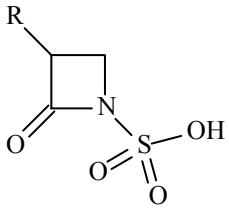
(**6**)



(**7**)



(**8**)



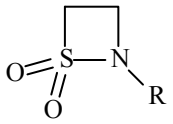
(**9**)

Unfortunately, due to bacterial resistance as discussed above, the effectiveness of the *β*-lactam antibiotics has decreased in recent years and is causing major problems in the health care industry.[17-20] The resistance towards the *β*-lactam antibiotics, as discussed earlier, is primarily due to *β*-lactamases,[21] which open the *β*-lactam ring of the antibiotics, and then are able to hydrolyse the acyl-enzyme intermediate, thus destroying the antibiotic and regenerating the enzyme (Figure 1.19).

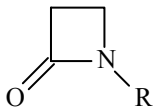
Research groups are therefore investigating novel *β*-lactam compounds and analogues, which are more stable towards the *β*-lactamase enzyme[22,23] and can hence inhibit the transpeptidase enzyme or which inhibit the *β*-lactamase. The Page group here at Huddersfield has been investigating novel *β*-sultams as inhibitors of both of these enzymes.

1.1.7 Physico-chemical properties and reactivity of *β*-sultams

β-Sultams (**10**) are four-membered heterocyclic sulfonamides and are the sulfonyl analogues of *β*-lactams (**11**).



(**10**)



(**11**)

Amide resonance occurs in *β*-lactams but the corresponding sulfonamide resonance probably does not occur in *β*-sultams. The *β*-sultam ring is less stable compared with the *β*-lactam ring because of the increased distortion of the *β*-sultam ring, due to the C-S and N-S bonds which are longer than the corresponding C-C and C-N bonds of the *β*-lactam ring[24] (Figure 1.21). Sulfonamides are usually more stable than amides and *β*-sultams are the first class of sulfonamides that go against this "rule".

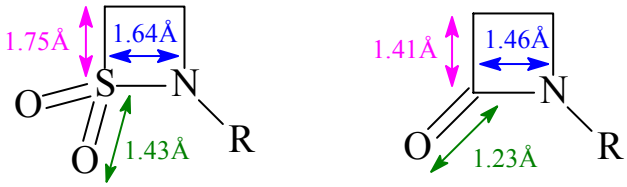


Figure 1.21 Comparison of bond lengths of *β*-sultam with *β*-lactam

The sulfonylation of serine proteases is, prior to work at Huddersfield, a largely unexplored area for the inhibition of these enzymes compared with the traditional acylation processes. In addition to their normal acyl substrates, serine proteases are known to react with other electrophilic centres such as phosphoryl derivatives.[25] The main reason why sulfonylation of serine enzymes is not that well studied is because sulfonyl derivatives are usually much less reactive than their acyl counterparts.[26]

Recently, it has been shown by Page *et al.* that the rates of alkaline hydrolysis of *N*-alkyl (**12**) and *N*-aryl (**14**) *β*-sultams are 10^2 to 10^3 fold greater than those for the corresponding *β*-lactams[27] (**13**) and (**15**) (Figure 1.22). *β*-Sultams also show rate enhancements of $10^9$and 10^7, respectively, compared with the acid and base catalysed hydrolysis of the corresponding acyclic

sulfonamides[28] (**16**), whose rate of alkaline hydrolysis is 10^4 fold slower than the acyclic amide (**17**).

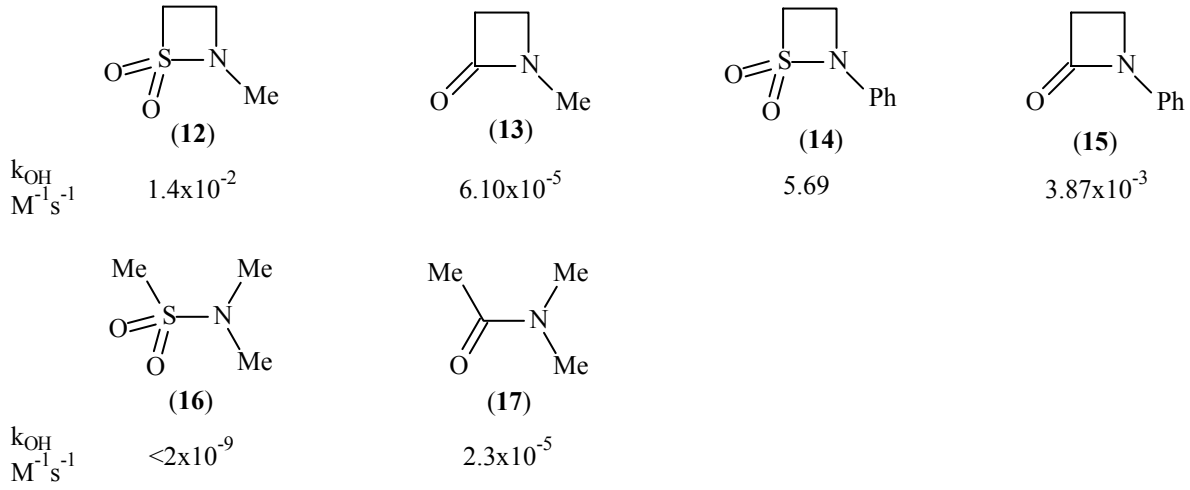


Figure 1.22 Comparison of rates of alkaline hydrolysis of *β*-sultam with *β*-lactam

β-Sultams could therefore act as sulfonylating agents of serine enzymes and inactivate the enzyme by forming a stable adduct (**18**) (Figure 1.23).

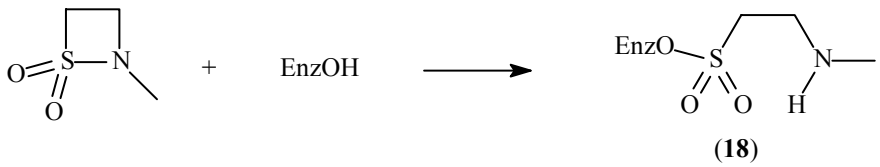


Figure 1.23 Formation of a stable sulfonate ester

The main theme of this thesis is the attempted synthesis of monocyclic *β*-sultams and their conversion into bicyclic analogues. For this reason, this introduction will review methods available already for the synthesis of mono- and bicyclic *β*-sultams. This review will also highlight the reactivity of *β*-sultams, but only on those occasions where the *β*-sultam ring (rather than side-chain substituents) is involved.

1.2 Literature review on the synthesis and the reactivity of 1,2-thiazetidin-1,1-dioxides (*β*-sultams)

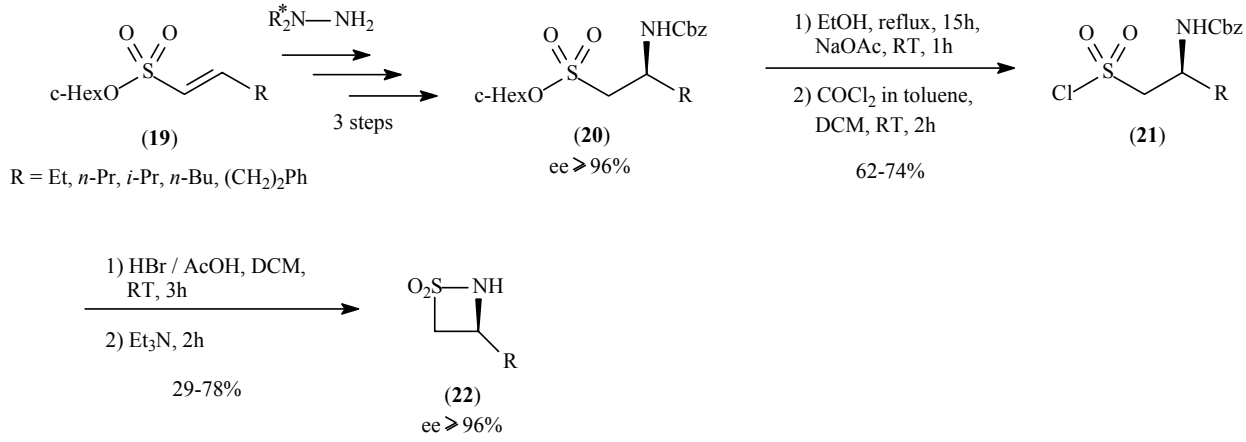
1.2.1 Synthesis of the *β*-sultam ring

The usual methods to synthesise the *β*-sultam ring are either through intramolecular cyclisation of 2-aminoethanesulfonic acid derivatives or 2-hydroxyethanesulfonamides, or through [2+2] cycloadditions of imines with sulfene derivatives or alkenes with *N*-sulfonylamines. Most of these methods have been reviewed.[29,30] Therefore, this review will cover the recent advances in the construction of this four-membered heterocycle reported in the literature from 1996 to early 2009.

The main advances in the formation of 1,2-thiazetin-1,1-dioxides rely on the development of asymmetric syntheses using the known methodologies described above.

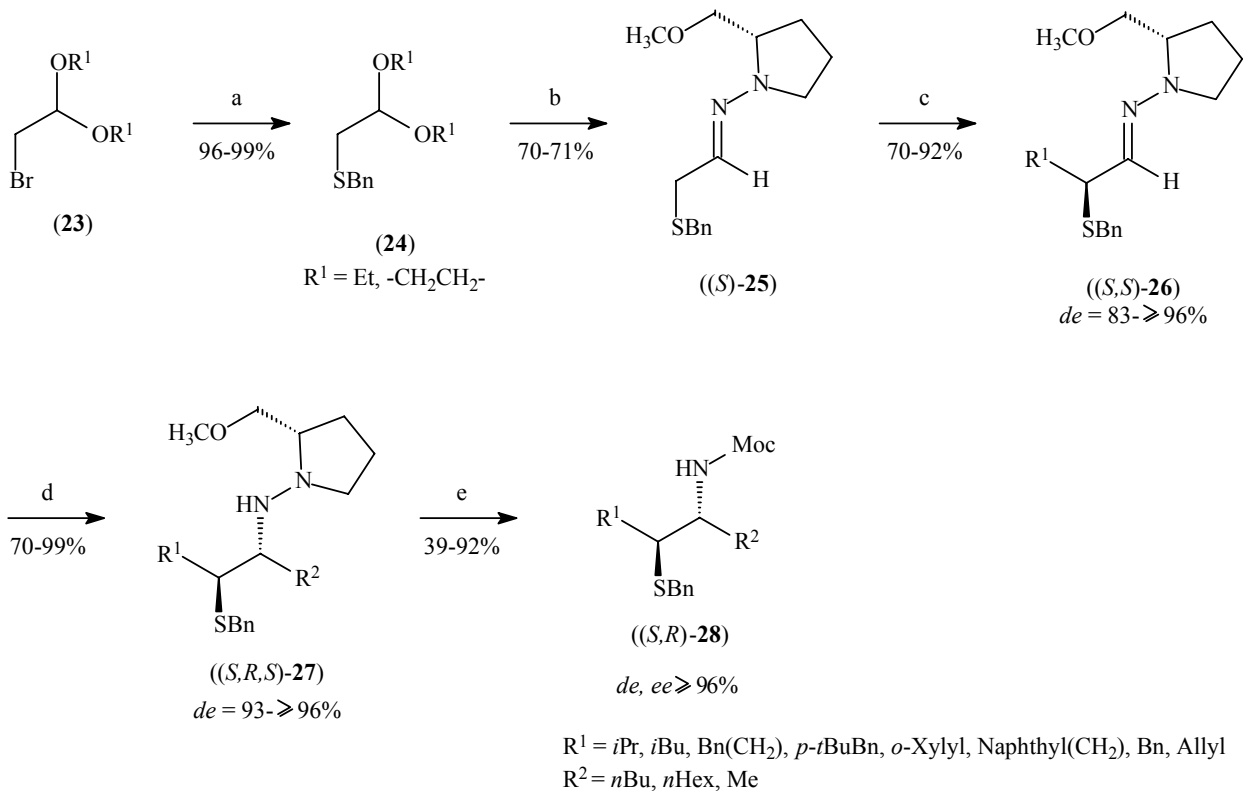
1.2.1.1 Intramolecular cyclisation of 2-aminoethanesulfonic acid derivatives

One of the most reliable approaches to synthesise diastereomerically or enantiomerically pure heterocycles is to introduce the chirality in an open chain precursor and subsequently close the ring in an intramolecular fashion. Enders *et al.* developed an asymmetric synthesis of 3-substituted *β*-sultams using this approach.[31,32] The key step is the chiral synthesis of taurine derivatives from the Lewis acid catalysed aza-Michael addition of an enantiomerically pure hydrazine to alkenylsulfonic esters (**19**), followed by cleavage of the chiral auxiliaries and protection of the amine to give the *N*-protected 1,2-aminosulfonate esters (**20**) (Scheme 1.1).[33] Deprotection and ring closure gave the *β*-sultam (**22**).



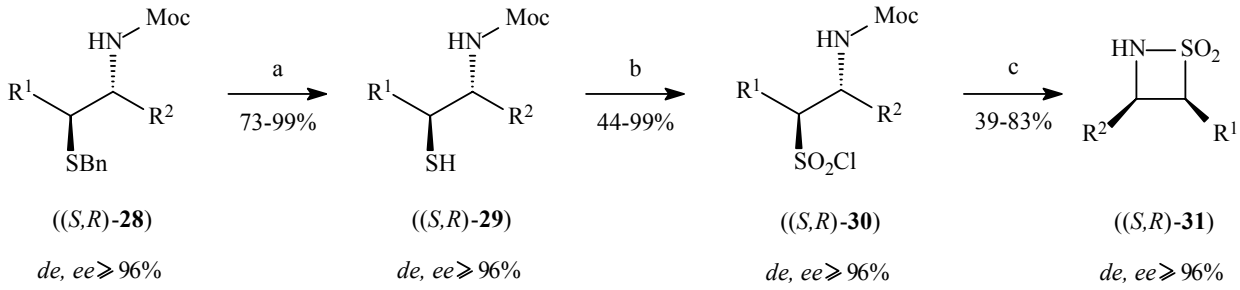
Scheme 1.1

The Enders group also reported a diastereo- and enantioselective synthesis of *cis*-3,4-disubstituted *β*-sultams.[34] Once again, the key step was the introduction of chirality in an open chain precursor. This was achieved by the asymmetric synthesis of *anti*-1,2-sulfanyl amines from chiral hydrazines (Scheme 1.2).[35] For example, treatment of the bromoacetal (**23**) by lithium benzylthiolate afforded the *α*-sulfanylated acetal (**24**), which upon acidic hydrolysis and direct reaction with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) gave the corresponding SAMP hydrazone ((*S*)-**25**). The hydrazone ((*S*)-**25**) was alkylated with various alkyl halides by metallation with lithium diisopropylamide (LDA) to yield the *α*-sulfanylated hydrazone ((*S,S*)-**26**) with high diastereomeric excess. Subsequent nucleophilic 1,2-addition to the C=N double bond with organocerium reagents gave the benzylsulfanylated hydrazines ((*S,R,S*)-**27**). Mild reductive cleavage of the N-N hydrazine bond with a borane-tetrahydrofuran complex , followed by protection of the amine with methoxycarbonyl chloride afforded the desired *anti*-1,2-sulfanyl amines ((*S,R*)-**28**).



Scheme 1.2 a) 1. BnSH, *n*BuLi, THF, 0˚C; 2. **23**, THF, reflux, 4 h; b) 1. 6N HCl, Et_2O, reflux, 7 h ; 2. SAMP, $MgSO_4$, DCM, RT ; c) 1. LDA, THF, -20˚C, 2 h ; 2. R^1X, -100˚C to RT; d) $R^2Li/CeCl_3$, THF, -100˚C to RT; e) 1. BH_3·THF, THF, reflux, 4 h; 2. MocCl, K_2CO_3, DCM, reflux, 3 d.

With compounds ((*S,R*)-**28**) in hand, the formation of the *β*-sultam ring was undertaken (Scheme 1.3).[34] *N*-Protected 1,2-amino thiols ((*S,R*)-**29**) were obtained by cleavage of the *S*-benzyl group of compounds ((*S,R*)-**28**) with lithium in ammonia without epimerisation. Subsequent oxidation of the thiol moiety with H_2O_2 in methanol with an excess of ammonium heptamolybdate, followed by direct conversion of the corresponding amino sulfonic acids to their sodium salts, and chlorination using a phosgene solution in toluene afforded the *N*-protected 1,2-aminosulfonyl chlorides ((*S,R*)-**30**). Finally, the ring closure was performed by cleavage of the Moc-protecting group with HBr-AcOH and *in situ* cyclisation with an excess of triethylamine, yielding the *β*-sultams ((*S,R*)-**31**) with excellent diastereomeric and enantiomeric excesses.

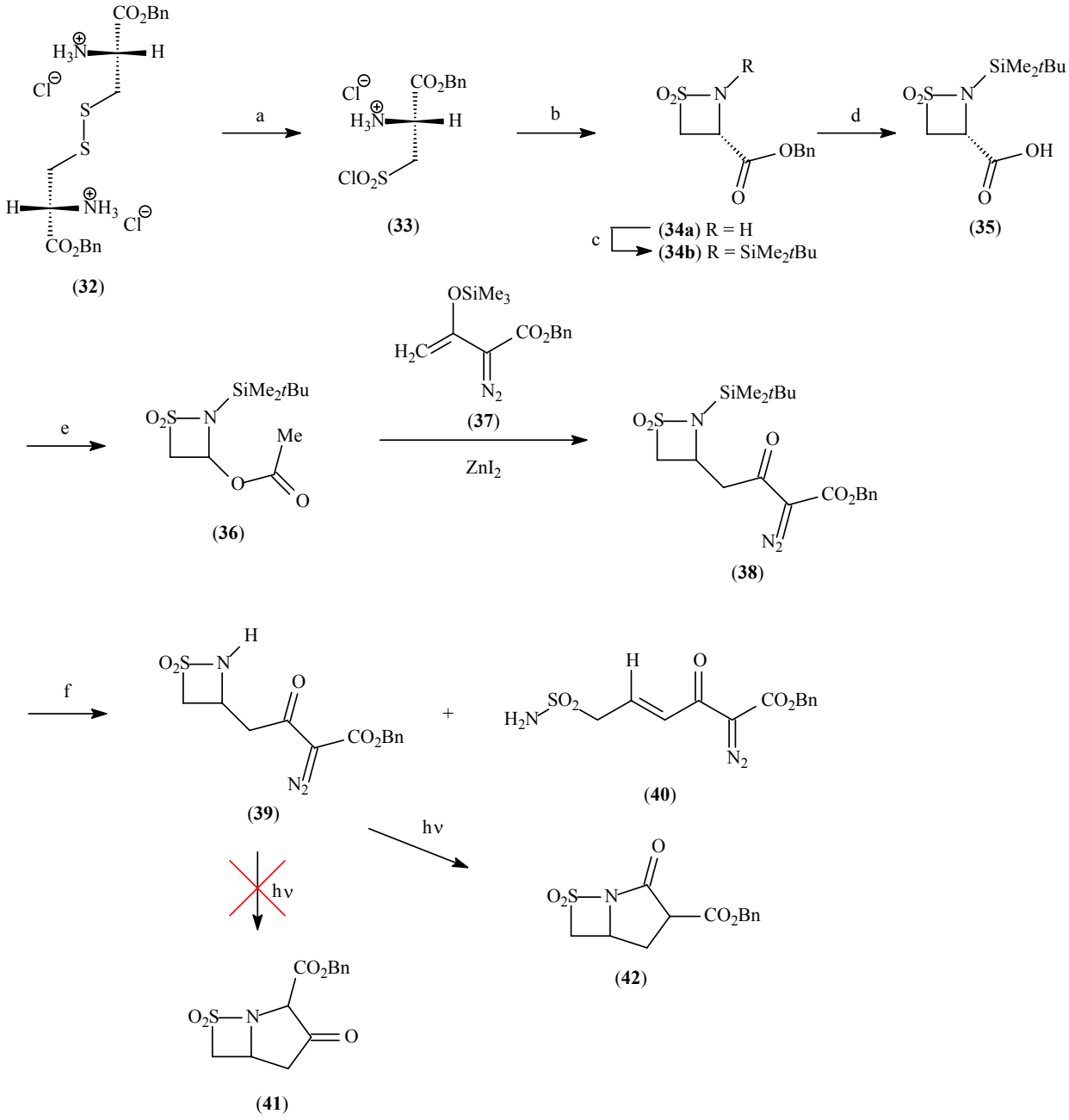


((*S,R*)-**28**) ((*S,R*)-**29**) ((*S,R*)-**30**) ((*S,R*)-**31**)

de, ee ⩾ 96% *de, ee* ⩾ 96% *de, ee* ⩾ 96% *de, ee* ⩾ 96%

Scheme 1.3 a) Li/NH_3, -33˚C, 30 min; b) 1. H_2O_2, $(NH_4)_6Mo_7O_{21}$, MeOH; 2. NaOAc, DCM, RT; 3. $COCl_2$ in toluene, DCM, DMF, RT; c) 1. DCM, HBr-AcOH, 7 d, RT; 2. Et_3N, 2 h, 0˚C

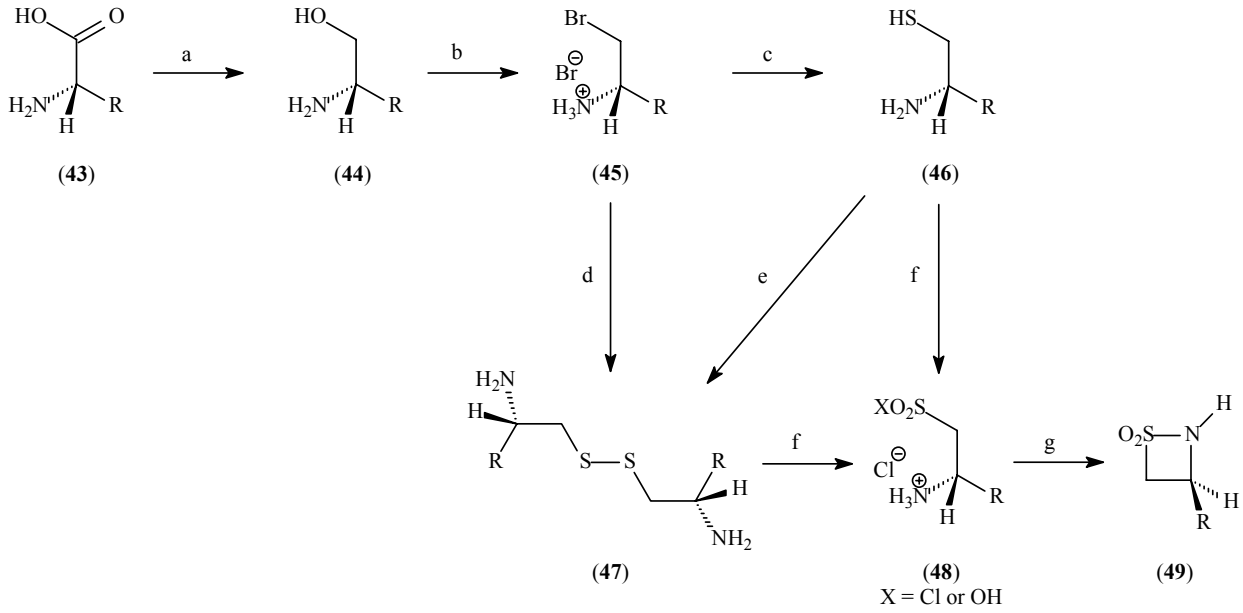
In 1997, Otto *et al.* synthesised bicyclic *β*-sultams from 3-acetoxy-1,2-thiazetidin-1,1-dioxide (**36**) (Scheme 1.4).[36] Oxidative chlorination of benzyl L-cystine ester dihydrochloride (**32**), obtained from the esterification of L-cystine with benzyl alcohol, gave the 2-aminosulfonyl chloride hydrochloride (**33**). Cyclisation in chloroform in the presence of ammonia afforded the *β*-sultam (**34a**), which was silylated with *tert*-butylchlorodimethylsilane to form the more stable *N*-protected *β*-sultam (**34b**). The *β*-sultam (**35**) was obtained by hydrogenation of the benzyl ester. Treatment of compound (**35**) with lead tetraacetate and copper acetate afforded the 3-acetoxy-*β*-sultam (**36**) with loss of the stereochemistry. Compound (**38**) was obtained by the reaction of (**36**) with the silyl enol ether of benzyl *α*-diazoacetoacetate (**37**) in the presence of zinc iodide. Desilylation with tetrabutylammonium fluoride (TBAF) in THF gave the deprotected *β*-sultam (**39**), but also caused a type of retro-Michael addition to form the open-chained sulfonamide (**40**) as a side-product. Photochemical cyclisation of the deprotected *β*-sultam (**39**) afforded the bicyclic *β*-sultam (**42**) instead of the expected bicyclic *β*-sultam (**41**).



Scheme 1.4 a) Cl_2, H_2O; b) NH_3, $CHCl_3$; c) *n*-BuLi, THF, -78˚C, TBDMS-Cl; d) H_2, Pd-C; e) $Pb(OAc)_4$, $Cu(OAc)_2$, MeCN; f) TBAF, THF.

In 2004, Otto *et al.* reported the asymmetric synthesis of the *β*-sultam ring from enantiomerically pure *α*-amino acids (Scheme 1.5).[37] The amino acids (**43a-e**) were reduced with $LiAlH_4$ in THF to their corresponding 2-aminoethanols (**44a-e**), which were converted to the bromo compounds (**45a-e**), either by reaction with HBr, with a mixture of HBr and PBr_3, or with thionyl bromide. These salts (**45a-e**) were transformed, either into the thiols (**46**) with thiourea and tetraethylenepentamine, or into the disulfides (**47**) with iodine in ethanol. The air sensitivity of thiols (**46**) afforded immediate oxidation to the corresponding sulfonyl chlorides (**48**) with

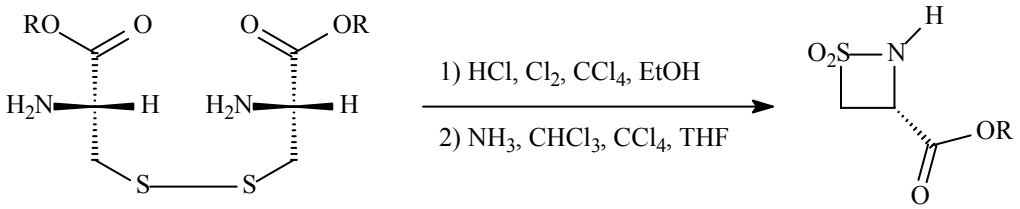
Cl_2/HCl in a mixture of ethanol and carbon tetrachloride. Cyclisation of compounds (**48**) with ammonia in chloroform at 0˚C afforded the enantiomerically pure 3-substituted *β*-sultams (**49a-e**). The disulfides (**47**) could also be oxidised with Cl_2/HCl in ethanol and carbon tetrachloride, thus providing an alternative route to compounds (**48**) and (**49**).



a R = Me, **b** R = *i*-Pr, **c** R = *i*-Bu, **d** R = *s*-Bu, **e** R = $PhCH_2$

Scheme 1.5 a) $LiAlH_4$, THF; b) HBr, Ph_3P or $SOBr_2$; c) Thiourea, EtOH; d) $Na_2S_2O_3$, I_2, EtOH; e) I_2, EtOH; f) HCl, Cl_2, CCl_4, EtOH; g) NH_3, $CHCl_3$, CCl_4, THF.

The Otto group also reported[37] the synthesis of *β*-sultams (**51a-b**) from L-cystine dialkyl ester hydrochlorides (**50a-b**), obtained from L-cystine, by oxidative chlorination (Scheme 1.6).



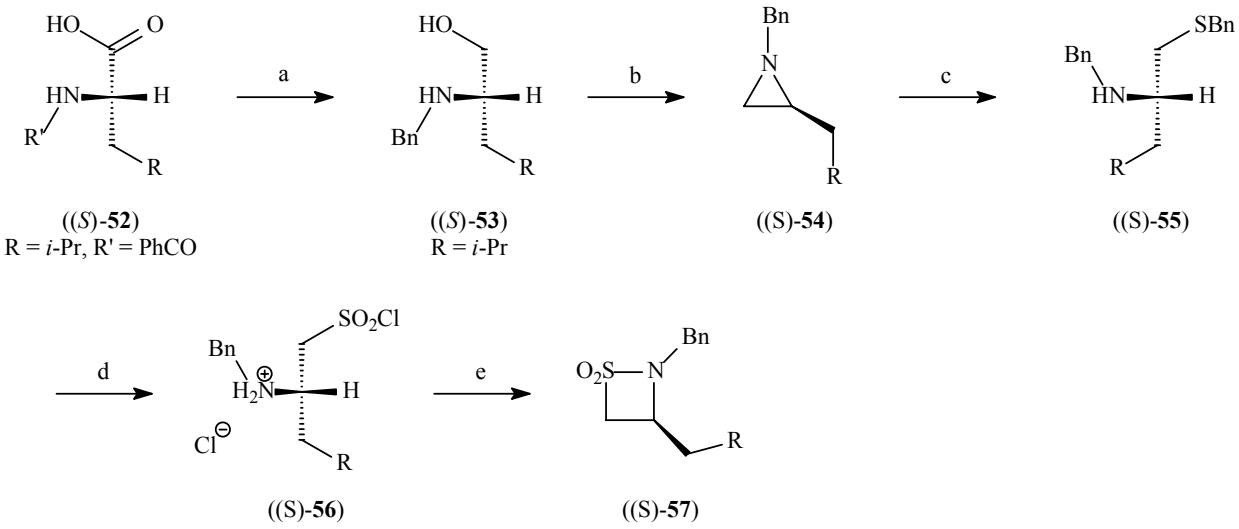
(**50a**) R = Me
(**50b**) R = Et

(**51a**) R = Me
(**51b**) R = Et

Scheme 1.6

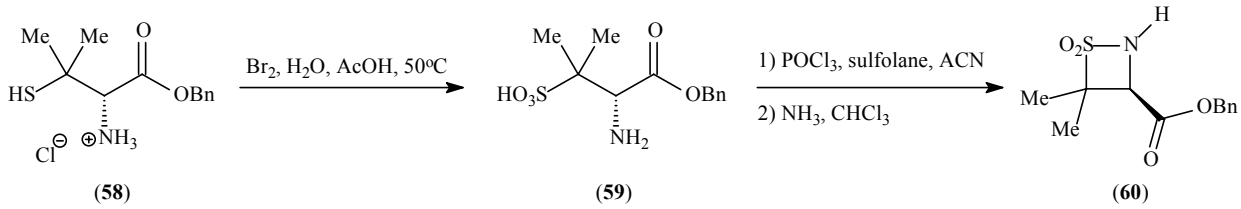
N-Substituted *β*-sultams may be synthesised by deprotonation of the nitrogen with a base (Et_3N, NaOH, or $NaNH_2$) at low temperature, followed by alkylation or acylation. However, this

method may not be appropriate in a stereoselective synthesis of 1,2-thiazetidin-1,1-dioxides, since deprotonation may lead to partial racemisation. Therefore, Otto *et al.* introduced the *N*-substituent into the starting material using *N*-benzoyl-L-leucine ((S)-**52**) (Scheme 1.7).[37] Reduction of *N*-benzoyl-L-leucine ((*S*)-**52**) with lithium aluminium hydride in THF yielded the *N*-benzylated 1,2-amino alcohol ((*S*)-**53**), which was cyclised to the optically active *N*-benzylated aziridine ((*S*)-**54**) with triphenylphosphine in acetonitrile. Ring opening by nucleophilic substitution with sodium benzyl thiolate afforded the sulfide ((*S*)-**55**). Oxidative chlorination of compound ((*S*)-**55**) gave the corresponding sulfonyl chloride ((*S*)-**56**). Subsequent cyclisation with ammonia in chloroform, THF and carbon tetrachloride afforded the optically active *β*-sultam ((*S*)-**57**).



Scheme 1.7 a) $LiAlH_4$, THF; b) Ph_3P, Et_3N, CCl_4, MeCN; c) Na/EtOH, $PhCH_2SH$; d) HCl, Cl_2, $CHCl_3$, CCl_4, 0˚C; e) NH_3, $CHCl_3$, THF, CCl_4.

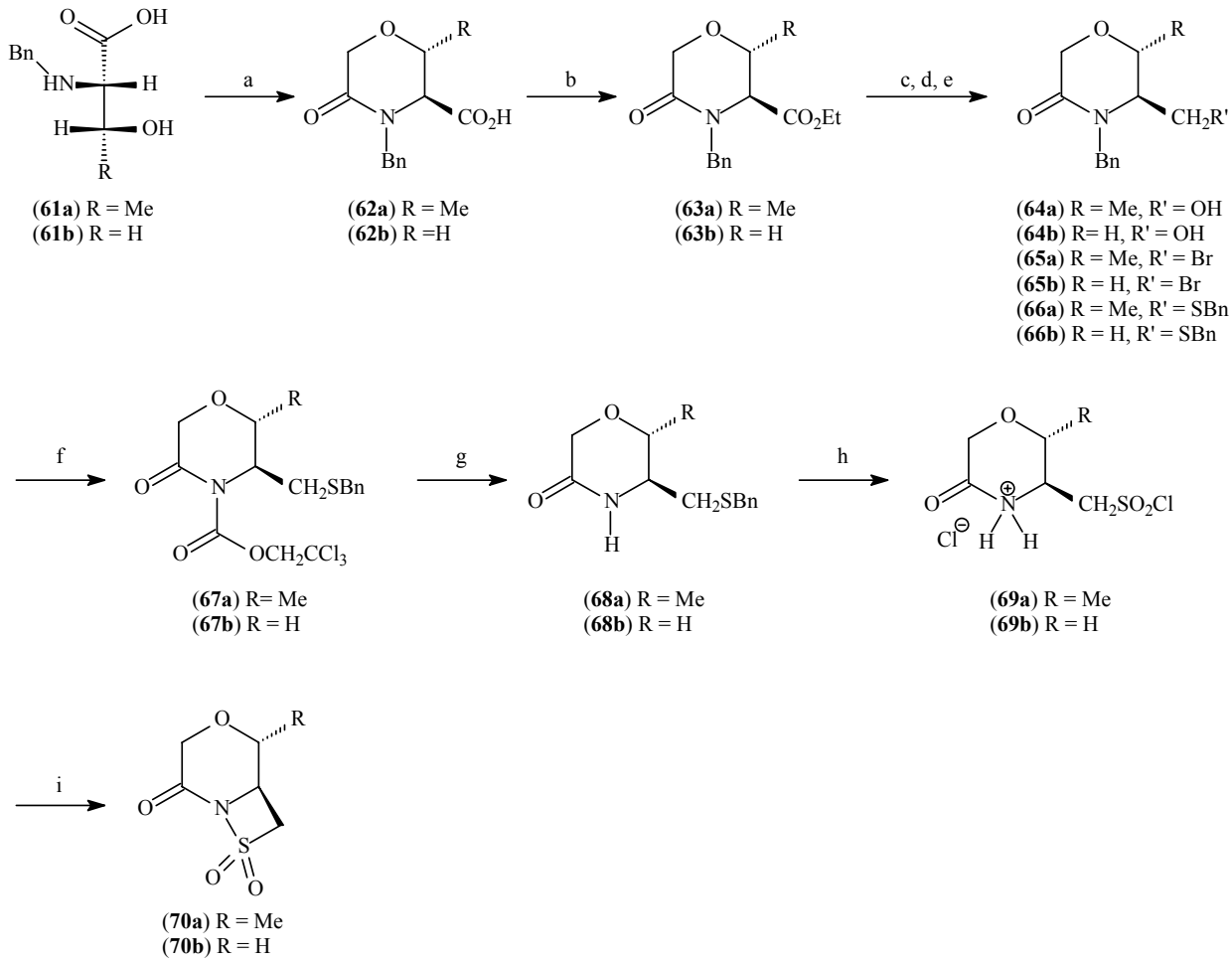
Otto *et al.* also synthesised the 4,4-dimethyl-1,2-thiazetidin-3-carboxylate 1,1-dioxide (**60**) from D-penicillamine benzyl ester hydrochloride (**58**) (Scheme 1.8).[37] Oxidation of compound (**58**) with bromine in dilute acetic acid yielded the taurine derivative (**59**) which, after chlorination with phosphorus oxychloride in acetonitrile and sulfolane, and subsequent cyclisation with triethylamine gave the enantiomerically pure *β*-sultam (**60**).



(**58**) (**59**) (**60**)

Scheme 1.8

The same research group also performed the stereospecific synthesis of bicyclic *β*-sultams (**70a**) and (**70b**) from *N*-benzylated L-threonine (**61a**) and L-serine (**61b**) (Scheme 1.9).[37] Cyclisation of the starting materials with chloroacetyl chloride afforded the morpholine derivatives (**62a**) and (**62b**), which, after esterification to (**63a**) and (**63b**), were reduced with $LiAlH_4$ to the corresponding alcohols (**64a**) and (**64b**). The latter were converted via the bromo compounds (**65a**) and (**65b**) into the benzyl sulfides (**66a**) and (**66b**). Replacement of the benzyl group by the (2,2,2-trichloroethoxy)carbonyl group afforded compounds (**67a**) and (**67b**), which upon treatment with zinc in glacial acetic acid resulted in conversion to the morpholine derivatives (**68a**) and (**68b**). Oxidative chlorination gave the sulfonyl chlorides (**69a**) and (**69b**). Cyclisation with ammonia in chloroform yielded the bicyclic *β*-sultams (**70a**) and (**70b**).



(**61a**) R = Me
(**61b**) R = H

(**62a**) R = Me
(**62b**) R =H

(**63a**) R = Me
(**63b**) R = H

(**64a**) R = Me, R' = OH
(**64b**) R= H, R' = OH
(**65a**) R = Me, R' = Br
(**65b**) R = H, R' = Br
(**66a**) R = Me, R' = SBn
(**66b**) R = H, R' = SBn

(**67a**) R= Me
(**67b**) R = H

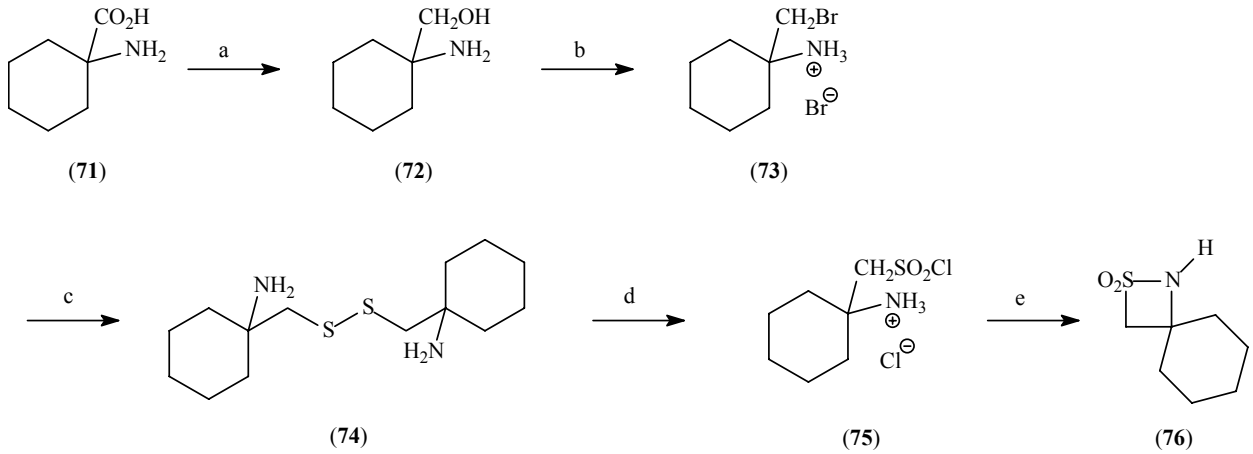
(**68a**) R = Me
(**68b**) R = H

(**69a**) R = Me
(**69b**) R = H

(**70a**) R = Me
(**70b**) R = H

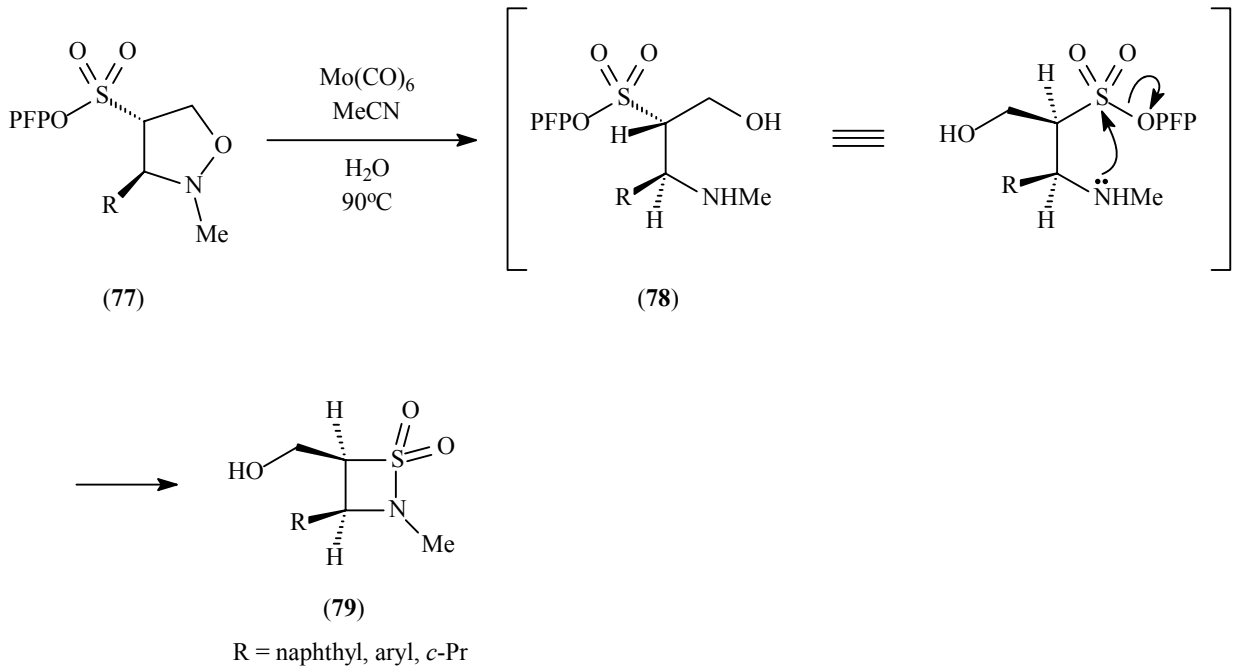
Scheme 1.9 a) $CH_2ClCOCl$, NaOH; b) $SOCl_2$, EtOH; c) $LiAlH_4$, THF; d) Ph_3P, CBr_4, MeCN; e) NaOH, BnSH, EtOH; f) Cl_3CCH_2OCOCl, K_2CO_3; g) Zn, AcOH; h) HCl, Cl_2, $CHCl_3$, CCl_4; i) NH_3, $CHCl_3$.

Finally, the Otto group has reported the synthesis of the 3-*spiro*-cyclohexyl-*β*-sultam (**76**) (Scheme 1.10). Reduction of 1-aminocyclohexanecarboxylic acid (**71**) with lithium aluminium hydride yielded the 1,2-aminoalcohol (**72**), which was transformed to the hydrobromide salt (**73**) with hydrobromic acid and phosphorus tribromide. Treatment with sodium metabisulfite and iodine gave the disulfide (**74**). Oxidative cleavage with chlorine afforded the chlorosulfonyl ammonium chloride (**75**), and subsequent ring closure with ammonia in chloroform yielded the *β*-sultam (**76**).[37]



Scheme 1.10 a) $LiAlH_4$; b) HBr, PBr_3; c) $Na_2S_2O_3$, I_2, H_2O; d) HCl, Cl_2, CCl_4, EtOH; e) NH_3, $CHCl_3$.

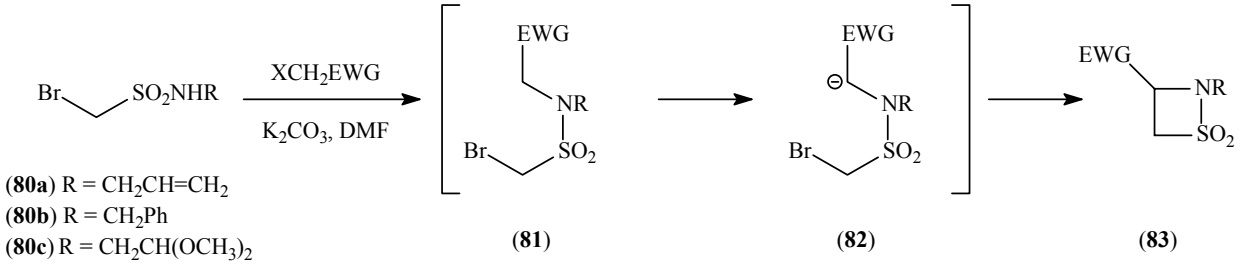
Recently, Caddick *et al.* have developed an interesting and original stereoselective synthesis of *β*-sultams from isoxazolidines substituted by a pentafluorophenyl (PFP) sulfonate moiety (Scheme 1.11).[38] Isoxazolidines (**77**) were prepared from the regio- and stereoselective 1,3-dipolar cycloaddition of the corresponding vinyl sulfonate with a series of nitrones.[39] Mild reductive N-O bond cleavage with $Mo(CO)_6$ afforded the 2-aminosulfonate ester (**78**), which simply underwent an intramolecular cyclisation to form the *β*-sultams (**79**) *via* a nucleophilic substitution of the amine on the sulfonate ester, releasing the stable pentafluorophenolate anion as a good leaving group.



Scheme 1.11

1.2.1.2 Intramolecular cyclisation of bromomethanesulfonamides

In 2004, Paquette *et al*. described the synthesis of *β*-sultams (**83**) from *N*-substituted bromomethanesulfonamides (**80**) by reaction with *α*-halo ketones, esters, or nitriles in DMF with two equivalents of potassium carbonate (Scheme 1.12).[40]



(**80a**) R = $CH_2CH{=}CH_2$
(**80b**) R = CH_2Ph
(**80c**) R = $CH_2CH(OCH_3)_2$

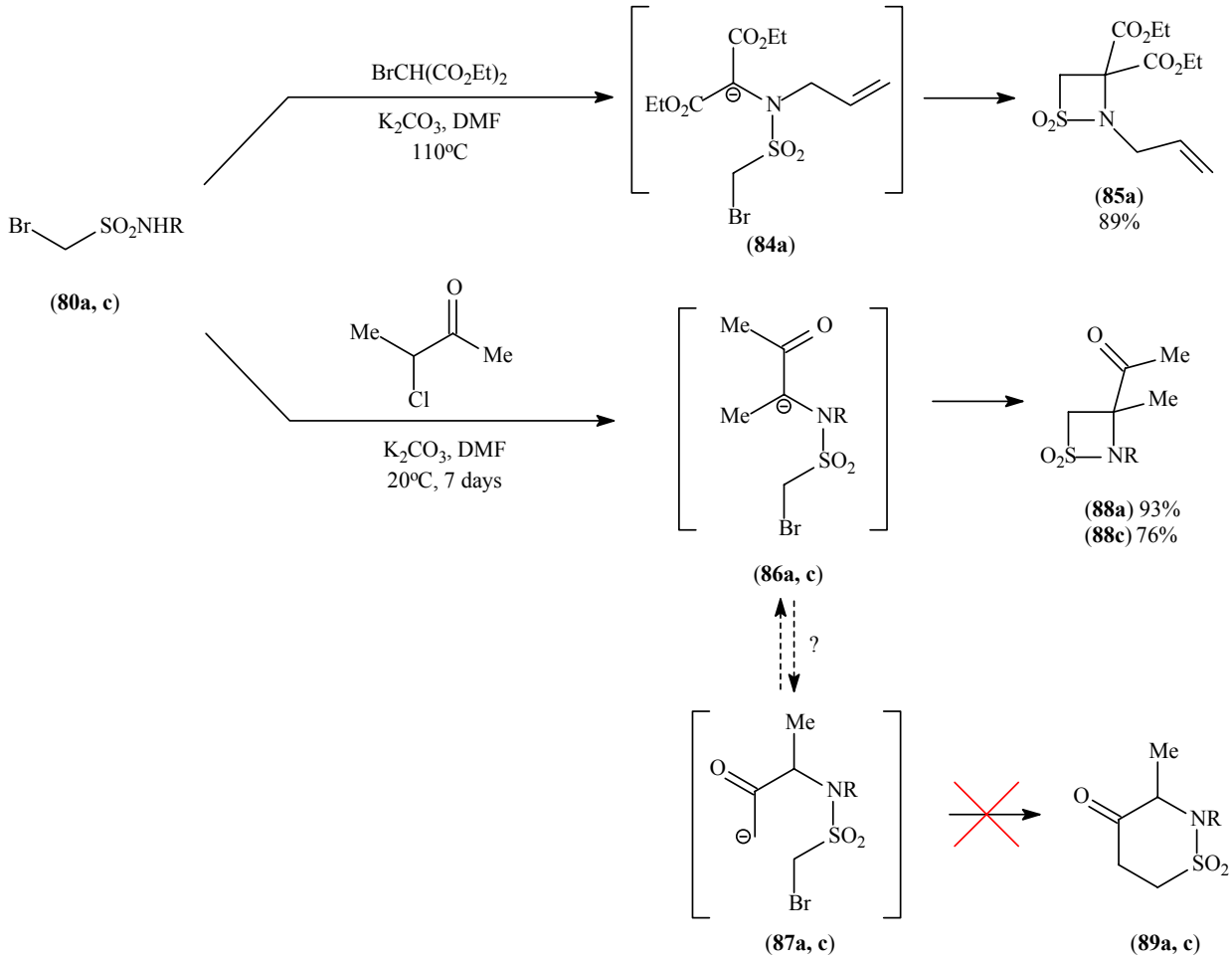
(**81**) (**82**) (**83**)

	R	X	EWG	Yield of (**83**), %
(**83d**)	$-CH_2CH{=}CH_2$	Cl	$-COCH_3$	59
(**83e**)	$-CH_2CH{=}CH_2$	Br	-COPh	81
(**83f**)	$-CH_2CH{=}CH_2$	Br	-COOEt	56
(**83g**)	$-CH_2CH{=}CH_2$	Br	-CN	61
(**83h**)	$-CH_2Ph$	Br	-COOEt	70

Scheme 1.12

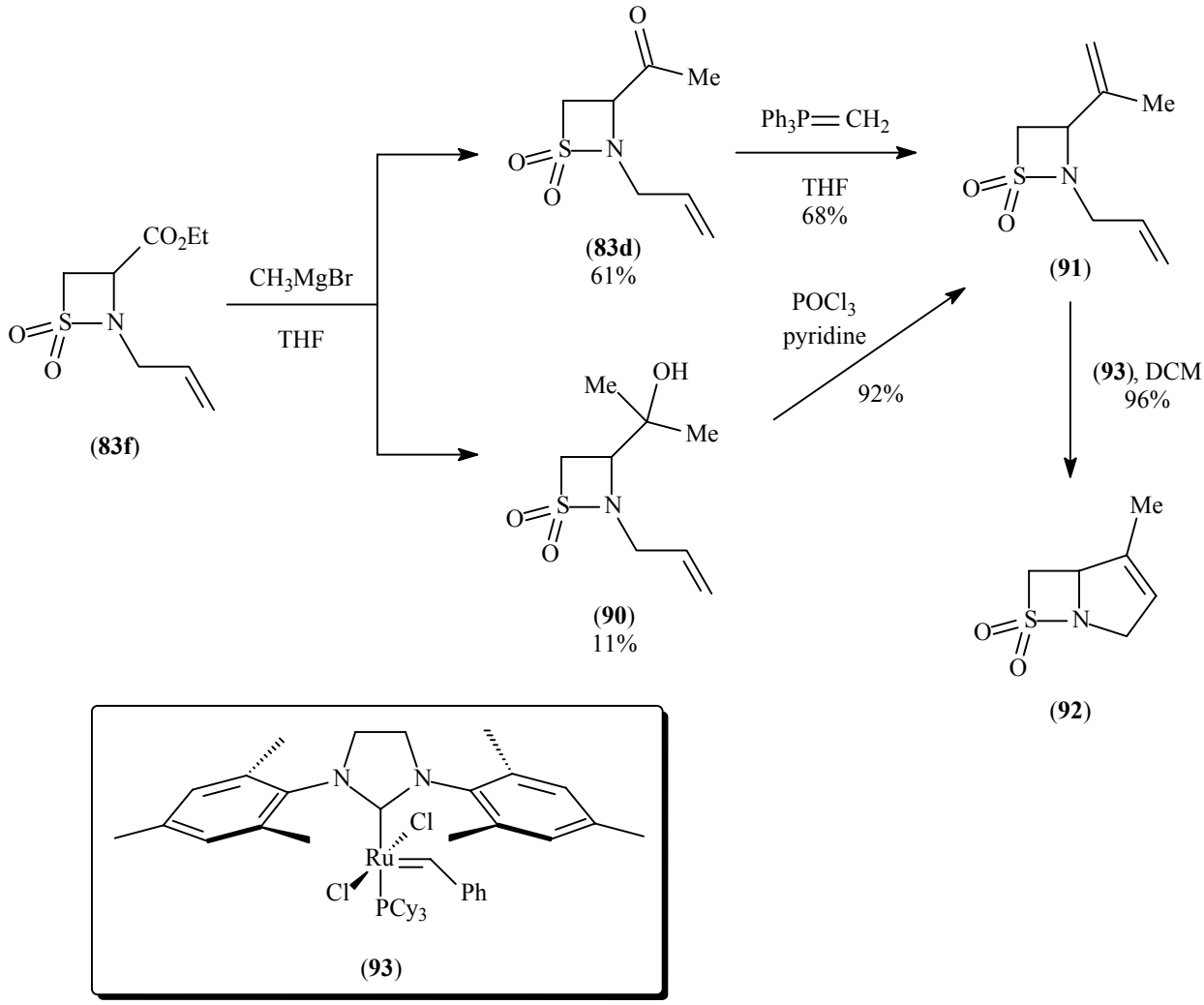
The bromomethanesulfonamides (**80**) were prepared by reacting the relevant primary amine in DCM with DMAP and Hünig's base with the corresponding bromomethanesulfonyl chlorides, obtained by reaction of dibromomethane with sodium sulfite, tetrabutylammonium hydrogen sulfonate, and phosphorus pentachloride.[41,42]

This process also performed nicely with secondary halides such as diethyl bromomalonate and 3-chlorobutan-2-one (Scheme 1.13). In the latter example, it is interesting to note that there is clearly no competition between (**86a,c**) and (**87a, c**) for the ring closure since only the four-membered ring (**88a,c**) is formed and the six-membered ring (**89a, c**) is not formed.



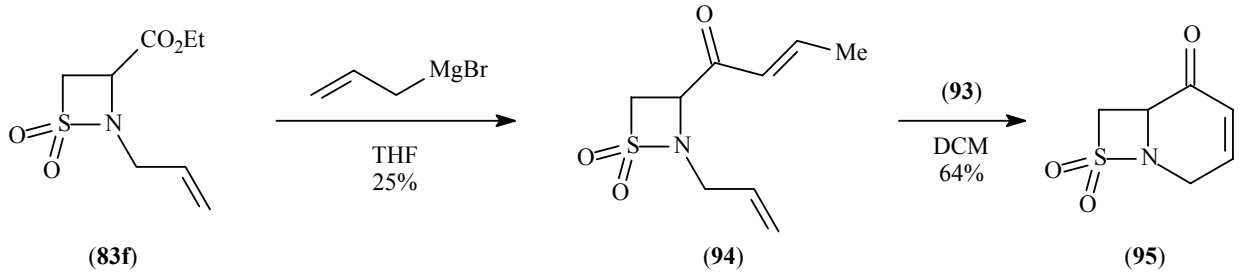
Scheme 1.13

With *β*-sultams (**83**) in hands, Paquette *et al.* undertook the synthesis of bicyclic derivatives (Scheme 1.14). The addition of methylmagnesium bromide to the ester (**83f**) gave the ketone (**83d**) and the alcohol (**90**). Compound (**83d**) was subjected to a Wittig olefination with methylenetriphenylphosphine, and compound (**90**) was dehydrated with phosphorus oxychloride in pyridine to afford the diene (**91**). Ring-closing metathesis (RCM) of (**91**) in the presence of (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride) (**93**) generated the bicyclic *β*-sultam (**92**).



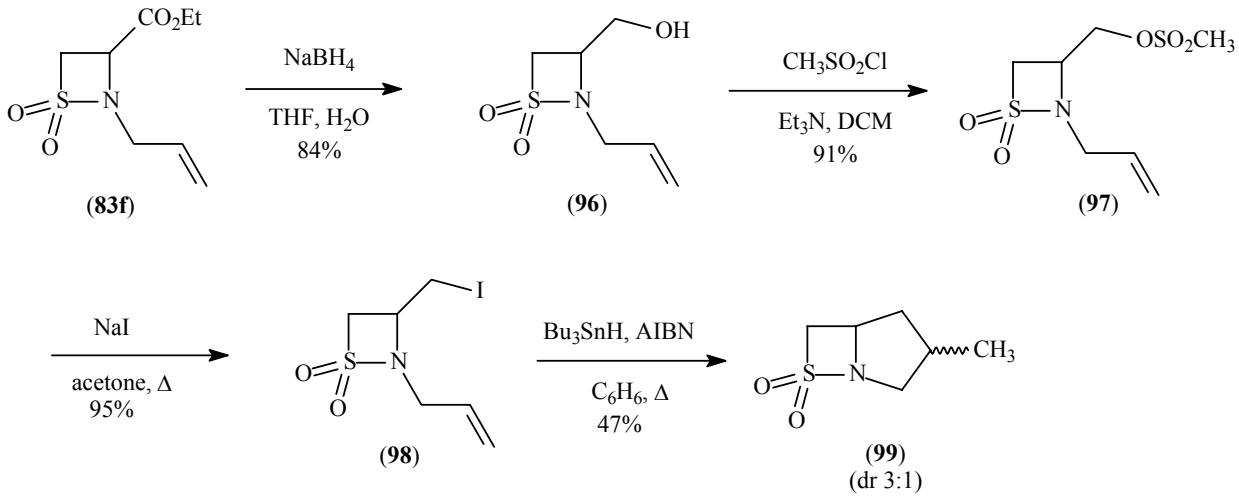
Scheme 1.14

A similar route employing the condensation of (**83f**) with one equivalent of allylmagnesium bromide resulted in the formation of the diene (**94**) (Scheme 1.15). RCM of (**94**) in the presence of the ruthenium catalyst (**93**) yielded the bicyclic *β*-sultam (**95**).



Scheme 1.15

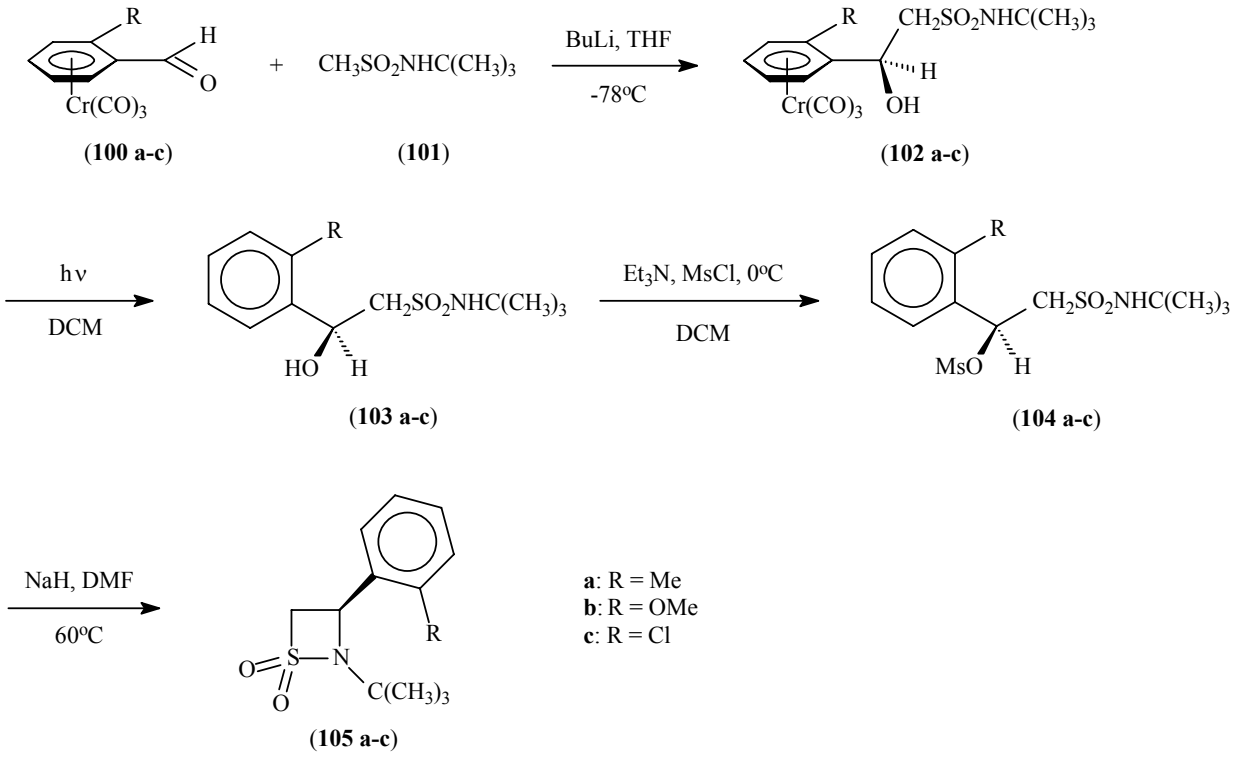
In a final adaptation, the same report detailed the synthesis of the *β*-sultam (**99**) from the allyl *β*-sultam (**83f**) (Scheme 1.16). Reduction of the ester afforded the corresponding alcohol (**96**), which was converted to the mesylate (**97**) with methanesulfonyl chloride in the presence of triethylamine. Heating with sodium iodide in acetone gave the primary iodide (**98**), which was converted to a primary radical with tributyltin hydride in heated benzene to undergo a cyclisation, affording the *β*-sultam (**99**) as a 3:1 mixture of diastereoisomers.



Scheme 1.16

1.2.1.3 Intramolecular cyclisation of 2-hydroxyethanesulfonamides

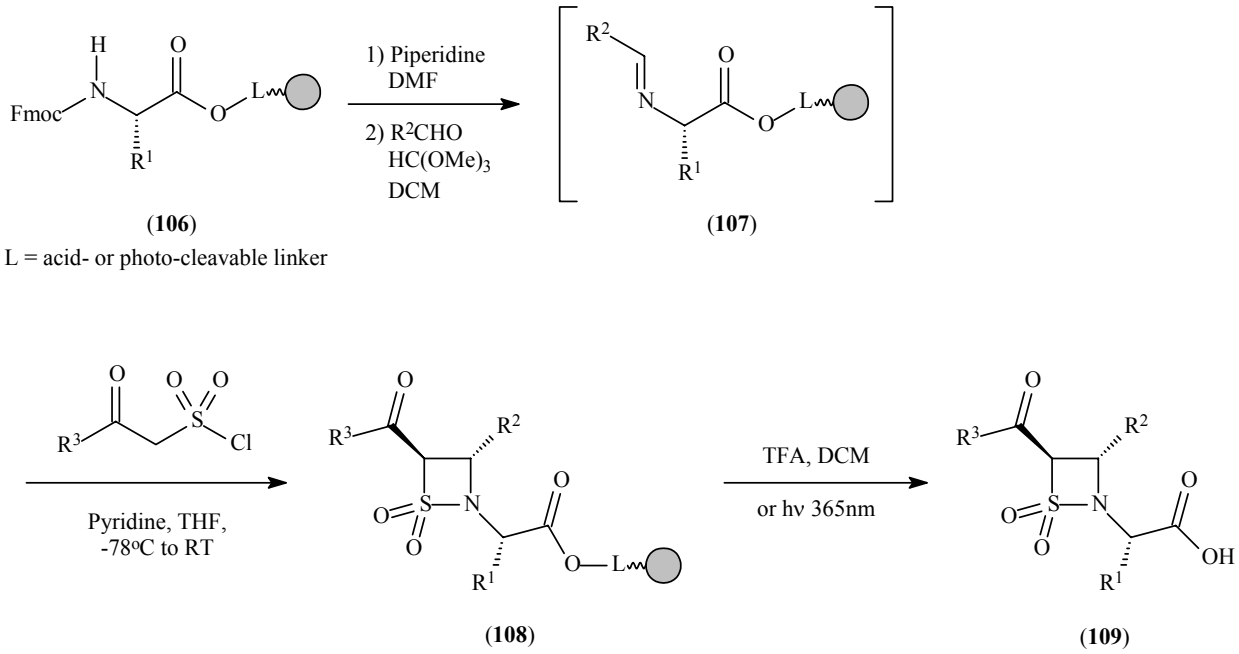
In 1999, Baldoli *et al.* reported the stereoselective synthesis of 3-aryl-*β*-sultams using chiral tricarbonyl(η^6-arene)chromium(0) complexes (Scheme 1.17).[43] Nucleophilic addition of the *N*-*tert*-butylmethanesulfonamide (**101**) using butyllithium in dry THF at -78˚C on optically pure tricarbonyl(2-substituted benzaldehyde)chromium(0) complexes (**100 a-c**) afforded the complexed 2-hydroxyethanesulfonamides (**102 a-c**). Exposure of a solution of compounds (**102 a-c**) in DCM to air and sunlight yielded the uncomplexed 2-hydroxysulfonamides (**103 a-c**). Mesylation of the hydroxyl group followed by intramolecular nucleophilic substitution using sodium hydride as a base in DMF at 60˚C gave the *β*-sultams (**105 a-c**) in good yield with high enantiopurity (e.e. ≥ 98%).



Scheme 1.17

1.2.1.4 [2+2] Cycloaddition reactions

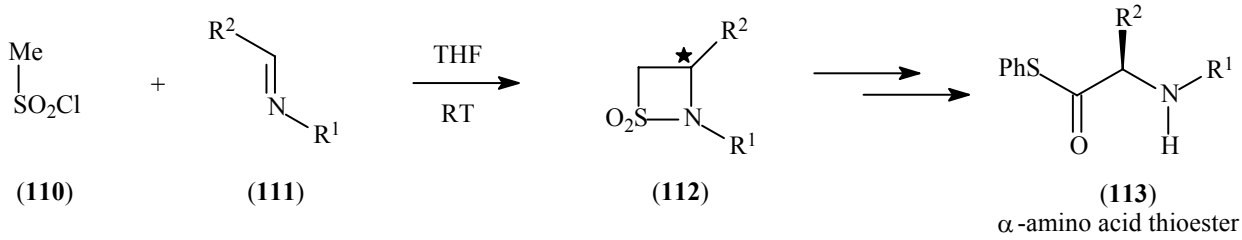
In 1997, Gordeev *et al.* reported the first solid-phase synthesis of *β*-sultams based on the [2+2] cycloaddition of activated sulfenes with imines (Scheme 1.18).[44] Condensation of immobilised amino acids (**106**) with aldehydes in the presence of piperidine gave rise to the formation of imines (**107**). Addition of chlorosulfonyl acetates as reactive sulfene precursors to imines (**107**) in the presence of pyridine as a base in THF at -78˚C followed by gradual warm-up to RT resulted in the stereospecific formation of *trans*-*β*-sultams (**108**). Acidolytic or photolytic cleavage from the solid support afforded the free *β*-sultams (**109**). The diastereoselectivity of the [2+2] cycloaddition might be accounted for by a two-step mechanism starting with the sulfonylation of the imines (**107**) to generate sulfonyliminium intermediates, which cyclise to *β*-sultams (**108**) in the presence of a base.[45]



(**106**) (**107**) (**108**) (**109**)

Scheme 1.18

Kataoka *et al.* described an interesting enantioselective synthesis of *α*-amino acid thioesters (**113**) based on a 1,3-asymmetric induction in the [2+2] cycloaddition of a sulfene intermediate with a chiral imine to form the *β*-sultam ring, followed by a Pummerer reaction.[46] The key step is the ring formation of the *β*-sultam (**112**) from mesyl chloride (**110**) and imine (**111**) (Scheme 1.19) and the results are summarised in Table 1.1.



(**110**) (**111**) (**112**) (**113**)

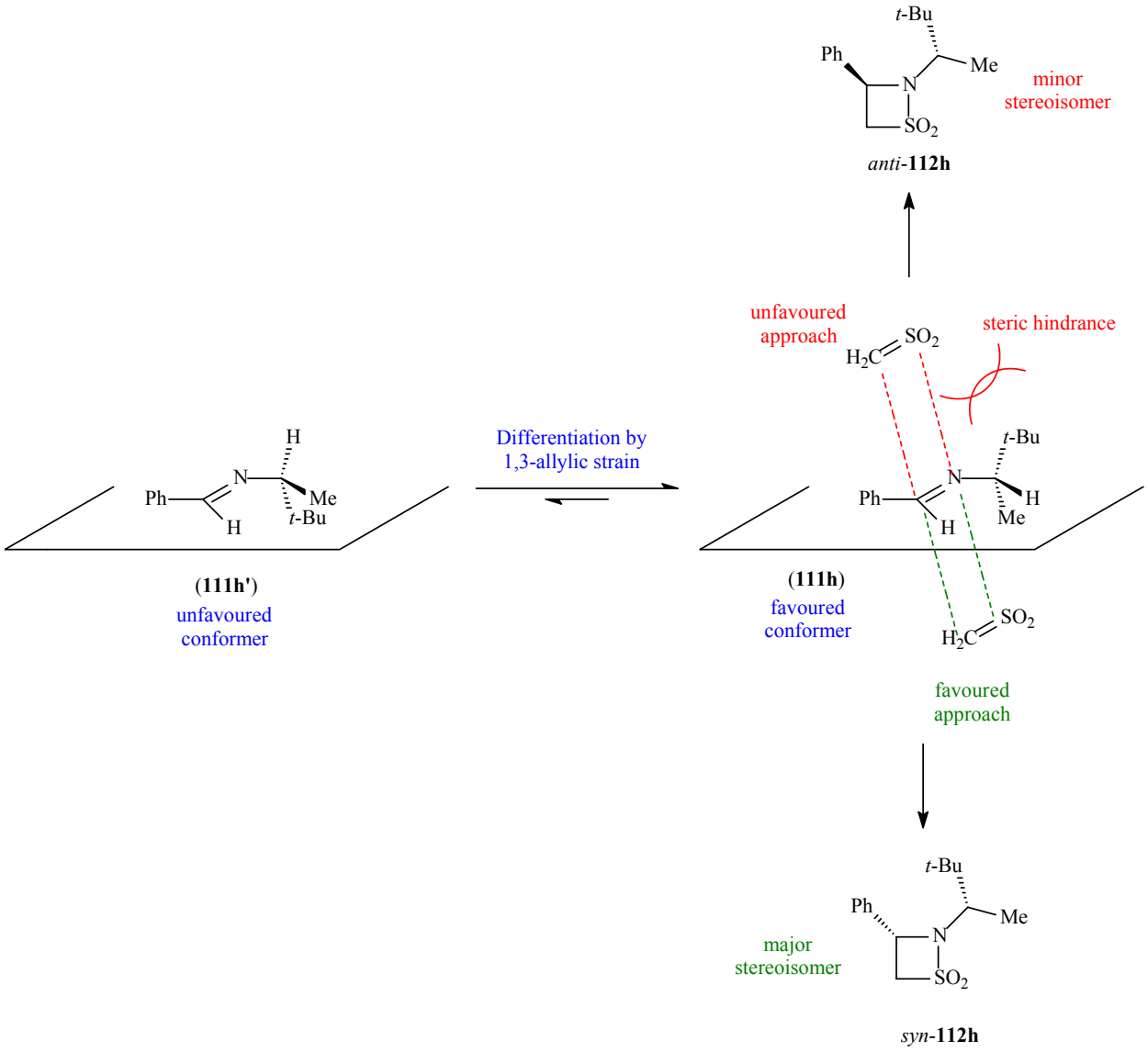
Scheme 1.19

R^1	R^2	Product (% Yield)[b]
(*R*)-*α*-methylbenzyl	Ph	**112a** (70, 42% de)[c]
(*S*)-*α*-methylbenzyl	*t*-Bu	**112b** (32, 45% de)[c]
(*R*)-*α*,4-dimethylbenzyl	Ph	**112c** (72, 44% de)[c]
rac-1-(1-naphtyl)ethyl	Ph	**112d** (53, 47% de)[c]
rac-1-indanyl	Ph	**112e** (36, 50% de)[c]
rac-1-cyclohexylethyl	Ph	**112f** (60, 67% de)[d]
(1*R*, 2*R*, 3*R*, 5*S*)-isopinocampheyl	Ph	**112g** (54, 80% de)[d]
rac-1-*tert*-butylethyl	Ph	**112h** (67, >95% de)[d]
rac-1-(methoxymethyl)propyl	Ph	complex mixture
(*R*)-2-(methoxymethyl)pyrrolidinyl	Ph	complex mixture

[a] 2 equivalents of imines were used based on MsCl. [b] Isolated yield based on MsCl. Diastereomeric excess was calculated by the ^{1}H NMR spectrum of the reaction mixture. [c] Separable stereoisomers. [d] Inseparable stereoisomers.

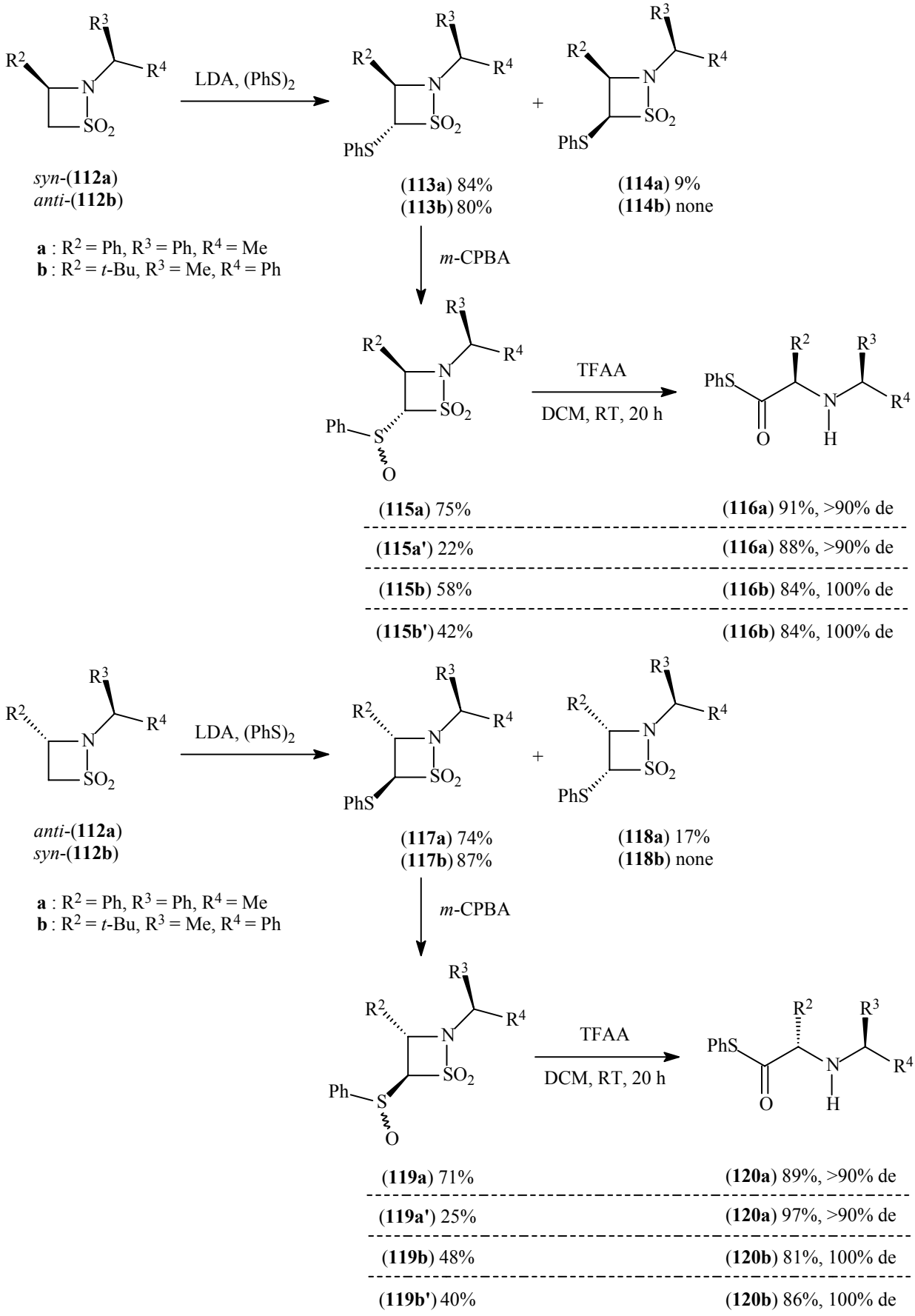
Table 1.1 1,3-Asymmetric induction in the [2+2] cycloaddition of a sulfene intermediate and chiral imines[a]

The mechanism for the stereoselectivity is illustrated below for the formation of *β*-sultam (**112h**) obtained with the best diastereomeric excess (Scheme 1.20) and can be explained by a 1,3-allylic strain responsible for the differentiation between conformers (**111h**) and (**111h'**).[47] In order to minimise this strain, the most stable conformer (**111h**) reacts with the sulfene generated from the reaction of mesyl chloride (**110**) and an imine. Thus, the approach of the sulfene takes place from the opposite face to the bulky *tert*-butyl group to form the *syn*-isomer as the major product. Contribution from the less stable conformer (**111h'**) to form the *anti*-isomer is negligible.



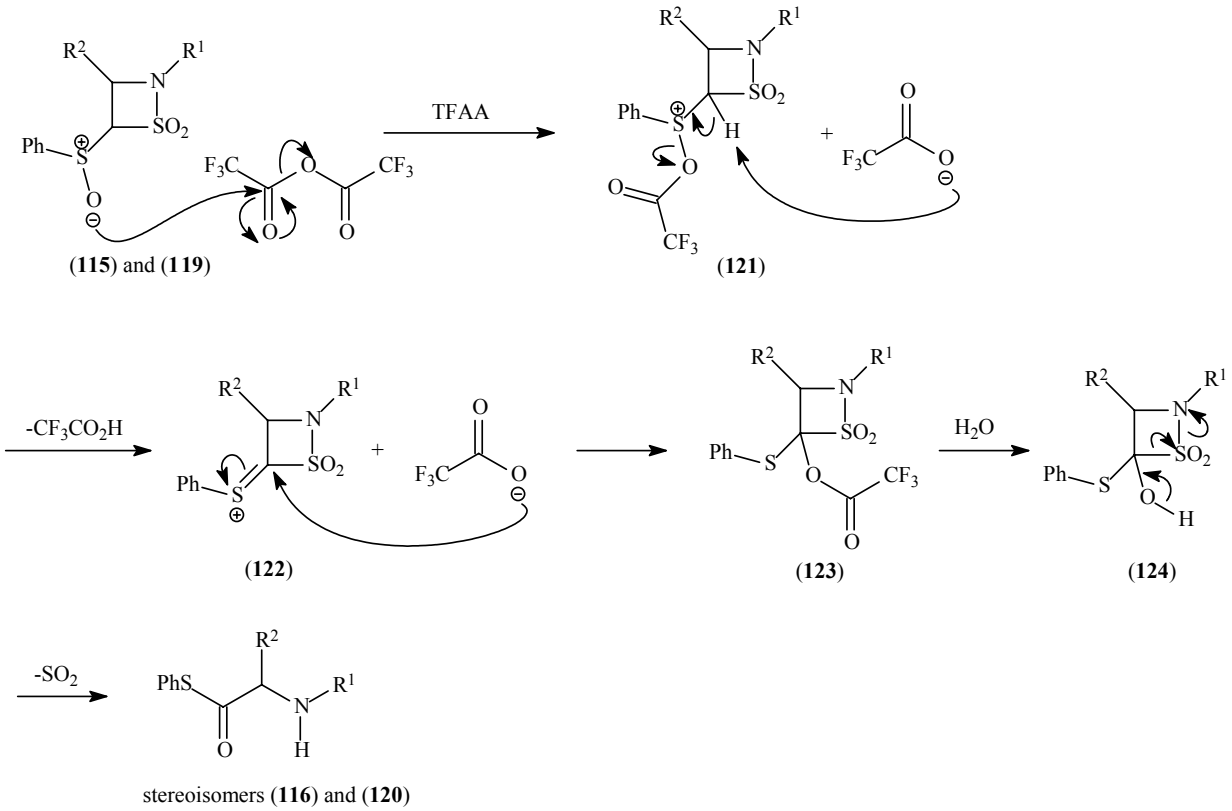
Scheme 1.20 Mechanism of the 1,3-asymmetric induction in the formation of *β*-sultam (**112h**)

From the *β*-sultams (**112a,b**), they prepared the precursors for the Pummerer reaction and synthesised the *α*-amino acid thioesters (**116**) and (**120**) (Scheme 1.21). Sulfenylation of compounds (**112a,b**) with LDA and diphenyl disulfide afforded the 3-substituted-4-phenylsulfanyl-*β*-sultams (**113**) and (**117**), which were oxidised with *m*-CPBA to the corresponding 3-substituted-4-phenylsulfinyl-*β*-sultams (**115**) and (**119**). Treatment with trifluoroacetic anhydride (TFAA) gave the *α*-amino acid thioesters (**116**) and (**120**).


LDA, (PhS)2
m-CPBA
TFAA
DCM, RT, 20 h
syn-(112a)
anti-(112b)
a : R2 = Ph, R3 = Ph, R4 = Me
b : R2 = t-Bu, R3 = Me, R4 = Ph
(113a) 84%
(113b) 80%
(114a) 9%
(114b) none
(115a) 75%
(115a') 22%
(115b) 58%
(115b') 42%
(116a) 91%, >90% de
(116a) 88%, >90% de
(116b) 84%, 100% de
(116b) 84%, 100% de
anti-(112a)
syn-(112b)
(117a) 74%
(117b) 87%
(118a) 17%
(118b) none
(119a) 71%
(119a') 25%
(119b) 48%
(119b') 40%
(120a) 89%, >90% de
(120a) 97%, >90% de
(120b) 81%, 100% de
(120b) 86%, 100% de

Scheme 1.21

The mechanism of the Pummerer reaction applied to the *β*-sultams (**115**) and (**119**) is illustrated below (Scheme 1.22).

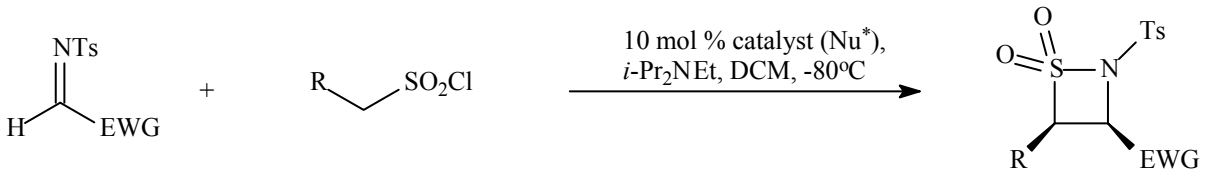


Scheme 1.22

Nucleophilic addition of the sulfoxides (**115**) and (**119**) to trifluoroacetic anhydride generates the sulfonium intermediate (**121a,b**), which undergoes a *β*-elimination to form the thionium ion intermediates (**122a,b**). Nucleophilic addition of trifluoroacetate on the electrophilic thionium ion affords the *α*-substituted sulfides (**123a,b**). Subsequent hydrolysis and SO_2 extrusion allows the *β*-sultam ring opening to afford the *α*-amino acid thioesters (**116**) and (**120**).

Kataoka also reported the *β*-elimination and N-S bond cleavage of 3-aryl-1,2-thiazetidin-1,1-dioxides with organometallics to form (*E*)-vinylsulfonamides and/or sulfones,[48,49] and the C-N bond cleavage of 4-silyl-substituted 1,2-thiazetidin-1,1-dioxides resulting in the formation of (*E*)-vinylsulfonamides.[49,50]

Recently, Peters *et al.* reported a catalytic asymmetric synthesis of *β*-sultams (Scheme 1.23).[51]

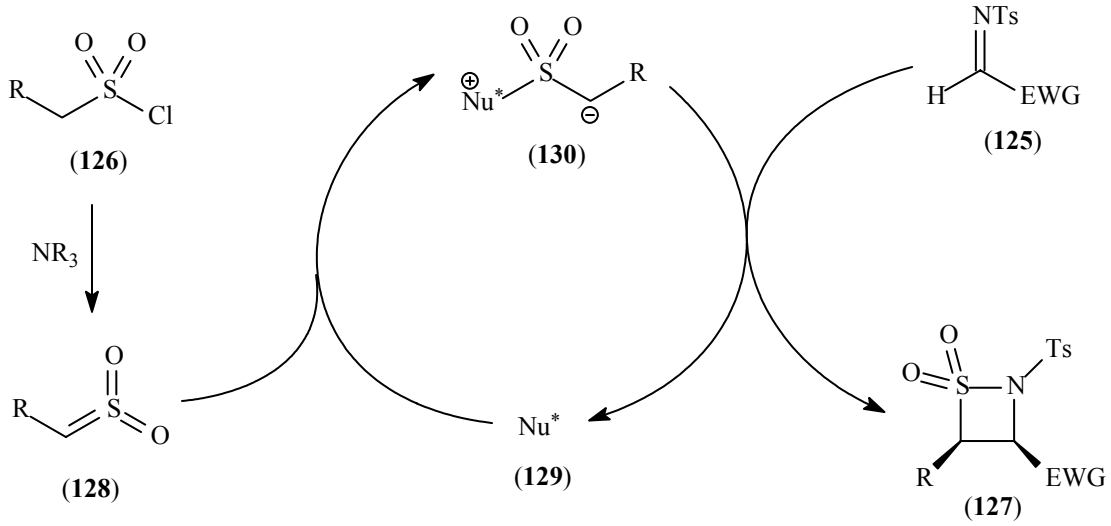


(**125**) (**126a-e**) (**127a-e**)

R	product	yield (%)	dr	ee (%)
Et	**127a**	82	20:1	79
n-Pr	**127b**	81	18:1	91
$(CH_2)_2Cl$	**127c**	78	11:1	94
CH_2Ph	**127d**	94	21:1	94
$(CH_2)_2OC_6H_4OMe$	**127e**	95	13:1	87

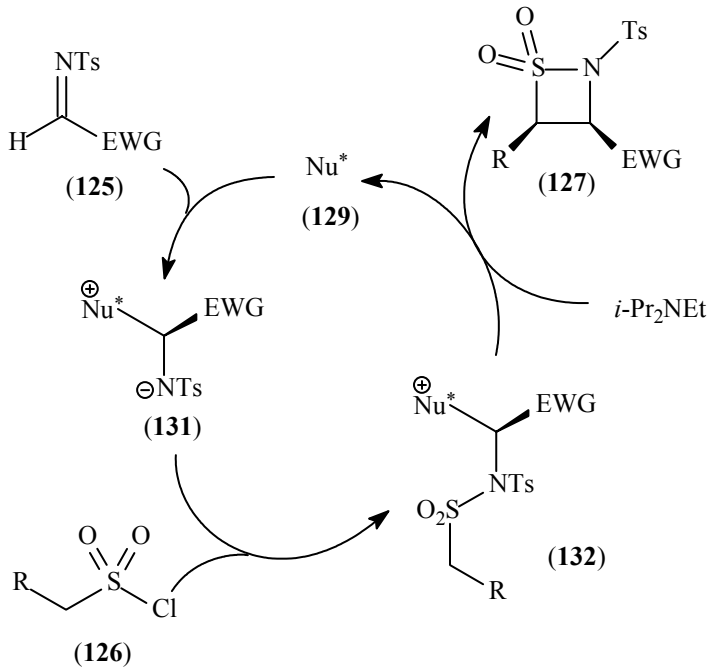
Scheme 1.23

The initial aim of this work was to form the zwitterionic nucleophilic intermediate (**130**) generated by the addition of a catalytic amount of an enantiomerically pure nucleophile (**129**) to the sulfenes (**128**) which would then undergo an asymmetric formal [2+2] cycloaddition with electron-poor imines (**125**) (Scheme 1.24).



Scheme 1.24

However, deuteration experiments demonstrated that the sulfene (**128**) is not generated in significant amounts to confirm this mechanism. Instead, the proposed mechanism for the formation of *β*-sultams (**127a-e**) is as follows (Scheme 1.25).



Scheme 1.25

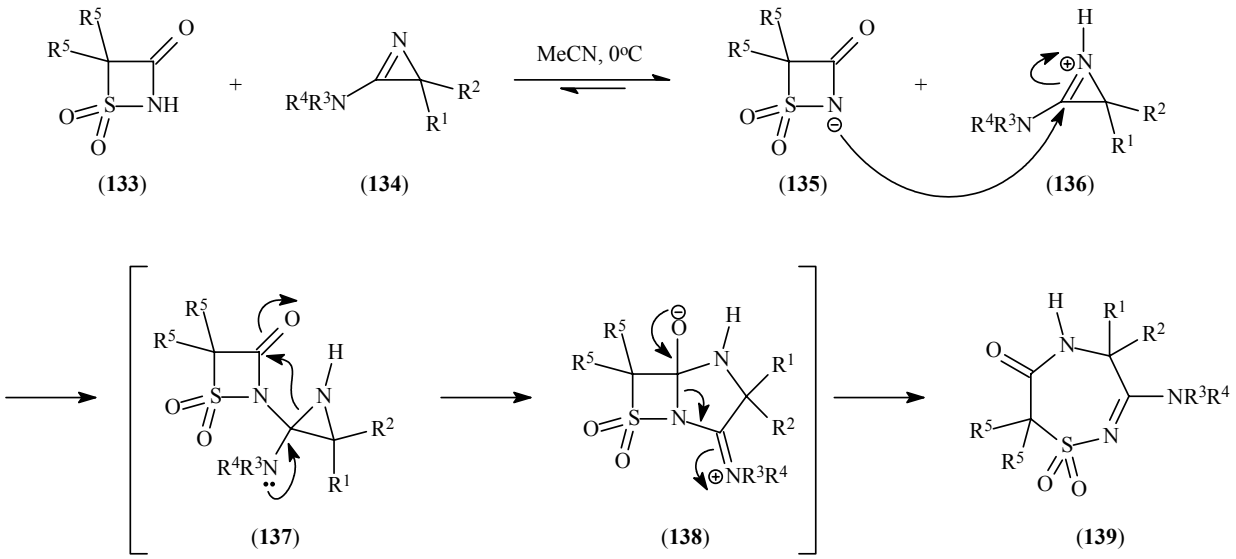
The nucleophilic catalyst (Nu^*) (**129**) forms a zwitterionic aminal intermediate (**131**) by nucleophilic addition to the imine (**125**). The negatively charged nitrogen in the intermediate (**131**) undergoes a nucleophilic substitution on the sulfonyl chloride (**126**) without prior

formation of the sulfene to form the sulfonamide (**132**), which would then be deprotonated at the α position of the sulfonyl group to form a carbanion. Subsequent intramolecular nucleophilic substitution of the zwitterionic species releases the catalyst with diastereoselective formation of the β-sultam ring (**127**).

1.2.2 Chemical transformations and reactivity of the β-sultam ring

1.2.2.1 Ring enlargement of the β-sultam ring

In 1996, Heimgartner *et al.* synthesised 1,2,5-thiadiazepine derivatives by the reaction of 1,2-thiazetidin-3-on-1,1-dioxides with 3-amino-2*H*-azirines (Scheme 1.26).[52] After protonation of the azirines (**134**) by the relatively acidic 3-oxo-β-sultams (**133**), nucleophilic addition of the anion (**135**) on the amidinium (**136**) afforded the aziridines (**137**), which underwent a ring enlargement to produce the zwitterionic intermediate (**138**). The latter rearranged through a second ring expansion to yield the 1,2,5-thiadiazepines (**139**) in high yields (Table 1.2).

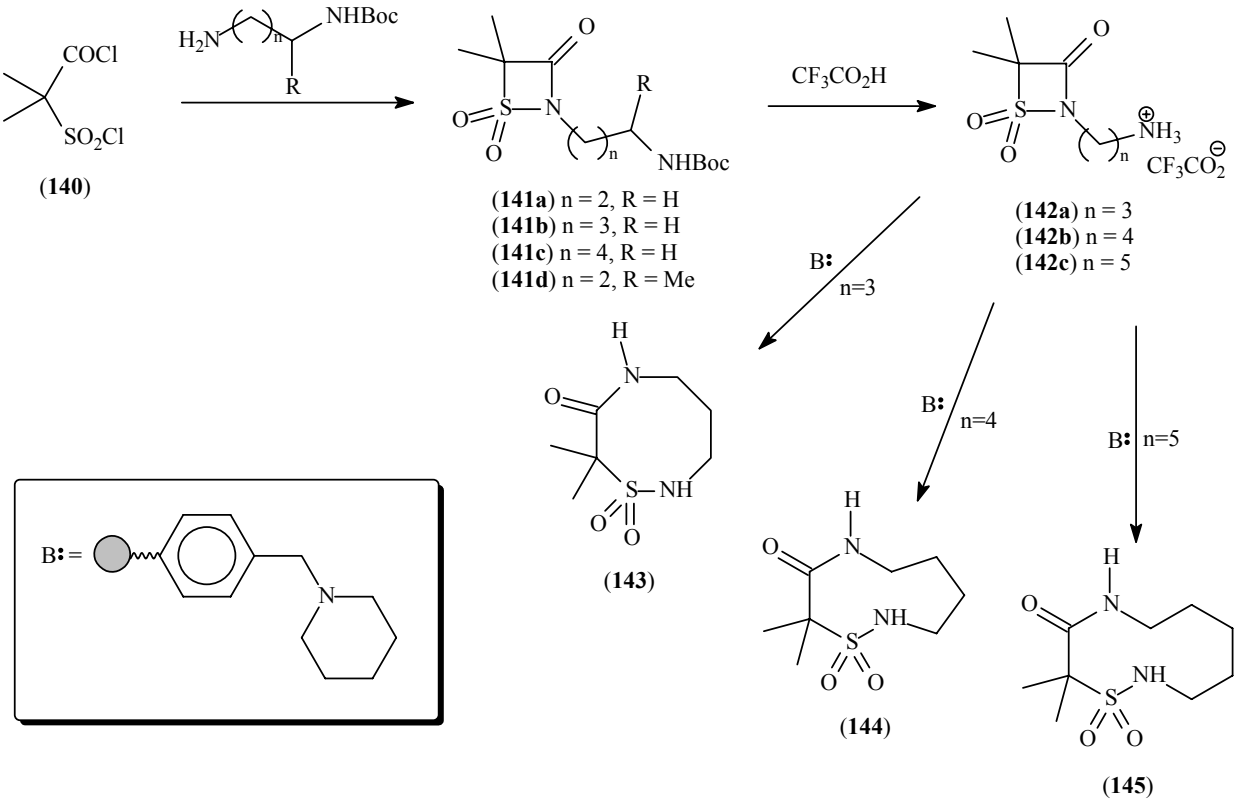


Scheme 1.26

	R^1	R^2	R^3	R^4		R^5	Product (%)
134a	Me	Me	Me	Me	**133a**	Me	**139a** (31)
134b	Me	Me	Me	Ph	**133a**		**139b** (91)
134c	$(CH_2)_4$		Me	Ph	**133a**		**139c** (79)
134d	Me	*i*-Bu	Me	Ph	**133a**		**139d** (80)
134a	Me	Me	Me	Me	**133b**	Et	**139e** (60)
134b	Me	Me	Me	Ph	**133b**		**139f** (73)
134d	Me	*i*-Bu	Me	Ph	**133b**		**139g** (81)

Table 1.2 Formation of 1,2,5-thiadiazepin-6-on-1,1-dioxides (**139**)

The Heimgartner group also carried out transamidation reactions of 2-(aminoalkyl)-3-oxo-*β*-sultams[53] (Scheme 1.27) to investigate whether this class of compounds would undergo a ring expansion, and if so, at which electrophilic centre the intramolecular nucleophilic attack would occur.

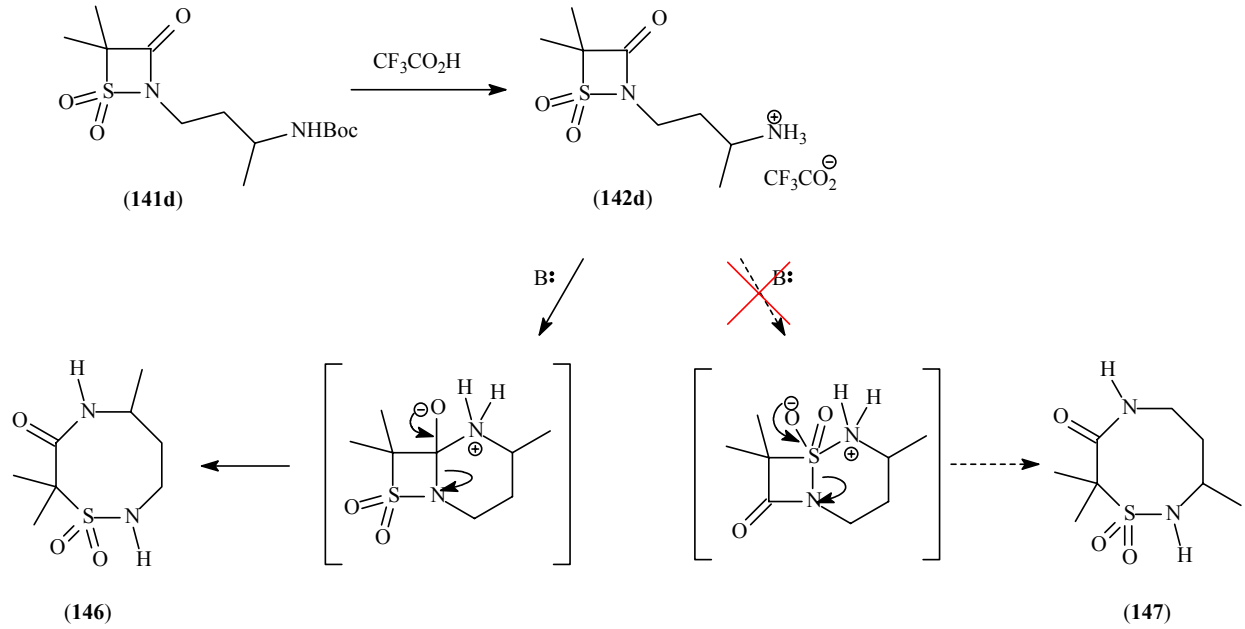


Scheme 1.27

Thus, 2-(aminoalkyl)-3-oxo-*β*-sultams (**141**) were prepared from the dichloride (**140**).[54,55] The mono-Boc-protected diamines were synthesised following the procedure from the literature.[56-59]

The Boc group was removed with trifluoroacetic acid to give the ammonium trifluoroacetate salts (**142**), which were treated with a polymer-bound base, (piperidinomethyl)polystyrene, to afford the ring enlarged compounds (**143**), (**144**) and (**145**) in satisfactory yields.

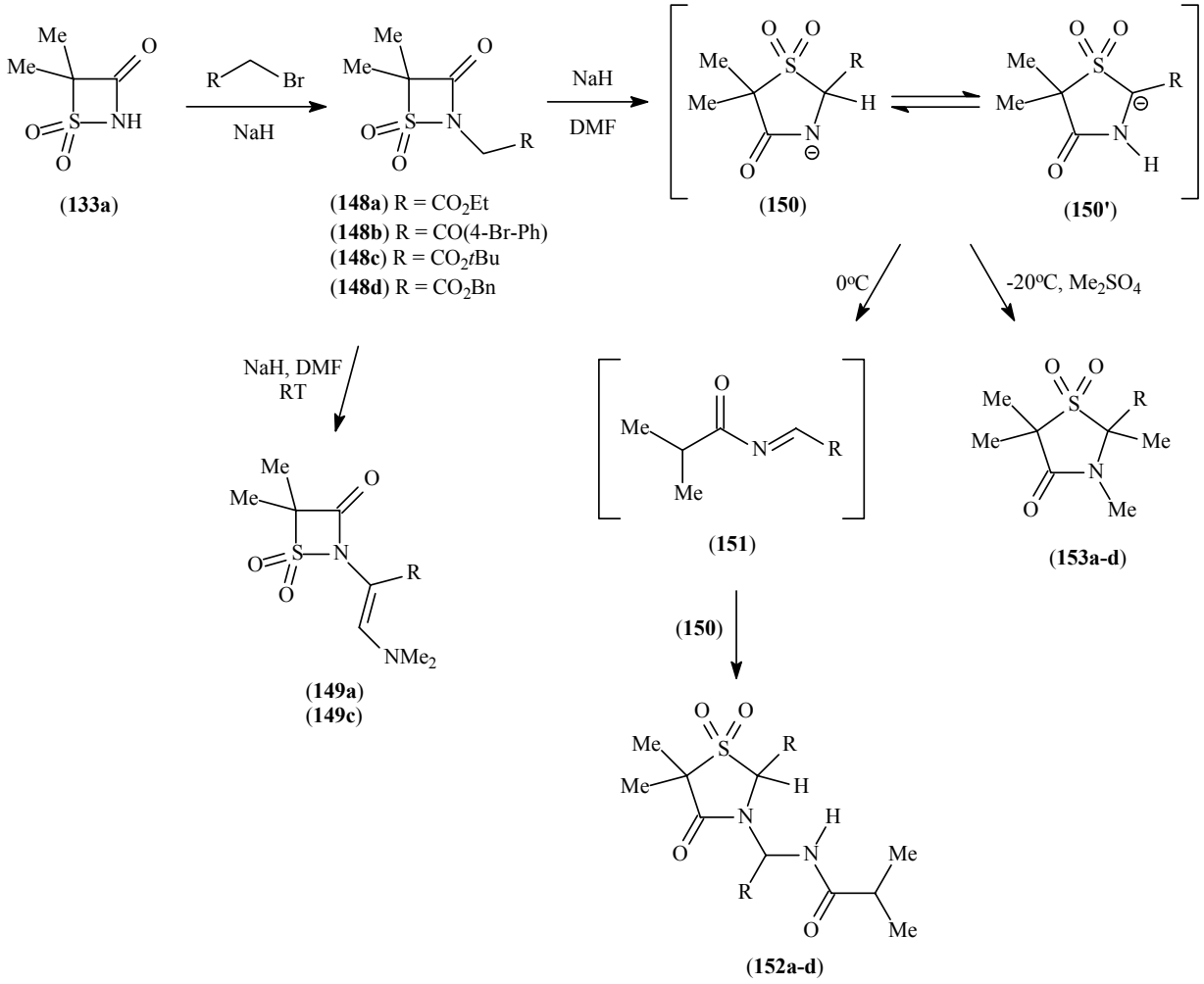
In order to elucidate whether the intramolecular nucleophilic attack was occurring at the carbonyl or at the sulfonyl centre, the same sequence was performed with the 3-oxo-*β*-sultam (**141d**) (Scheme 1.28). Deprotection of (**141d**) with trifluoroacetic acid followed by basification with a large excess of (piperidinomethyl)polystyrene afforded the ring expanded compound (**146**) as a single product, indicating that the transamidation was taking place at the carbonyl, rather than at the sulfonyl to afford compound (**147**).



Scheme 1.28

In 1997, Otto *et al.* reported the formation of 1,3-thiazolidin-4-ones from *N*-substituted 3-oxo-*β*-sultams (Scheme 1.29).[60] 3-Oxo-*β*-sultam (**133a**) was synthesised following a modified procedure described in the literature.[54,61] *N*-Alkylation using sodium hydride in DMF afforded the corresponding *N*-substituted 3-oxo-*β*-sultams (**148 a-d**). Treatment of compounds (**148a-d**) with NaH in DMF gave interesting results, where the course of the reaction seemed to be strongly dependent on the amount of DMF used and on the temperature. When compounds (**148a**) and (**148c**) were treated at room temperature with a large excess of DMF with 2 equivalents of NaH, the products (**149a**) and (**149c**) of the base-catalysed condensation with DMF were isolated. When the reaction was carried out with *N*-substituted 3-oxo-*β*-sultams (**148a-d**) at 0˚C in about half the amount of DMF, the 1,3-thiazolidin-4-ones (**152a-d**) were

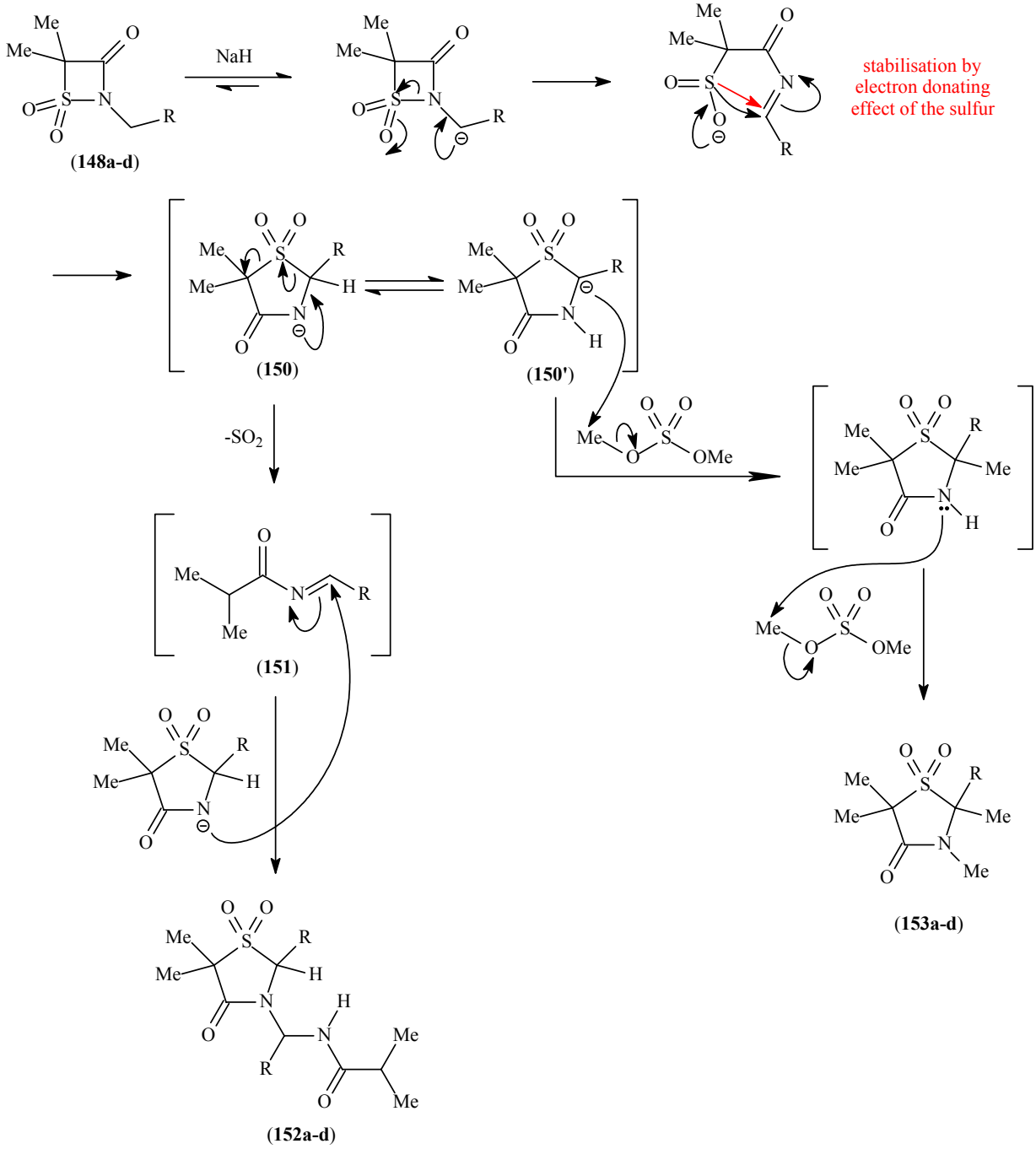
isolated in reasonable yields (52-61%). When the reaction was performed at -20˚C with dimethylsulfate, the 1,3-thiazolidin-4-ones (**153a-d**) were isolated.



Scheme 1.29

The formation of compounds (**152**) and (**153**) can be accounted for by the deprotonation of the methylene group attached to the nitrogen in compound (**148**) by NaH, followed by the insertion of this carbon between the nitrogen and the sulfonyl group by ring opening *via* the S-N bond cleavage to form an imine derivative intermediate stabilised by the sulfur atom (Scheme 1.30). A possible competition of the cleavage between the S-N and C-N bond could be expected, but ring opening through the C-N bond cleavage would result in a less stabilised ring opened intermediate. The ring closure of this stabilised imine derivative to the favoured five-membered ring resulted in the formation of the tautomeric anions (**150**) / (**150'**). The tautomer (**150**) loses SO_2 to give the acylimine (**151**) as an excellent Michael acceptor. Nucleophilic addition of the

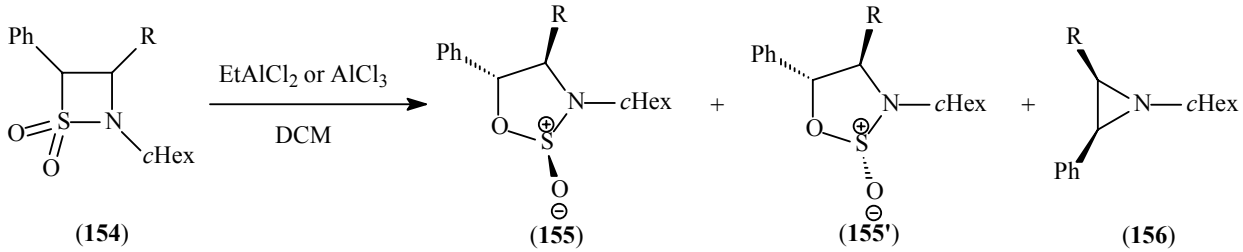
tautomer (**150**) on the acylimine (**151**) afforded compounds (**152**). The formation of compounds (**153**) is a simple double methylation of the tautomer (**150'**).



Scheme 1.30

The ring transformation of the *β*-sultam ring with Lewis acids *via* C-S bond cleavage has been reported by the Kataoka group.[62,63] Depending on the reaction conditions, these transformations

can result in a ring enlargement to form *trans*-1,2,3-oxathiazolidin-2-oxides or in a ring contraction to form *syn*-aziridines (Scheme 1.31).

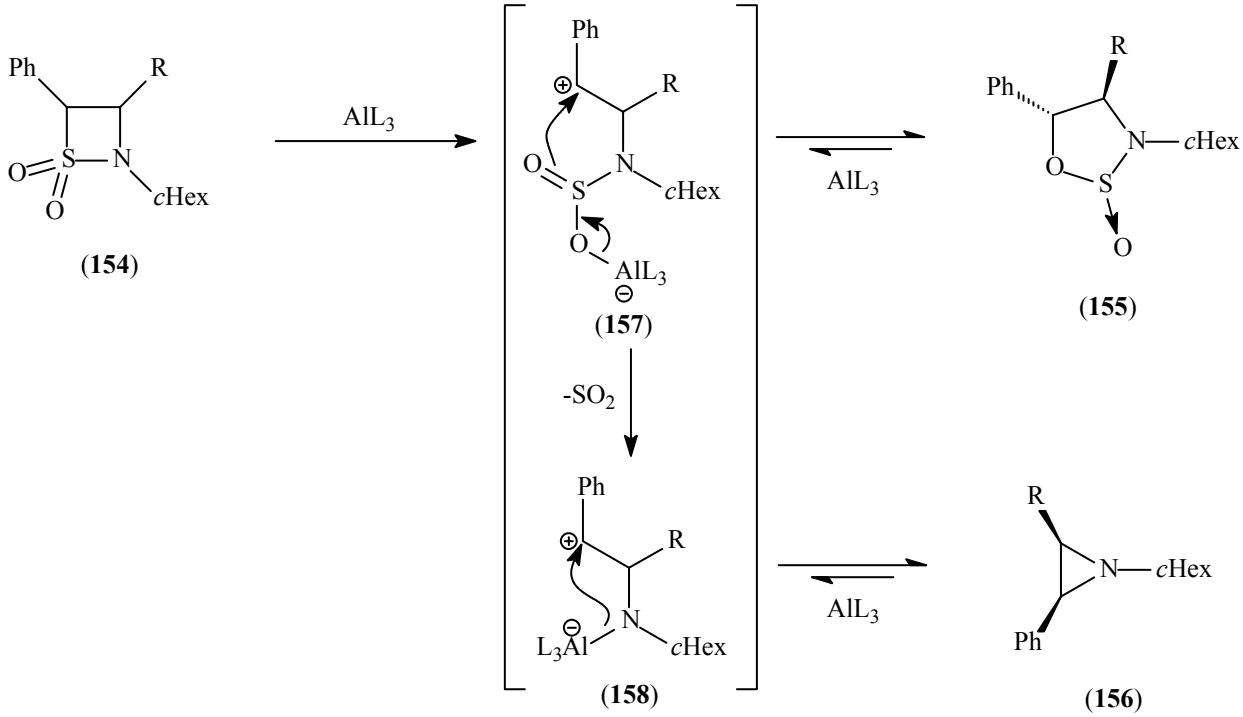


Scheme 1.31

β-Sultam		Conditions (equivalents)	Products (% yield, ratio)
Compound No.	R		
154a-cis	3-Pyridyl	$EtAlCl_2$ (2.0), RT, 12 h	**155a** / **155'a** (65%, 70 / 30)
154a-cis	3-Pyridyl	$EtAlCl_2$ (4.5), reflux, 60 h	**155a** / **155'a** (5%, 80 / 20), **156a** (62%)
154a-trans	3-Pyridyl	$EtAlCl_2$ (1.4), RT, 12 h	No reaction
154b-cis	4-Pyridyl	$EtAlCl_2$ (4.5), 0˚C, 22 h	**155b** / **155'b** (49%, 90 / 10), **156b** (11%)
154b-cis	4-Pyridyl	$AlCl_3$ (4.0), reflux, 28 h	**155b** / **155'b** (8%, 91 / 9), **156b** (54%)
154c-cis	2-Pyridyl	$EtAlCl_2$ (2.2), RT, 14 h	**155c** / **155'c** (40%, 90 / 10), **156c** (18%)
154c-cis	2-Pyridyl	$AlCl_3$ (4.0), RT, 27 h	**155c** / **155'c** (9%, 94 / 6), **156c** (18%)
154d-cis	*p*-$NO_2C_6H_4$	$EtAlCl_2$ (1.0), 0˚C, 12 h	**155d** / **155'd** (18%, 95 / 5)
154e-cis	*p*-CNC_6H_4	$AlCl_3$ (1.5), RT, 14 h	**156e** (23%)
154f (cis : trans = 1 : 1.8)	*t*-Butyl	$EtAlCl_2$ (1.1), RT, 12 h	**155f** (93%)

Table 1.3 Ring transformation of *β*-sultam (**154**) with $EtAlCl_2$ or $AlCl_3$

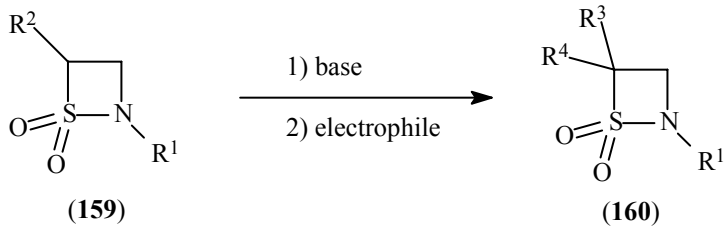
The mechanism of formation of compounds (**155**), (**155'**) and (**156**) is described in Scheme 1.32. The C-S bond of the *β*-sultam (**154**) is cleaved by the coordination of the Lewis acid to the sulfonyl group under the influence of the steric repulsion generated by the substituents at the C-3 and C-4 carbons to form the cationic intermediate (**157**), which cyclises by a nucleophilic attack of the oxygen on the cation to provide stereoselectively the *anti*-1,2,3-oxathiazolidin-2-oxides (**155**). It is also possible to postulate that the intermediate (**157**) undergoes an extrusion of SO_2 to generate the cationic intermediate (**158**), which cyclises to the thermodynamically more stable *syn*-aziridine (**156**).[64,65]



Scheme 1.32

1.2.2.2 Functionalisation at the C-4 position of the *β*-sultam ring

Apart from the nitrogen, the only reactive site of the ring is at the *α*-position of the sulfonyl group, or C-4 position. Otto *et al.* described the deprotonation of *N*-protected *β*-sultams (**159**) and their subsequent reaction with electrophiles (Scheme 1.33).[66] Some of these reactions are summarised in table 1.4. Several functionalisations were performed such as aldol reactions, carboxylations, silylations, or halogenations.



Scheme 1.33

Starting material	R^1	R^2	Electrophile (eq.)	Base (eq.)	Product(s)	R^3	R^4	Yield (%)
159a	TBDPS	H	Ph_2CO (1.25)	BuLi (2.0)	**160a**	$C(OH)Ph_2$	H	41
159a	TBDPS	H	MeOCOCl (1.0)	BuLi (1.5)	**160b**	CO_2Me	CO_2Me	26
159a	TBDPS	H	DEAD (1.6)	LDA (1.6)	**160c**	CO_2Et	H	10
159b	TBDMS	H	$OC(CO_2Et)_2$ (3.0)	LDA (1.5)	**160d**	$C(OH)(CO_2Et)_2$	H	17
159b	TBDMS	H	CO_2	BuLi (1.5)	**160e**	CO_2H	H	45
159c	C_6H_{11}	H	TBDMSCl (1.0)	LDA (1.5)	**160f**	TBDMS	H	65
159a	TBDPS	H	Br_2 (2.0)	BuLi (2.0)	**160g**	Br	Br	29
					160h	Br	H	13
159c	C_6H_{11}	H	Br_2 (2.0)	BuLi (2.0)	**160i**	Br	Br	20
					160j	Br	H	15
159b	TBDMS	H	Br_2 (1.0)	BuLi (1.0)	**160k**	Br	TBDMS	17
159d	TBDMS	CO_2Me	I_2 (2.0)	LDA (1.5)	**160l**	I	CO_2Me	20

Table 1.4

In summary, the formation of the *β*-sultam ring either by intramolecular cyclisation or [2+2] cycloaddition reported in the literature requires multi-step syntheses over 5 steps. In the case of bicyclic *β*-sultams, once the *β*-sultam ring is formed, the synthesis of the precursor for the cyclisation is not straight forward, and again, several steps are needed. Sometimes, the cyclisation is performed by ring closure metathesis, which requires the use of relatively expensive reagents.

The aim of this project is to develop a novel, quick, and cheap synthesis of bicyclic *β*-sultams bearing the structural features known to be necessary for the synthesis of potential new anti-bacterial agents. This strategy has several advantages which fulfil this aim:

- the formation of the *β*-sultam ring can be performed in three steps from commercially or readily available reagents.
- the precursor for the cyclisation is synthesised in one step.
- the bicyclic structure is generated in one step by cycloaddition on the precursor.

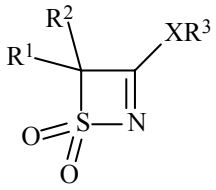
CHAPTER II

RESULTS AND DISCUSSION

2 Results and Discussion

2.1 Outline of discussion

Monocyclic and bicyclic *β*-lactams are well known as inhibitors of *β*-lactamases,[67,68] serine transpeptidases[69] and elastases. *β*-Sultams are less well explored but substantial work has been carried out at Huddersfield and has shown, for example, that monocyclic *β*-sultams can function as inhibitors of porcine pancreatic elastase.[70] The corresponding bicyclic *β*-sultams have attracted relatively little attention in the literature.[30,36,37,40,71] Thus, the synthesis of 1,2-thiazetin-1,1-dioxides (**161**) has been explored, and their potential as cycloaddition precursors for the synthesis of a series of novel bicyclic *β*-sultams will be discussed in this chapter.



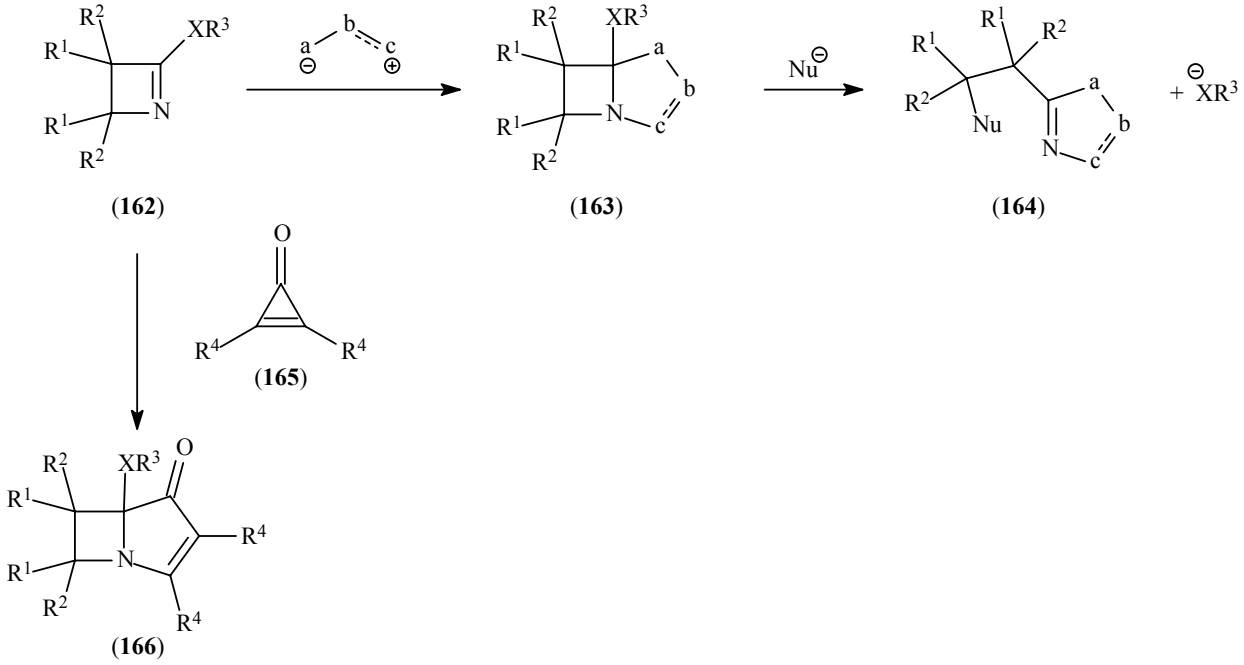
(**161**) X = O or S

Previous work[72,73] has shown that 1-azetines (**162**) (Scheme 2.1) are excellent dipolarophiles, furnishing the cycloadducts (**163**) with a range of 1,3-dipoles. This work also showed that the cycloadducts (**163**) could be ring opened with nucleophiles or upon heating to give excellent yields of the azoles (**164**). It also found that 1-azetines (**162**) react with cyclopropenones (**165**) to give adducts (**166**) in high yields.

1-Azetines are less challenging to make compared to 1,2-thiazetin-1,1-dioxides (**161**), and previous work carried out with 1-azetines (**162**) by our group had shown interesting results. Therefore, this PhD started by completing the work thus far performed with 1-azetines (**162)**. Thus, the first part of this thesis will focus on the work done with 1-azetines.

The second part of this chapter will describe approaches to the synthesis of the 1,2-thiazetin-1,1-dioxides (**161**) following several routes: one from 3-oxo-*β*-sultams, another exploring a literature route through the synthesis of isothiazolines and isothiazoles, and a final one through new ways to build the 4-membered ring. The subsequent reaction of 1,2-thiazetin-1,1-dioxides with 1,3-dipoles, cyclopropenones and their reactivity towards Diels-Alder reactions will be discussed.

The third part of the discussion will describe the reactivity of the sulfonimine moiety of the isothiazolines and isothiazoles synthesised through the literature route discussed in the second part towards 1,3-dipolar cycloadditions.

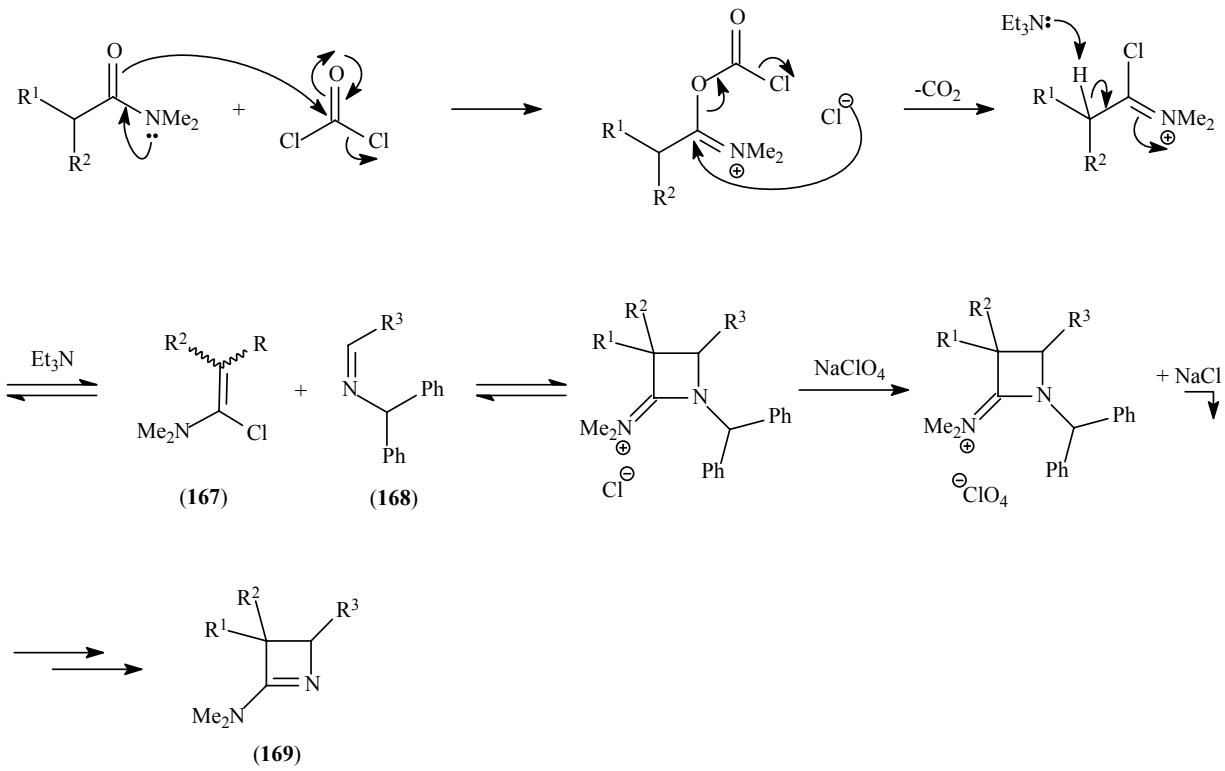


Scheme 2.1

2.2 Synthesis and reactivity of 1-azetines

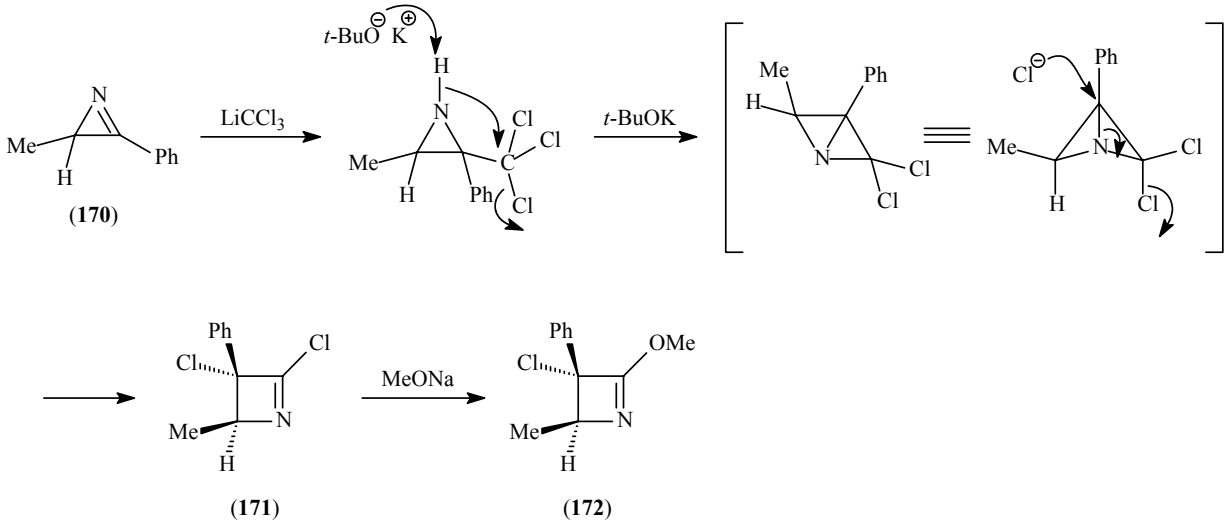
2.2.1 Synthesis of 1-azetines

Several synthetic routes to 1-azetines have been described in the literature. Simple alkyl and aryl-1-azetines can be formed through the thermal ring expansion of cyclopropyl azides,[74,75] whereas thermal rearrangement of 1-(alkylthio)cyclopropyl azides leads to 2-alkylthio-1-azetines.[76] Treatment of dimethylamides with phosgene in the presence of triethylamine gives *α*-chloroenamines (**167**), which react with benzhydryl imines (**168**) to afford 2-dimethylamino-1-azetines (**169**) after ion exchange, hydrogenation and basification (Scheme 2.2).[77]



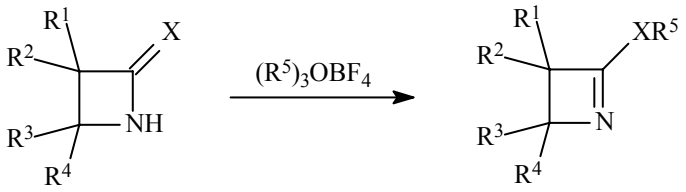
Scheme 2.2

2,3-Dichloro-1-azetine (**171**) was also formed by nucleophilic addition of trichlomethyllithium to azirine (**170**) and subsequent basification with potassium *tert*-butoxide (Scheme 2.3).[78,79] Treatment with sodium methoxide afforded the corresponding 2-methoxy-1-azetine (**172**).



Scheme 2.3

Few photochemical syntheses of 1-azetines have been reported[80,81] but do not represent a reliable route to this four-membered ring. Finally, *O*-alkylation of azetidin-2-ones (**173**, X = O) and *S*-alkylation of azetidin-2-thiones (**173**, X = S) (available from thionation of azetidin-2-ones) with trialkyloxonium tetrafluoroborates followed by basification affords a versatile route to 2-alkoxy-1-azetines (**174**, X = O) and the analogous 2-ethylthio-1-azetines (**174**, X = S), respectively (Scheme 2.4).[82-85]



(**173**)
X = O or S
R^1, R^2, R^3, R^4 = alkyl, aryl or H

(**174**)
R^5 = Me or Et

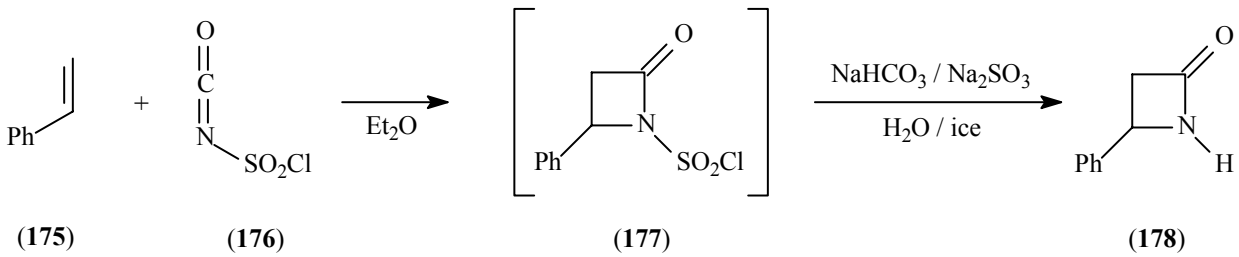
Scheme 2.4

In regard to preliminary studies[72,73,86] and to the synthetic strategy described in Scheme 2.1, we embarked upon the synthesis of 1-azetines following the latter route. 1,2-Thiazetin-1,1-dioxides, the sulfonyl analogues, are expected to have a similar reactivity, so that 1-azetines can be regarded as model systems too.

2.2.1.1 Synthesis of 2-ethylthio-4-phenyl-1-azetine

2.2.1.1.1 Synthesis of 4-phenylazetidin-2-one

The *β*-lactam ring was synthesised by the chlorosulfonyl isocyanate (**176**) to styrene (**175**) [2+2] cycloaddition (Scheme 2.5). The *N*-chlorosulfonyl *β*-lactam (**177**) was not isolated and sodium sulfite was used as a reducing agent from a known method to give the azetidinone (**178**).[87-90]



(**175**) (**176**) (**177**) (**178**)

Scheme 2.5

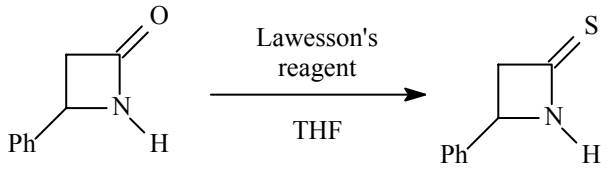
The evidence for the structure of the azetidinone was provided by the spectroscopic data. The ^{1}H NMR spectrum was consistent with the ring formation, showing a doublet of doublets at 4.67 ppm for the benzylic proton with *J*=5.2 Hz and 2.3 Hz, indicating the coupling with the *anti* proton and the *syn* proton, respectively, and two other signals at 3.38 and 2.80 ppm for the two protons of the CH_2 with *J*=14.8 Hz. The characteristic broad singlet for the NH appears at 6.97 ppm and the five aromatic protons also appear at ~7.34 ppm. The ^{13}C NMR spectrum shows a signal at 168.48 ppm for the carbonyl, 3 signals for the 3 aromatic CHs, a CH at 50.15 ppm and a CH_2 at 47.60 ppm. The IR and MS data further confirmed the structure of the azetidinone.

2.2.1.1.2 Synthesis of 4-phenylazetidin-2-thione

The most exploited route to thioamides is the thionation of their amide analogues. A wide range of thionating agents has been used for the thionation of carbonyl compounds.[91,92] Amongst the large amount of methods developed to thionate amides or lactams to thioamides or thiolactams, improved methods with phosphorus pentasulfide (P_4S_{10}) combined with Na_2CO_3,[93] hexamethyldisiloxane (HMDO) assisted or not by microwave irradiation,[94-98] alumina,[99,100] silica under microwave irradiations[101,102] have been disclosed. Many reagents designed for thionation are also available such as Lawesson's reagent,[103-105] Davy's reagent,[106,107] or Heimgartner's reagent.[108,109] Methods proceeding through prior activation of the amide include combinations of trifluoromethanesulfonic anhydride and pyridine with aqueous ammonium sulfide,[110] oxalyl chloride or phosphorus oxychloride with benzyltriethylammonium tetrathiomolybdate,[111] phosphorus oxychloride with hexamethyldisilathiane (HMDST),[112] and trialkyloxonium tetrafluoroborates with sodium hydrosulfides.[113]

High yields, convenient handling, easy work-up, commercial availability, and use of mild conditions make Lawesson's reagent a very attractive thionating reagent. Furthermore, it has been reported in many thionations of amides, and lactams.[114-118] Thus, it was our reagent of

choice for the thionation of the *β*-lactam ring (**178**), giving the desired compound (**179**) in 61% (Scheme 2.6).



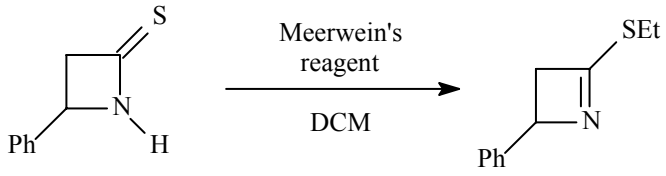
(**178**) (**179**)

Scheme 2.6

The main evidence of successful thionation are the chemical shift in the ^{13}C NMR spectrum from 168.48 ppm (C=O) to 204.42 ppm (C=S), as well as the shift of the absorption on IR from 1705 cm^{-1} (C=O) to 1486 cm^{-1} (C=S). In the ^{1}H NMR spectrum, the presence of the ring is confirmed by the doublet of doublets at 5.18 ppm for the benzylic proton with *J*=4.6 and 1.8 Hz along with the signals at 3.51 ppm and 3.02 ppm for the *anti* and *syn* protons of the adjacent CH_2, respectively.

2.2.1.1.3 Synthesis of 2-ethylthio-4-phenyl-1-azetine

The alkylation of thioamides or thiolactams is a very well known method to access imidates or cycloimidates.[119] Amongst the alkylating reagents available, triethyloxonium tetrafluoroborate (Meerwein's reagent) has become the reagent of choice for the *O*- or *S*-alkylation of amides and thioamides.[119,120] Thus, the final step to give the desired 1-azetine (**180**) was performed by *S*-alkylation of the 1-azetidin-2-thione (**179**) using triethyloxonium tetrafluoroborate,[83,85] in 23% yield (Scheme 2.7). The yield seemed to be affected by the quality of the batch of Meerwein's reagent; better yields were obtained with fresh solutions of Meerwein's reagent, which is known to be decomposed by moisture.[120] On the other hand, 4-phenyl-1-azetine (**180**) was volatile, making its isolation and handling difficult.



(**179**) (**180**)

Scheme 2.7

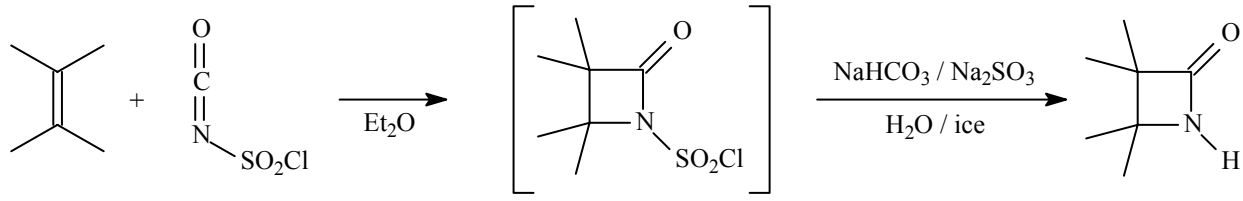
The evidence of the presence of the ethyl group was provided by the ^{1}H NMR spectrum with the appearance of a quartet at 3.06 ppm and a triplet at 1.40 ppm. The evidence of *S*-alkylation was provided by ^{13}C NMR data on one hand, with a shift from 204.42 ppm (C=S) to 183.56 ppm (C=N), and the IR data on the other hand, showing a shift in absorption from 1486 cm^{-1} (C=S) to 1655 cm^{-1} (C=N), along with the disappearance of the NH broad absorption at 3136 cm^{-1}. Both of them confirm the occurrence of the *S*-alkylation, and disclaim the *N*-alkylation. The presence of the ring is still confirmed by ^{1}H NMR, with the characteristic doublet of doublets at 5.02 ppm for the benzylic proton, showing coupling constants of 4.3 Hz with the *anti* proton and 2.0 Hz with the *syn* proton of the CH_2 at 3.56 ppm and 2.96 ppm, respectively.

Given the low yields obtained with Meerwein's reagent, other alkylating reagents could be attempted. The regioselective alkylation of ambident compounds, such as lactams, thiolactams, pyridin-2-ones, or hydroxypyridines is a recurrent goal in heterocyclic chemistry, and several alkylating reagents have been reported in the literature to achieve this regioselective reaction. However, there is no general procedure to perform selectively the *O*-, *S*- or *N*-alkylation of amides or thioamides because the alkylation is dependent on the nature of the substrate, the solvent, and the alkylating reagent. Thus, according to the desired regioselectivity, the reaction conditions can be tuned to favour the formation of the desired product. Only the most common alkylating agents used for the alkylation of ambident species are outlined here such as halides,[121-125] tosylates,[125,126] dimethylsulfate,[127] methyl orthocarboxylates,[128] the Mitsunobu-type reactions,[129,130] the use of silver salts in non polar solvents,[125,126,131], diazomethane[61,131-134] or diazoethane,[135] trimethylsilyldiazomethane,[136] and the alkyldiphenylsulfonium salts.[137] In the case of a successful thionation of 3-oxo-*β*-sultams (see later), the alkylating method described by Brzozowski *et al.*[127] to alkylate an *α*-thioxosulfonamide would probably be the first to be attempted in regard to our strategy.

2.2.1.2 Synthesis of 3,3,4,4-tetramethyl-1-azetine

2.2.1.2.1 Synthesis of 3,3,4,4-tetramethylazetidin-2-one

Formation of the *β*-lactam ring was done in the same fashion as described above. Hence, [2+2] cycloaddition of CSI (**176**) with 2,3-dimethylbut-2-ene (**181**) afforded the desired target (**183**) in 75% yield (Scheme 2.8).



(**181**) (**176**) (**182**) (**183**)

Scheme 2.8

Spectroscopic data provided evidence of the formation of the azetidinone. The IR spectrum showed a broad band at 3187 cm^{-1} (NH) and a strong absorption at 1704 cm^{-1} (C=O). On the ^{1}H NMR spectrum, the presence of the NH was further confirmed by a broad singlet at 6.00 ppm, and two sets of methyl groups at 1.39 and 1.23 ppm. The structure of the ring was confirmed by the ^{13}C NMR spectrum. The carbonyl group was present at 174.91 ppm, the two quaternary sp^3 carbons of the azetidinone ring appeared at 58.18 and 54.54 ppm, and the two sets of methyl groups appeared at 24.40 and 19.06 ppm. Further support was provided by consistent MS data.

2.2.1.2.2 Synthesis of 3,3,4,4-tetramethylazetidin-2-thione

Thionation was carried out with Lawesson's reagent, as previously described, to give in excellent yield the thioxo analogue (**184**) (Scheme 2.9).

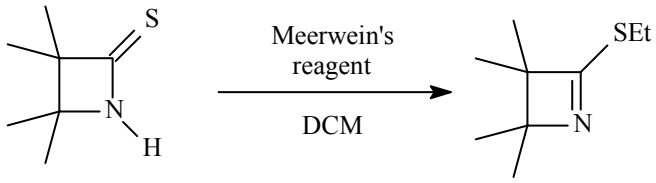
(**183**) (**184**)

Scheme 2.9

The main evidence for successful thionation was provided by the IR spectrum with a shift in absorption from 1704 cm^{-1} (C=O) to 1494 cm^{-1} (C=S), and by ^{13}C NMR spectroscopy with a shift from 174.91 ppm (C=O) to 212.29 ppm (C=S). The structural assignment was further supported by MS data.

2.2.1.2.3 Synthesis of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine

S-Alkylation was carried out using Meerwein's reagent, as discussed above, to afford the corresponding *S*-alkylated product (**185**) in 31% yield (Scheme 2.10).



(**184**) (**185**)

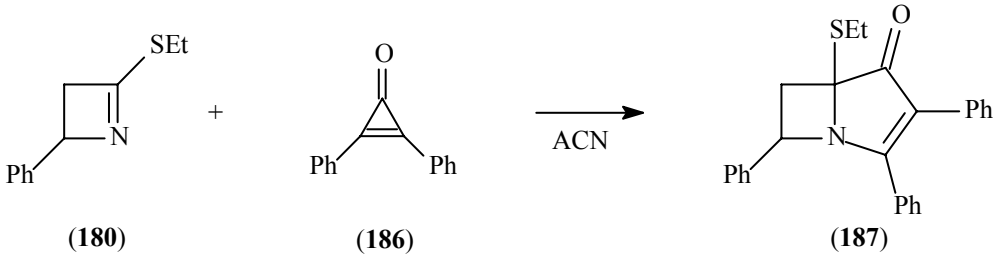
Scheme 2.10

The evidence of the presence of the ethyl group was provided by the ^{1}H NMR spectrum with the appearance of a quartet at 2.96 ppm and a triplet at 1.33 ppm with a coupling constant of 7.4 Hz. The evidence of *S*-alkylation was provided by the ^{13}C NMR data on one hand, with a shift from 212.29 ppm (C=S) to 186.98 ppm (C=N), and the IR data on the other hand, showing a shift in absorption from 1494 cm^{-1} (C=S) to 1532 cm^{-1} (C=N), along with the disappearance of the NH broad absorption at 3116 cm^{-1}. All the data were consistent with the occurrence of the *S*-alkylation rather than the *N*-alkylation.

2.2.1.3 Reactivity of 2-ethylthio-4-phenyl-1-azetine

2.2.1.3.1 Cycloaddition with diphenylcyclopropenone

On the basis of the known reactivity of electron rich imines with diphenylcyclopropenone (DPP),[86,138-141] 4-phenyl-1-azetine (**180**) was reacted with DPP (**186**) to afford the corresponding azabicyclo[3.2.0]hept-2-ene (**187**) in 64% yield (Scheme 2.11) as a mixture of diastereoisomers in a 1.6/1 ratio.



(**180**) (**186**) (**187**)

Scheme 2.11

The structure of the product was confirmed by the complex ^{1}H NMR spectrum. Firstly, the fifteen aromatic protons were present as a series of multiplets in the range of 7.61-6.81 ppm.

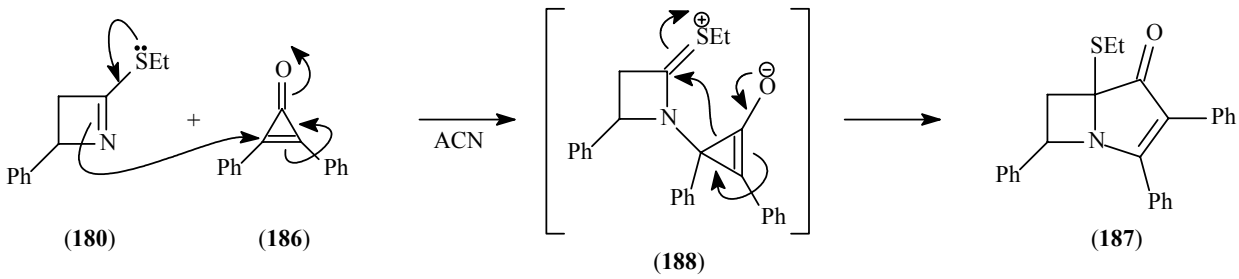
Secondly, the presence of the three protons of the four-membered ring was confirmed by two sets of signals, confirming that the product was formed as a mixture of diastereoisomers. The first set appeared as a triplet at 5.57 ppm for the benzylic CH with *J*=8.2 Hz, and two doublets of doublets at 3.00 ppm and 2.93 ppm for each proton of the CH_2 with *J*=8.2 and 13.1 Hz. The second set appeared as a doublet of doublets at 4.25 ppm for the benzylic CH with *J*=5.5 and 9.6 Hz indicating the *syn* and *anti* relationship with the two protons of the adjacent CH_2, respectively. A doublet of doublets at 3.16 ppm with *J*=9.6 and 12.6 Hz was seen for the proton of the CH_2 in an *anti* position relative to the benzylic CH, and a doublet of doublets at 2.48 ppm with *J*=5.5 and 12.6 Hz for the proton of the CH_2 in a *syn* position relative to the benzylic CH.

Thirdly, the CH_2 of the ethyl group appeared as 3 overlapping doublets of quartets at 2.66, 2.60 and 2.54 ppm with *J*=7.4 and 12.3 Hz, indicating the diastereotopic relationship between the two protons of the CH_2 close to a chiral centre. The fourth doublet of quartets could not be identified due to the complex overlapping. The CH_3 of the ethyl group appears as two triplets at 1.24 and 1.23 ppm with *J*=7.4 Hz, indicating once again the formation of the product as a diastereomeric mixture.

The presence of two diastereoisomers was also confirmed by the doubling of each signal in the ^{13}C NMR spectrum. As a matter of convenience, only the most characteristic assignments are outlined here: the carbonyl at 202.69 and 202.29 ppm, the unsaturated carbon of the enone in β position at 176.83 and 174.66 ppm, the unsaturated carbon of the enone in α position at 126.00 and 123.66 ppm, the benzylic CH of the 4-membered ring at 66.50 and 65.85 ppm, the CH_2 of the 4-membered ring at 35.01 and 31.74 ppm, the CH_2 of the ethyl group at 23.55 and 23.44 ppm, the CH_3 of the ethyl group at 14.49 and 14.47 ppm.

The MS data further supported the proposed structure with an accurate measured mass (*m/z*) of 398.1569 for a required mass of 398.1573.

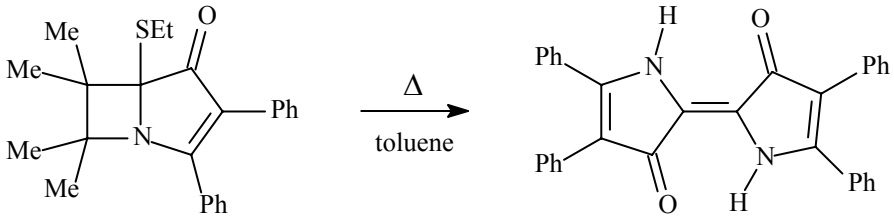
The mechanism of the reaction involves the electron-donating thioethyl group of the azetine, which activates the nucleophilicity of the nitrogen (Scheme 2.12). A nucleophilic attack of the nitrogen on the Michael acceptor forms the intermediate (**188**), consisting of an enolate and an activated electrophilic carbon. The enolate undergoes an intramolecular nucleophilic attack on the electrophilic carbon, resulting in the formation of the product (**187**) through the ring expansion of diphenylcyclopropenone (**186**).



Scheme 2.12

2.2.1.3.2 Thermolysis of 5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-1-one: synthesis of 2-(ethylthio)-triphenylpyridine

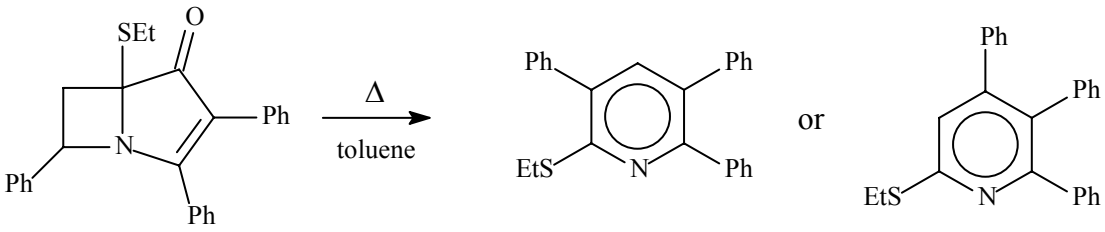
Previous work had shown that the cycloadduct (**189**) resulting from the addition of 3,3,4,4-tetramethyl-1-azetine with DPP gave the dimer (**190**) (Scheme 2.13).[86] It was therefore interesting to investigate whether compound (**187**) would behave similarly.



(**189**) (**190**)

Scheme 2.13

In the event, the thermolysis of the cycloadduct (**187**) was carried out in refluxing toluene until disappearance of the starting material to afford a surprising tetrasubstituted pyridine (**191** or **192**) as the major product (Scheme 2.14), albeit in ~20% yield.



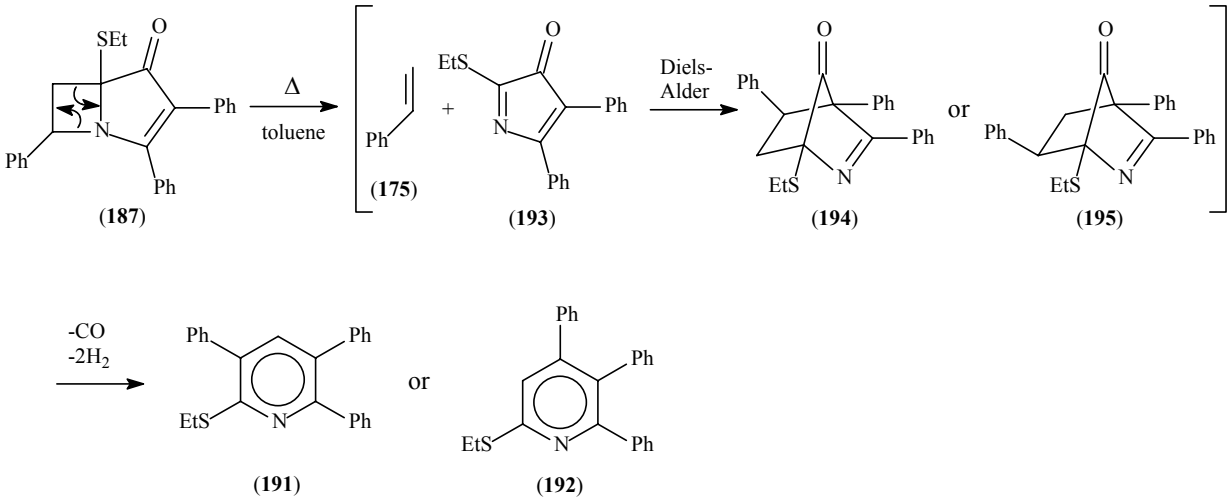
(**187**) (**191**) (**192**)

Scheme 2.14

Spectroscopic analysis allowed the determination of the structure of the product. In the ^{1}H NMR spectrum, a quartet at 3.29 ppm and a triplet at 1.46 ppm with J=7.3 Hz suggested that the thioethyl group was still present in the molecule and that the two protons of the CH_2 were not diastereotopic anymore. The remaining signals were all in the aromatic region and were integrating to sixteen protons, suggesting that the three phenyl groups of the starting material were probably still present in the product together with an extra aromatic proton, but the 4-membered ring was no longer present in the molecule. This was confirmed by the ^{13}C NMR spectrum, with the presence of ten CHs in the aromatic region between 131.50 and 121.56 ppm, the presence of one CH_2 at 24.47 ppm and one CH_3 at 14.91 ppm, and the disappearance of the CH and CH_2 of the 4-membered ring. This also confirms the presence of an extra aromatic CH in the molecule.

In the IR spectrum, the absence of a strong absorption band at ~1675 cm^{-1} indicated the loss of the unsaturated carbonyl.

With those spectroscopic data in hand and considering the structure of the starting material, the formation of the pyridine was suggested through the reaction cascade shown in Scheme 2.15.



Scheme 2.15

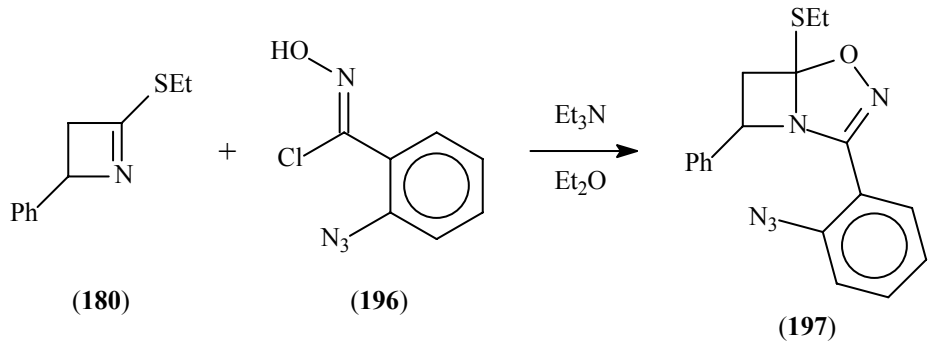
The first step of the proposed mechanism is a retro [2+2] cycloaddition of compound (**187**) driven by the release of the strain of the 4-membered ring to liberate styrene (**175**) and the heterodienone (**193**), which then undergo a hetero Diels-Alder cyclisation to form a 2-azabicyclo[2.2.1]hept-2-en-7-one (**194** or **195**) as an intermediate. The final step of this sequence is a CO extrusion with loss of hydrogen gas to form the corresponding pyridine (**191** or **192**) driven by the aromaticity of the final product. The cheletropic extrusion of carbon monoxide from cyclopentadienone derivative Diels-Alder cycloadducts is a well-known process to generate aromatic molecules.[142-151]

The structural determination was confirmed by HRMS analysis with a measured accurate mass (*m/z*) of 367.1385 for a required mass of 367.1389.

2.2.1.3.3 1,3-Dipolar cycloaddition with 2-azidobenzohydroximoyl chloride: synthesis of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene

As stated in the introduction of this chapter, we were interested in the reactivity of 1-azetines towards cycloadditions, and the chemistry of their subsequent cycloadducts. For these purposes, 1-azetine (**180**) was reacted with 2-azidobenzohydroximoyl chloride (**196**) (Scheme 2.16) to

yield the corresponding cycloadduct (**197**) as a single diastereoisomer. Hydroximoyl chlorides can be prepared by chlorination of the corresponding aldoximes employing different halogenating agents.[152] The nitrile oxide was then generated *in situ* by dehydrohalogenation using triethylamine.[152-155]



(**180**) (**196**) (**197**)

Scheme 2.16

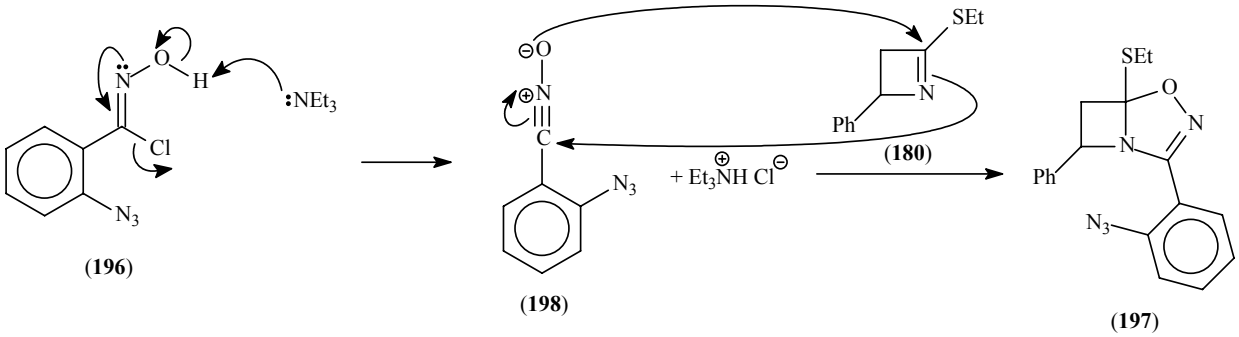
The structure of cycloadduct (**197**) was determined by spectroscopic analysis. The ^{1}H NMR spectrum indicates the presence of nine aromatic protons in the molecule. The benzylic proton of the 4-membered ring next to the nitrogen appears deshielded at 4.81 ppm as a doublet of doublets with *J*=9.3 and 5.4 Hz, indicating the *anti* and *syn* relationship with the two protons of the adjacent CH_2, respectively. Those two protons in *anti* and *syn* position relative to the benzylic proton appear at 3.69 and 2.72 ppm with *J*=13.1 and 9.3 Hz, and *J*=13.1 and 5.4 Hz, respectively. The two diastereotopic protons of the CH_2 in the thioethyl group appear at 2.86 and 2.75 ppm as doublets of quartets with *J*=12.6 and 7.5 Hz. The methyl group appears at 1.36 ppm as a triplet with *J*=7.5 Hz.

On the ^{13}C NMR spectrum, the C=N carbon appears at 158.55 ppm, and the seven signals between 139 and 119 ppm confirm the presence of seven different aromatic CHs in the molecule. The quaternary carbon of the ring junction appears at 110.92 ppm, and the presence of the thioethyl group is indicated by the signals at 45.22 and 14.58 ppm for the CH_2 and the CH_3, respectively. The CH and the CH_2 of the 4-membered ring appear at 66.79 and 22.52 ppm, respectively. One quaternary aromatic carbon is missing due to overlapping. The connectivity of the structure has been determined by HSQC and HMBC analysis.

On the IR spectrum, the presence of the azide and the C=N is confirmed by strong absorption at 2114 cm^{-1} and a medium absorption at 1683 cm^{-1}, respectively.

HRMS analysis with an accurate mass (*m/z*) of 351.1145 (for 351.1148 required) further supported the proposed structure.

The mechanism of the reaction is a concerted [3+2] 1,3-dipolar cycloaddition between the nitrile oxide (**198**) and the C=N double bond of the 1-azetine (**180**) to form the product (**197**) in 63% yield (Scheme 2.17).

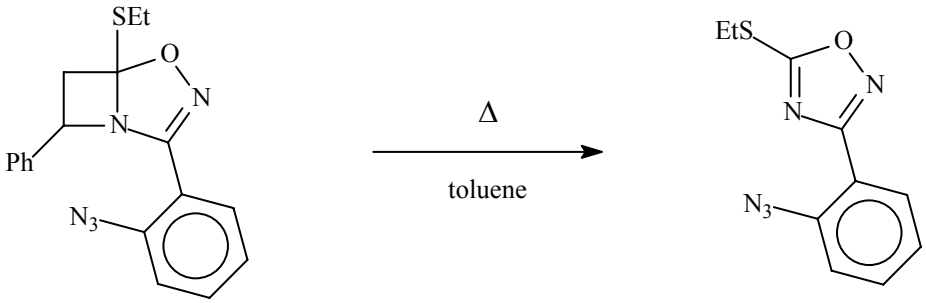


Scheme 2.17

2.2.1.3.4 Thermolysis of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo-[3.2.0]hept-2-ene

As discussed above, thermolysis of the adducts obtained from 1-azetines with DPP gave some interesting results.[73,86] Thus, adduct (**197**) was also thermolysed and the reaction monitored, in order to see if further interesting reactions could be discovered, particularly given the presence of the azide group.

The thermolysis of the cycloadduct (**197**) was carried out in refluxing toluene until disappearance of the starting material (after 47h) to afford the stable fully conjugated 1,2,4-oxadiazole (**199**) as the only identified product (~20% yield), through a retro [2+2] cycloaddition (Scheme 2.18).



(**197**) (**199**)

Scheme 2.18

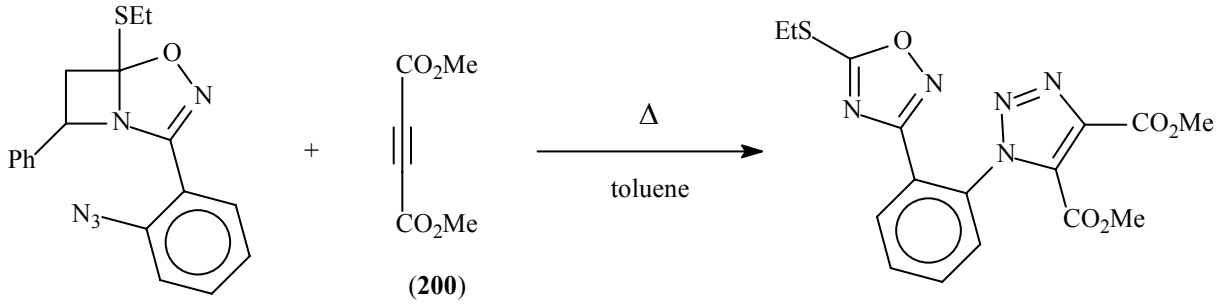
Spectroscopic data provided the evidence for the formation of the product. The simple ^{1}H NMR spectrum suggested the loss of styrene by the appearance of only four signals at 7.99, 7.55, 7.27 and 7.19 ppm, indicating only four aromatic protons were present in the molecule. The presence of the thioethyl group is confirmed by a quartet at 3.34 ppm and a triplet at 1.54 ppm with J=7.4 Hz for the CH_2 and the CH_3, respectively.

^{13}C NMR, HSQC and HMBC analysis provided the connectivity of the molecule and further confirmed the proposed structure with the sp^2 carbon bearing the thioethyl substituent appearing at 177.62 ppm, the C=N carbon at 166.66 ppm, two quaternary aromatic carbons at 138.89 and 118.23 ppm, and four aromatic CHs at 132.09, 131.58, 124.87 and 119.34 ppm. Two signals for a CH_2 and a CH_3 at 27.27 and 14.77 ppm give evidence of the presence of the thioethyl group.

HRMS data confirmed the proposed structure of the product with a measured accurate mass (*m/z*) of 248.0603 for 248.0601 required, and IR spectroscopy confirmed that the azide was intact.

2.2.1.3.5 Reaction of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]-hept-2-ene with dimethylacetylene dicarboxylate (DMAD)

DMAD (**200**) is known to be an excellent dipolarophile.[156] With cycloadduct (**197**) in hand, we decided to investigate the reactivity of its azide moiety towards DMAD. The reaction was performed in refluxing toluene overnight (~20h) to afford, in 41% yield, the corresponding benzene ring (**201**) substituted with an oxadiazole ring on one hand, and a triazole ring on the other hand, formed *via* a retro [2+2] cycloaddition to form the oxadiazole and a 1,3-dipolar cycloaddition to form the triazole (Scheme 2.19).



(**197**) (**200**) (**201**)

Scheme 2.19

The structure of the product was determined by spectroscopic analysis. The ^{1}H NMR spectrum was consistent with the structure with three signals integrating to four protons in the aromatic region, and two singlets integrating to three protons each at 4.02 and 3.76 ppm, indicating the presence of the two methyl esters in the molecule. Evidence for the presence of the thioethyl group was provided by a quartet at 3.09 ppm and a triplet at 1.36 ppm with *J*=7.4 Hz for the CH_2 and the CH_3, respectively.

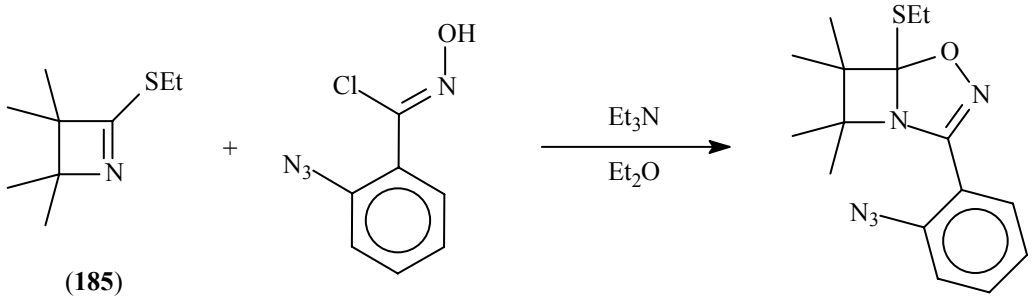
^{13}C NMR , HSQC and HMBC analysis provided the connectivity of the molecule and further confirmed the proposed structure with the sp^2 carbon bearing the thioethyl substituent appearing at 178.85 ppm, the C=N carbon at 165.49 ppm, two quaternary carbons at 160.40 and 158.10 ppm for the two carbonyls, two quaternary carbons at 133.78 and 133.14 ppm for the two sp^2 carbons of the triazole ring, two quaternary aromatic carbons at 139.06 and 124.20 ppm, and four aromatic CHs at 131.63, 131.37, 130.08 and 128.69 ppm. Two CH_3 appear at 53.31 and 52.74 ppm for the methyl esters, and two signals for a CH_2 and a CH_3 at 27.42 and 14.53 ppm give evidence of the presence of the thioethyl group.

In the IR spectrum, a strong absorption band at 1735cm^{-1} (C=O) supports the presence of the two methyl esters, and the loss of N_3 absorption supports successful cycloaddition. HRMS data confirmed the proposed structure with a measured accurate mass (*m/z*) of 390.0867 for 390.0867 required.

2.2.1.4 Reactivity of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine

2.2.1.4.1 1,3-Dipolar cycloaddition with 2-azidobenzohydroximoyl chloride: synthesis of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]-hept-2-ene

1-Azetine (**185**) was reacted with 2-azidobenzohydroximoyl chloride (**196**) in the presence of triethylamine to yield the corresponding cycloadduct (**202**) in 75% yield (Scheme 2.20).



(**185**) (**196**) (**202**)

Scheme 2.20

Spectroscopic analysis provided the evidence of the formation of the product. In the ^{1}H NMR spectrum, the four signals at 7.64, 7.46, 7.26 and 7.18 ppm indicate the presence of the four aromatic protons. The two diastereotopic protons of the CH_2 in the thioethyl substituent appear at 2.72 and 2.66 ppm as doublets of quartets with J=12.4 and 7.4 Hz. The four methyl groups attached to the 4-membered ring appear at 1.51, 1.31, 1.26 and 0.96 ppm as singlets, whereas the methyl from the ethylthio substituent appears at 1.29 ppm as a triplet with J=7.4 Hz.

In the ^{13}C NMR spectrum, the sp^2 carbon attached to the aromatic ring (C=N) appears at 156.69 ppm with a correlation on HMBC with the nearest aromatic proton. The two quaternary aromatic carbons and the four aromatic CHs appear at 137.84, 118.76, 131.18, 130.31, 124.35 and 119.21 ppm, respectively. The sp^3 quaternary carbon at the ring junction appears at 116.92 ppm with a correlation on HMBC with the two diastereotopic protons from the ethylthio substituent and the protons of the two nearest methyl groups attached to the 4-membered ring. The two sp^3 quaternary carbons of the 4-membered ring appear at 71.63 and 52.80 ppm, and the four methyl groups attached to them appear at 26.38, 20.86, 20.36 and 19.77 ppm. The presence of the ethylthio group is provided by a CH_2 and a CH_3 at 21.54 and 14.58 ppm, respectively.

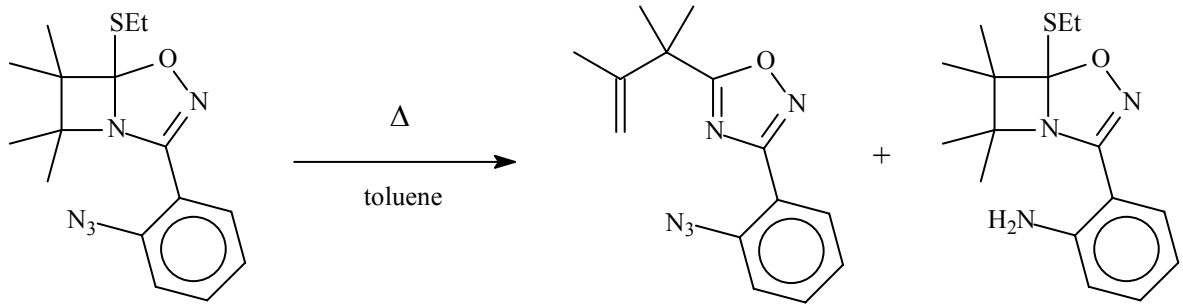
In the IR spectrum, the two very strong absorptions at 2127 and 2093 cm^{-1} confirm the presence of the azide, and the medium absorption at 1581 cm^{-1} confirms the presence of the C=N bond.

The proposed structure is further supported by HRMS analysis with a measured accurate mass (*m/z*) of 332.1540 for 332.1540 required.

The mechanism of this reaction is the same as the one described in Scheme 2.17 (section 2.2.1.3.3).

2.2.1.4.2 Thermolysis of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene

Upon thermolysis in refluxing toluene for 47 hours, the cycloadduct (**202**) underwent a ring opening of the 4-membered ring affording the corresponding oxadiazole (**203**) on one hand, and the transformation of the azide moiety into an amine affording the amine analogue (**204**) of the starting material on the other hand (Scheme 2.21). Compounds (**203**) and (**204**) were isolated in 10% and 22% yield, respectively.



(**202**) (**203**) (**204**)

Scheme 2.21

Spectroscopic analysis provided the evidence for the formation of the two products.

3-(2-azidophenyl)-5-(2,3-dimethylbut-1-en-3-yl)-1,2,4-oxadiazole (**203**)

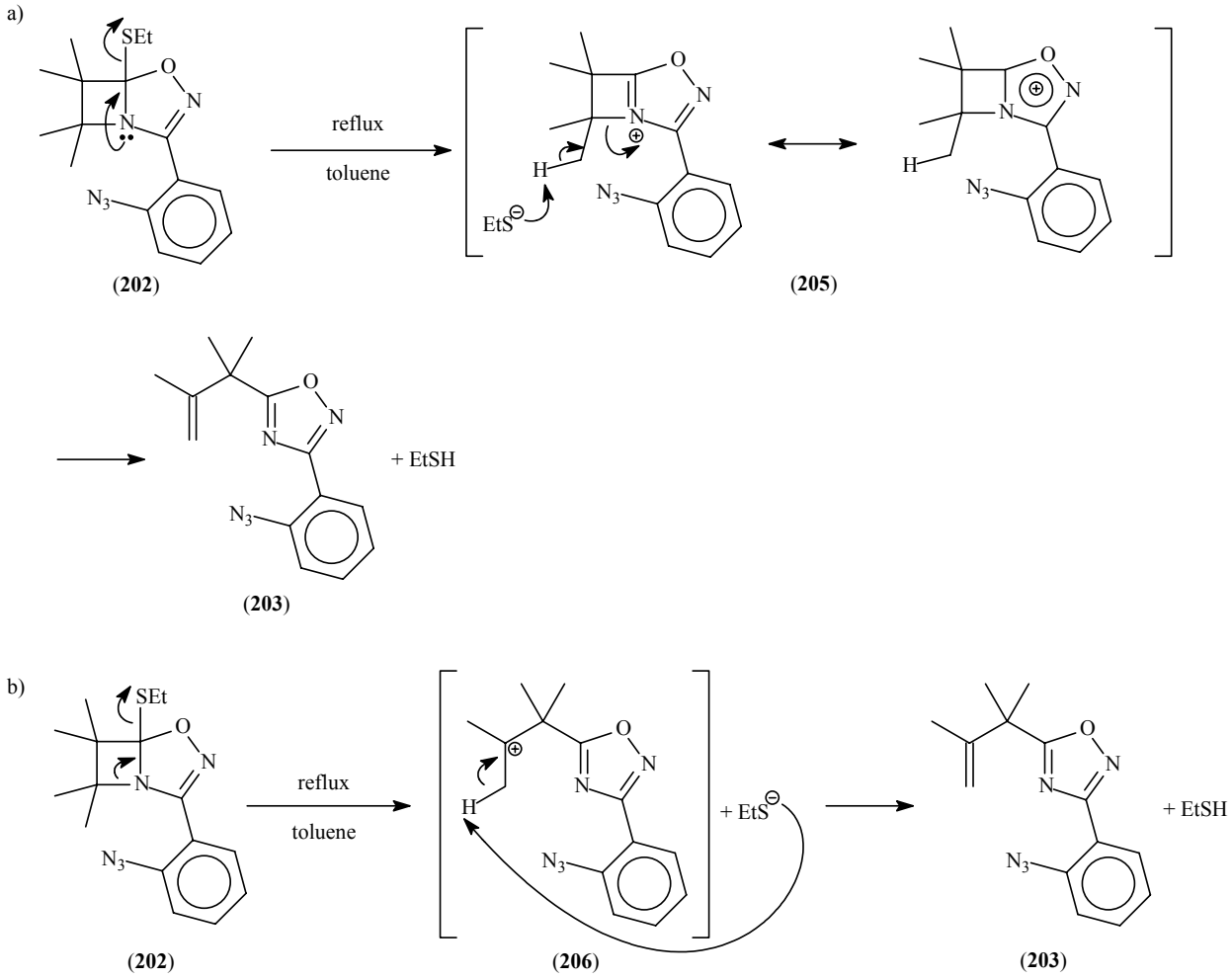
The IR spectrum showed two strong bands at 2128 and 2096 cm^{-1} which confirm that the azide moiety is still present in the molecule.

In the ^{1}H NMR spectrum, the presence of only two singlets, one integrating to three protons at 1.77 ppm and one integrating to six protons at 1.65 ppm, instead of four singlets integrating to three protons each suggested that two methyl groups were identical and the 4-membered ring had been altered. The appearance of two singlets integrating to one proton each at 4.98 and 4.95 ppm suggested the presence of a methylene group. The four signals at 8.00, 7.53, 7.31 and 7.26 ppm integrating to four protons suggested the aromatic ring was unchanged. The disappearance of the two protons around 2.60-2.70 ppm suggested the loss of the ethylthio group.

The ^{13}C NMR spectrum confirmed these suggestions with the appearance of a CH_2 at 111.81 ppm for the methylene, a quaternary sp^2 carbon at 138.79 ppm (**C**=CH_2) and a quaternary sp^3 carbon at 42.01 ppm (bearing the two methyl groups). Two deshielded signals appear at 183.82 and 166.14 ppm for the two quaternary sp^2 carbon of the oxadiazole ring, confirming the ring opening of the 4-membered ring. The loss of the ethyl group is further supported by the presence of only two types of CH_3.

MS data were consistent with the proposed structure of compound (**203**).

The mechanism of formation of compound (**203**) could follow two routes (Scheme 2.22). It could proceed through the loss of thioethoxide with participation of the lone pair of the adjacent nitrogen to form the oxadiazolium species (**205**) *via* an E_2-type mechanism (scheme 2.22a). The thioethoxide picks up a proton on one of the two methyl groups adjacent to the nitrogen to open the four-membered ring, hence releasing the strain of the ring and generating the more stable fully conjugated 1,2,4-oxadiazole (**203**). The other possible way is to form a "stable" tertiary cationic intermediate (**206**) with ring opening through an E_1-type mechanism and loss of thioethoxide, with the latter picking up a proton to form the olefinic double bond (scheme 2.22b).



Scheme 2.22

2-(2-aminophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene **(204)**

The disappearance of the two strong IR absorptions around 2100 cm^{-1} and the appearance of two broad bands at 3465 and 3349 cm^{-1} suggest the transformation of the azide into an amine.

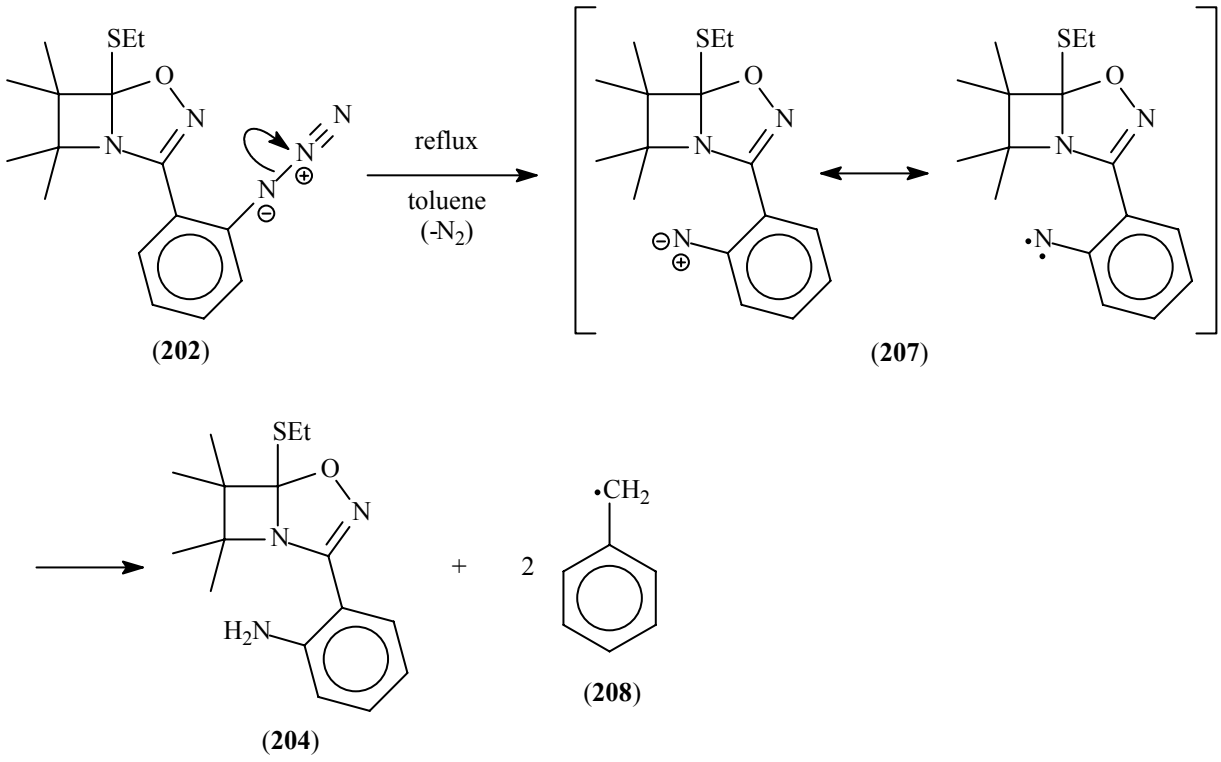
In the ^{1}H NMR spectrum, the broad singlet at 5.41 ppm integrating to two protons confirms the presence of the primary amine. The other signals suggest the rest of the molecule remains unchanged with four aromatic protons, four methyl substituents at 1.56, 1.33, 1.27 and 0.99 ppm as singlets, respectively. The multiplet and the triplet at 2.66 and 1.26 with J=7.4 Hz confirms the presence of the thioethyl group in the molecule.

On the ^{13}C NMR spectrum, the quaternary sp^2 carbon of the oxadiazoline ring appears at 159.77 ppm, the two quaternary aromatic carbons appear at 146.32 and 109.72 ppm, and the four aromatic CHs appear at 131.22, 129.70, 116.39 and 115.56 ppm. The quaternary sp^3 carbon

at the ring junction appears at 116.01 ppm, whereas the two other quaternary sp^3 carbons in the 4-membered ring appear at 71.81 and 51.67 ppm. The four methyl groups linked to the 4-membered ring appear at 26.49, 21.24, 20.97 and 19.68 ppm, and the CH_2 and the CH_3 at 21.72 and 14.63 ppm, respectively, confirm the presence of the ethylthio group.

MS data further supported the structure of this product, with fully consistent mass (*m/z*) of 306.2 ($[M+H]^+$) and 328.1 ($[M+Na]^+$).

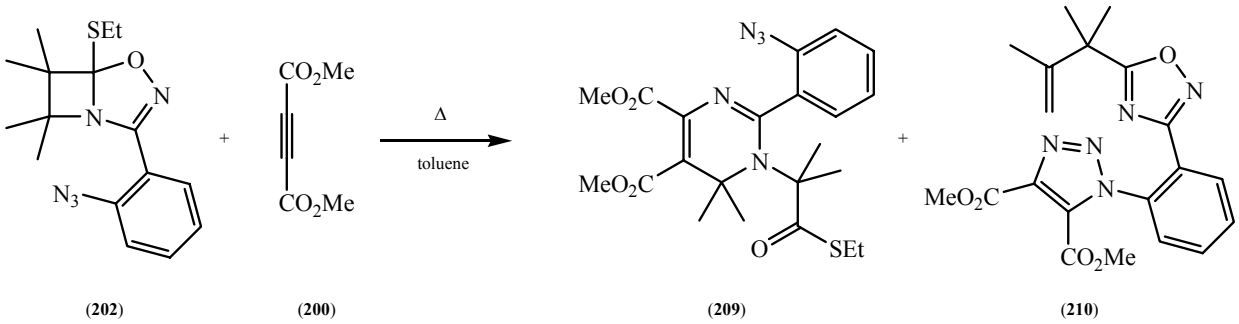
Azides are known to form nitrenes by thermal decomposition.[157,158] Under heating, the azide can lose spontaneously nitrogen to form a nitrene (**207**), which can then abstract two hydrogens from toluene to give the product (**204**) and a stablised benzylic radical (**208**) (Scheme 2.23).



Scheme 2.23

2.2.1.4.3 Reaction of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiaza-bicyclo[3.2.0]hept-2-ene with DMAD

The reaction of cycloadduct (**202**) with DMAD (**200**) was performed in toluene at reflux for 21 hours (Scheme 2.24) to afford a mixture of compound (**209**) (**35 mg, 25 %**) and (**210**) (**30 mg, 25 %**) in a ~1:1 ratio based upon ^{1}H NMR.



(**202**) (**200**) (**209**) (**210**)

Scheme 2.24

Spectroscopic analysis provided the evidence of the formation of the two products.

2-(2-azidophenyl)-4,4-dimethyl-5,6-dimethoxycarbonyl-3-(1-ethylthio-2-methylpropan-1-on-2-yl)-4*H*-pyrimidine (**209**):

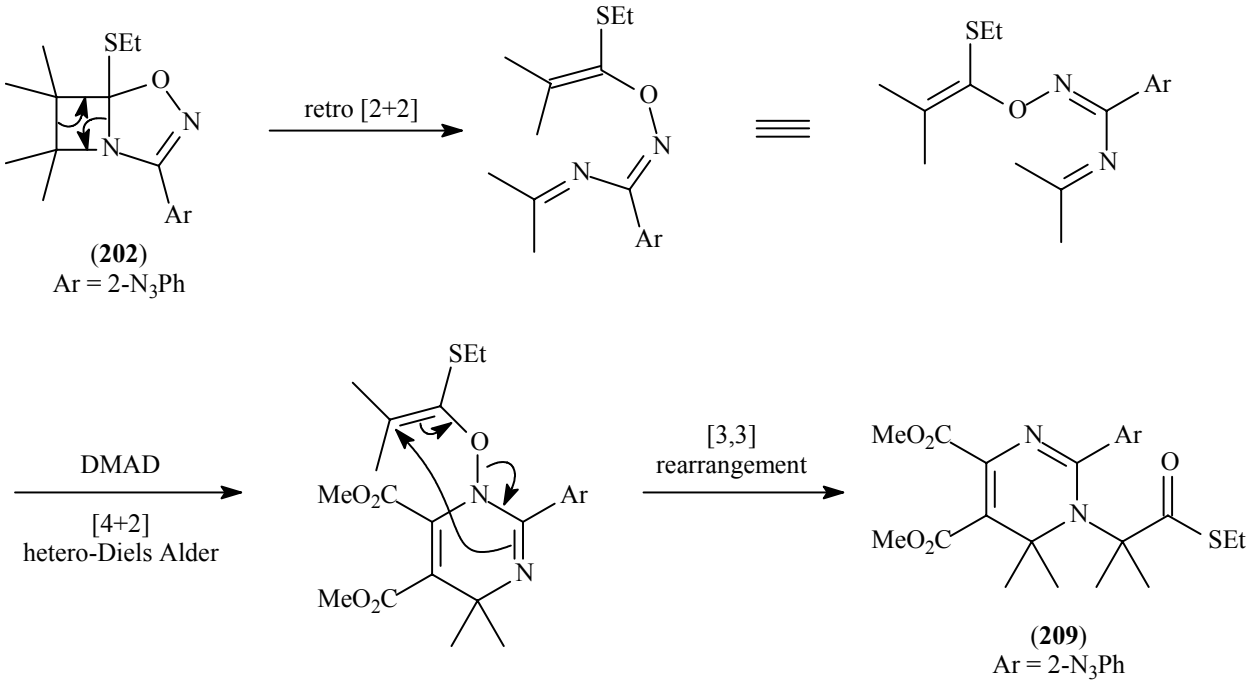
In the IR spectrum, the strong absorption at 2126 cm^{-1} confirmed the presence of the intact azide and the appearance of a strong absorption at 1734 cm^{-1} confirmed the presence of carbonyl groups in the molecule. The absorption at 1665 cm^{-1} supports the presence of a C=N functional group.

The ^{1}H NMR spectrum (appendix I) showed four signals integrating to one proton each between 7.60 and 7.20 ppm, indicating the presence of the aromatic ring. The two singlets at 4.01 and 3.88 ppm integrating to three protons suggested the presence of the two methoxy groups. The quartet at 2.83 ppm and the triplet at 1.22 ppm with J=7.4 Hz supported the presence of the thioethyl group, and the two singlets at 1.42 and 1.30 ppm integrating to six protons each suggested the presence of the four methyl groups. The fact that the two protons of the CH_2 from the ethyl group were a simple quartet suggested that the SCH_2CH_3 group was not attached to a chiral center anymore.

In the ^{13}C NMR spectrum (appendix II), a deshielded quaternary sp^2 carbon appeared at 204.22 ppm and two signals at 160.37 and 158.62 ppm for the two carbonyls of the methyl esters, along with the two signals at 133.04 and 131.89 ppm for the two quaternary sp^2 carbons of the pyrimidine ring bearing the methoxycarbonyl groups. The two peaks at 53.27 and 52.68 ppm confirmed the presence of the two methoxy groups. The C=N carbon appeared at 138.64 ppm. The two quaternary sp^3 carbons bearing the *gem* dimethyls appeared at 64.76 and 55.48 ppm, indicating they were in a significantly different electronic environment. This is supported by the HMBC data (appendix III). On HMBC, a correlation between the deshielded carbon at 204.22 ppm and the two protons of the CH_2 of the ethylthio group at 2.83 ppm suggested the presence of a thio ester or thione ester moiety.

The proposed structure is further supported by MS data with a measured accurate mass (*m/z*) of 474.1805 for 474.1806 required.

The mechanism for this unexpected reaction may proceed through a retro [2+2] cycloaddition of the four-membered ring to form a heterodiene, which then undergoes a [4+2] hetero Diels-Alder cyclisation with DMAD, followed by a [3,3]-rearrangement of the *N*-susbtituent into the thioester (**209**) (Scheme 2.25).



(**202**)
Ar = 2-N_3Ph

(**209**)
Ar = 2-N_3Ph

Scheme 2.25

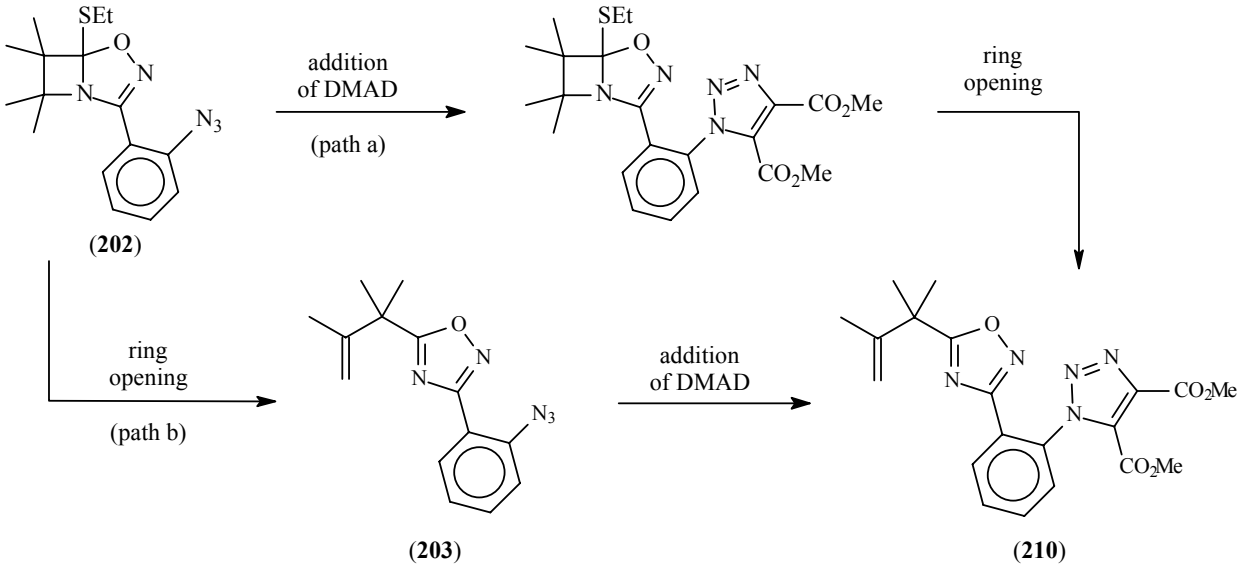
3-(2-(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl))phenyl-5-(2,3-dimethylbut-2-en-3-yl)-1,2,4-oxadiazole (**210**):

The ^{1}H NMR spectrum supported the presence of a methylene group with the appearance of two singlets at 4.88 and 4.82 ppm integrating to one proton each, suggesting the alteration of the 4-membered ring. Two singlets at 4.00 and 3.73 ppm integrating to three protons acknowledged the presence of the two methoxy groups. A singlet integrating to three protons at 1.60 ppm and another one integrating to six protons at 1.45 ppm, along with the absence of signals for the ethylthio group confirmed the ring opening of the 4-membered ring with loss of SEt.

The ^{13}C NMR spectrum exhibited four peaks at 184.46, 165.12, 160.38 and 158.16 ppm for the two quaternary sp^2 carbons of the oxadiazole ring and the two carbonyl groups of the triazole ring. The two quaternary sp^2 carbons of the triazole ring appear at 133.89 and 133.36 ppm, and the two methyls of the methoxy substituents appear at 53.20 and 52.65 ppm. The evidence of the unsaturated side chain on the oxadiazole ring is provided by a peak at 146.67 ppm for the quaternary sp^2 carbon bearing the methylene group, a peak at 111.75 ppm for the methylene, a peak at 41.79 ppm for the quaternary sp^3 carbon bearing the two methyl substituents, a peak at 25.40 ppm for the two identical CH_3s and a peak at 19.55 ppm for the vinylic CH_3, confirming the ring opening of the 4-membered ring.

MS data further support the structure of this compound with a measured accurate mass (*m/z*) of 412.1613 for 412.1615 required.

The formation of the ring opened analogue can proceed through two routes (Scheme 2.26): addition of DMAD on the azide moiety followed by the ring opening of the intermediate (path a), or the occurance of the ring opening before the addition of DMAD on the intermediate (**203**) (path b).



Scheme 2.26

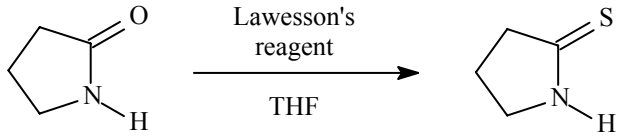
Having previously isolated compound (**203**), we decided to mix it with DMAD (**200**) in refluxing toluene to confirm that it is able to react and afford compound (**210**) through path b. This reaction was successfully performed in 24% yield, thus suggesting that compound (**210**) is formed *via* the ring opening prior to the addition of DMAD on the azide moiety (path b), a hypothesis seemingly confirmed as compound (**210**) was formed from compound (**202**) in the same yield.

2.2.2 Synthesis and reactivity of 3,4-dihydro-5-ethylthio-2*H*-pyrrole

In order to prove the efficiency of the methodology developed with 1-azetines, we decided to apply it to a 5-membered ring analogue. The success of this concept would allow easy access to pyrrolizidines, a structural core present in a wide range of biologically active natural products.[159-166]

2.2.2.1 Synthesis of pyrrolidin-2-thione

The thionation of pyrrolidin-2-one (**211**) proceeded easily using Lawesson's reagent to give the desired product (**212**) in 86% yield (Scheme 2.27).



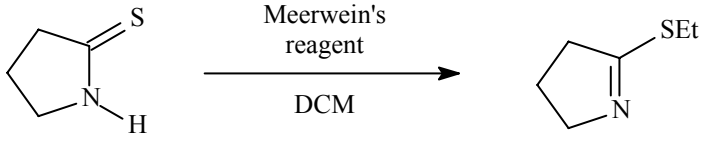
(**211**) (**212**)

Scheme 2.27

Spectroscopic analysis provided the evidence for the formation of the product. Both the IR spectrum with a broad absorption at 3153 cm^{-1} and the ^{1}H NMR spectrum with a broad singlet at 8.77 ppm confirmed the presence of the amine. The strong absorption at 1536 cm^{-1}, and the deshielded peak at 205.77 ppm in the ^{13}C NMR spectrum supported the presence of C=S. In the ^{1}H NMR spectrum, two triplets and a multiplet at 3.65, 2.90 and 2.20 ppm, respectively, integrating to two protons each for each for the three CH_2 confirmed the 5-membered ring was present.

2.2.2.2 Synthesis of 3,4-dihydro-5-ethylthio-2*H*-pyrrole

The alkylation was performed with Meerwein's reagent in DCM (Scheme 2.28). The recovery, and hence the yields, were poor, suggesting the product (**213**) was volatile, making its isolation and handling difficult. The procedure involved the use of potassium carbonate and aqueous work-up to isolate the imine from its HBF_4 salt. Thus, a modification of the original procedure described in the experimental (section 3.1.2.2) was attempted by using triethylamine followed by careful concentration and silica chromatography instead of potassium carbonate followed by vacuum filtration through Celite®, extraction and concentration. However, the recovery remained very low after chromatography. Hence, in order to overcome those problems, the handling of the product during the isolation was minimised, and the product was used as crude without further purification, and identified only by ^{1}H and ^{13}C NMR spectroscopy.



(**212**) (**213**)

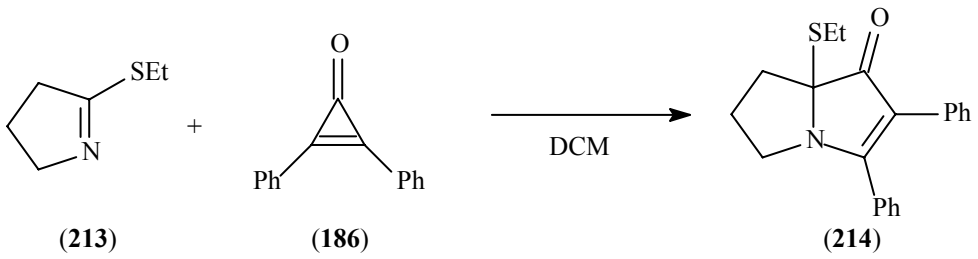
Scheme 2.28

NMR analysis provided the evidence of the proposed structure. On the ^{1}H NMR spectrum, three multiplets integrating to two protons each were seen at 3.78, 2.53 and 1.91 ppm, which suggested the presence of the three CH_2 of the ring. A quartet and a triplet with *J*=7.4 Hz at 2.98 and 1.27 ppm, respectively, confirmed the presence of the ethylthio moiety.

This was further confirmed by the ^{13}C NMR spectrum and DEPT data with loss of the C=S at ~206 ppm and a new peak at 172.59 ppm for the C=N carbon bearing the ethylthio group, four CH_2s at 60.70, 38.65, 24.97 and 23.34 ppm, and one CH_3 at 14.38 ppm.

2.2.2.3 Reaction of 3,4-dihydro-5-ethylthio-2*H*-pyrrole with DPP: synthesis of 2,3-diphenyl-5-ethylthio-1-azabicyclo[3.3.0]oct-2-en-4-one

This reaction was carried out in DCM instead of acetonitrile as stated in the original procedure with 1-azetines (scheme 2.29). The reason for this modification was the use of the starting material as a crude solution, which meant keeping it in the solvent of the previous reaction, as mentioned above. A few attempts were also made to perform the alkylation of the pyrrolidin-2-thione (**212**) and the ring expansion with DPP (**186**) in one pot, in the presence of triethylamine as a base, but the yields were lower (18-29%) than those obtained by using the crude starting material (53%).



(**213**) (**186**) (**214**)

Scheme 2.29

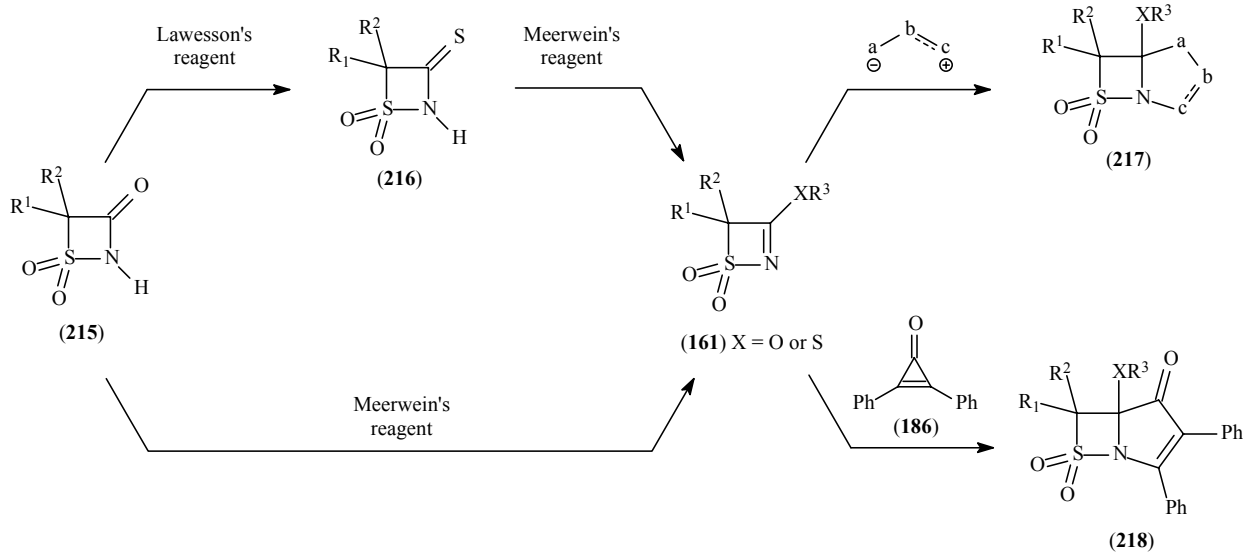
Spectroscopic analysis established the structure of the product. The ^{1}H NMR spectrum displays ten aromatic protons between 7.50 and 7.10 ppm. Two deshielded doublets of triplets with *J*= 11.1 and 6.6 Hz integrating to one proton each at 3.55 and 3.08 ppm confirmed the presence of the CH_2 attached to the nitrogen. The two diastereotopic protons of the CH_2 and the three protons of the CH_3 in the ethylthio substituent appeared as doublets of quartets with *J*=12.0 and 7.4 Hz at 2.65 and 2.56 ppm, and as a triplet with *J*=7.4 Hz at 1.20 ppm,

respectively. The two remaining CH_2s in the heterocycle appeared as a multiplet integrating to two protons at 2.23 ppm, and two multiplets integrating to one proton each at 2.07 and 1.94 ppm.

The mechanism involved in this reaction is the same as the one previously described with 1-azetines (Scheme 2.9, section 2.2.1.3.1). This brief investigation has shown that this is a valid route for the synthesis of pyrrolizidines and is now being explored by others.

2.3 Synthesis and reactivity of 1,2-thiazetin-1,1-dioxides

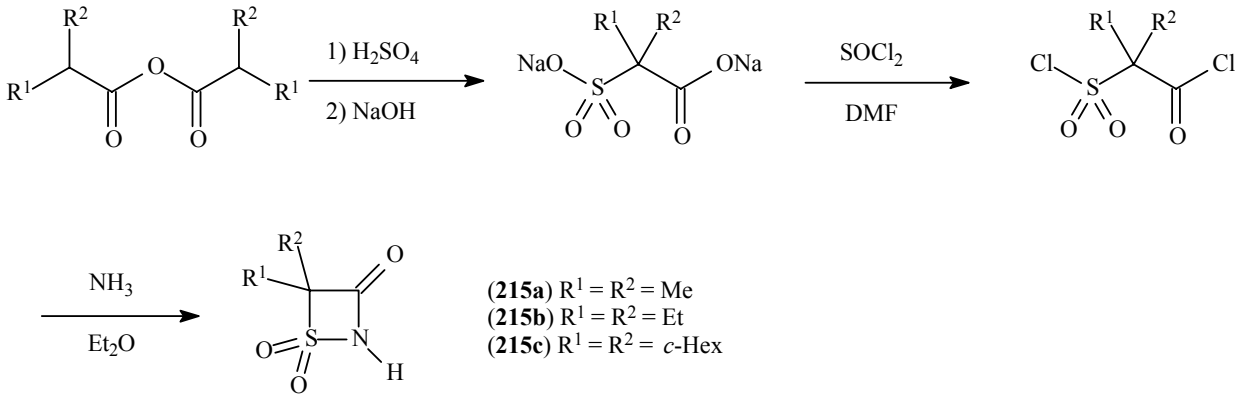
As mentioned in the outline of the discussion (section 2.1), the ultimate purpose of this project was to synthesise bicyclic *β*-sultams. To do so, the strategy was to use the methodology previously described for 1-azetines. Therefore, the synthesis of 1,2-thiazetidin-3-on-1,1-dioxides (**215**) was a key because their conversion to their thioxo analogues (**216**) with Lawesson's reagent and the alkylation of those analogues with Meerwein's reagent to access 1,2-thiazetin-1,1-dioxides (**161**) needed to be investigated (Scheme 2.30). Then, the behaviour of compound (**161**) towards cycloadditions to access our target molecules (**217**) and (**218**) would be the final goal. In this context, we embarked upon the synthesis of 3-oxo-*β*-sultams (**215**). Alternatively, *O*-alkylation of 1,2-thiazetidin-3-on-1,1-dioxides would give other potential templates for cycloaddition.



Scheme 2.30

2.3.1 Synthesis of 1,2-thiazetidin-3-on-1,1-dioxides (3-oxo-*β*-sultams)

3-Oxo-*β*-sultams (**215a-c**) were synthesised using the general methodology previously used in the laboratory[167] (Scheme 2.31). All the analytical data were compared to the data provided by this previous work and were consistent with the expected structures of the products.

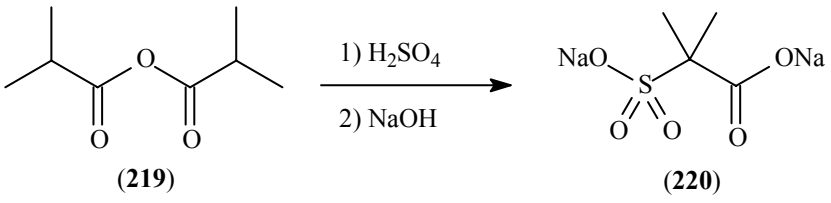


Scheme 2.31

2.3.1.1 Synthesis of 4,4-dimethyl-3-oxo-*β*-sultam

2.3.1.1.1 Synthesis of disodium 2-methyl-2-sulfonato propionate

Acid hydrolysis of commercially available isobutyric anhydride (**219**) with concentrated sulfuric acid followed by alkaline work-up afforded the desired disodium salt (**220**) (Scheme 2.32).



(**219**) (**220**)

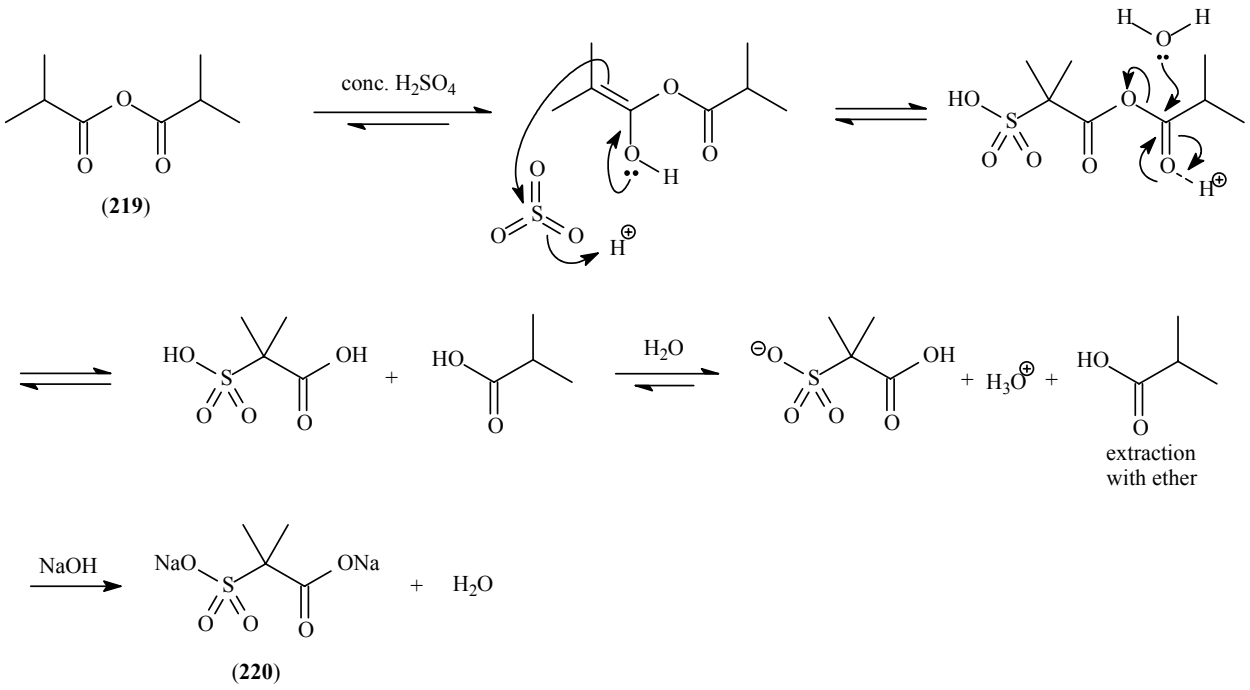
Scheme 2.32

Spectroscopic analysis of the product was consistent with the assigned structure. The ^{1}H NMR spectrum displayed one singlet integrating to six protons, and the ^{13}C NMR spectrum exhibited

the carbonyl at 177.67 ppm, the quaternary sp^3 carbon at 66.02, and a peak for the two CH_3s at 22.56 ppm.

The IR spectrum showed two strong bands at 1590 and 1577 cm^{-1} for the carboxylate ion (C=O) and a strong band at 1204 cm^{-1} for the sulfonate ion (SO_2).

The mechanism of the reaction is shown below (Scheme 2.33). The conversion of isobutyric anhydride (**219**) to disodium 2-methyl-2-sulfonato propanoate (**220**) presumably occurs by the formation of the enol under strong acid conditions, which then undergoes a nucleophilic attack on the oleum present in concentrated sulfuric acid to form the sulfonato anhydride. Subsequent hydrolysis of the anhydride by water forms the sulfonic acid and isobutyric acid. The latter is extracted with ether, whereas the sulfonic acid must be in an ionic form in water due to its stronger acidity, and remains in the aqueous layer, which is treated with sodium hydroxide to give the desired product (**220**).



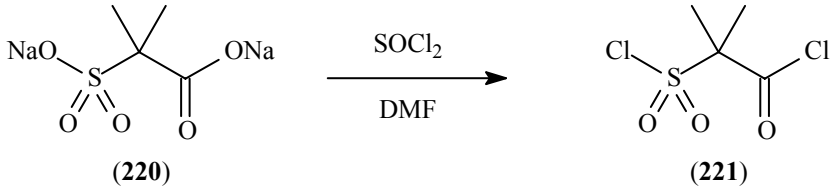
(**219**)

(**220**)

Scheme 2.33

2.3.1.1.2 Synthesis of 2-chlorosulfonyl-2-methylpropanoyl chloride

Chlorination of the disodium salt (**220**) with thionyl chloride in the presence of DMF yielded the corresponding dichloride (**221**) (Scheme 2.34).

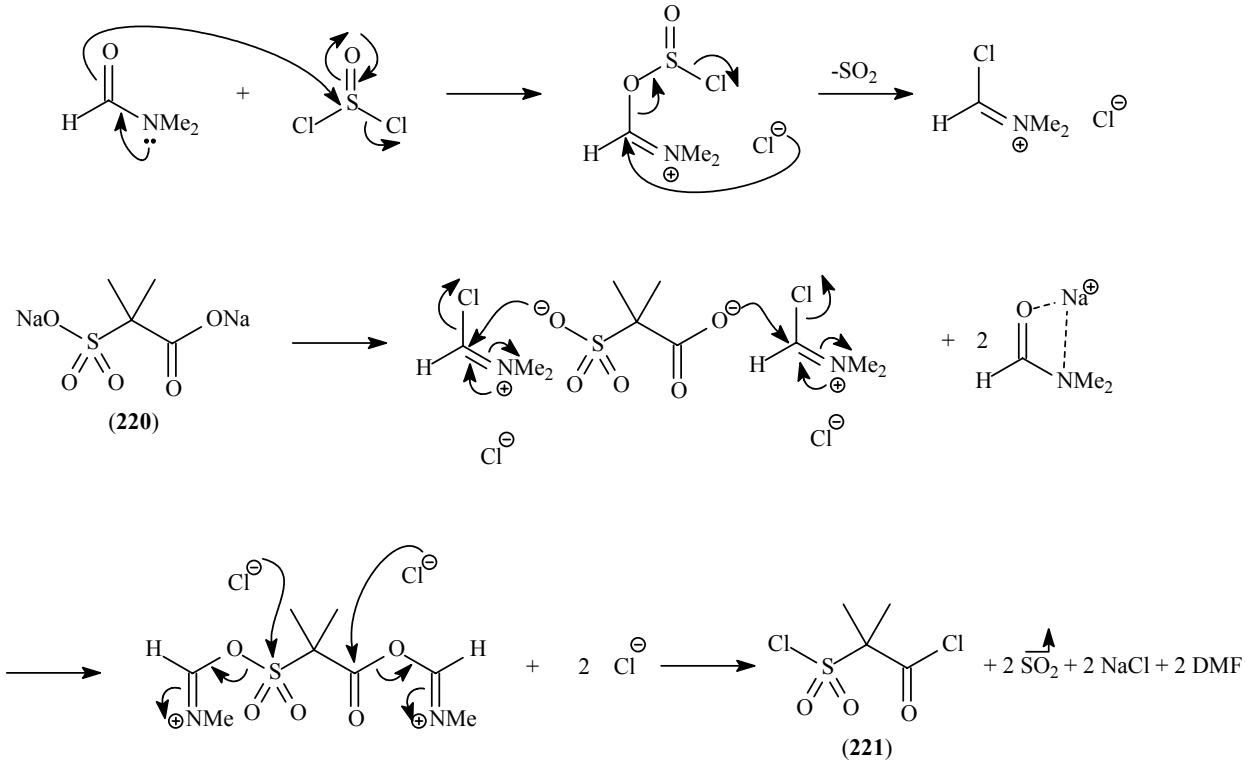


Scheme 2.34

Spectroscopic analysis was consistent with the formation of the product. On the IR spectrum, the presence of the carbonyl of the acyl chloride was confirmed by a band at 1763 cm^{-1}, and the sulfonyl chloride by two absorptions at 1364 and 1172 cm^{-1}.

The ^{1}H NMR spectrum displays a singlet integrating to six protons for the two methyl groups, and the ^{13}C NMR spectrum shows three peaks at 169.36, 85.37 and 22.20 for the carbonyl, the sp^3 quaternary carbon and the two CH_3s, respectively, which is consistent with the structure of the product.

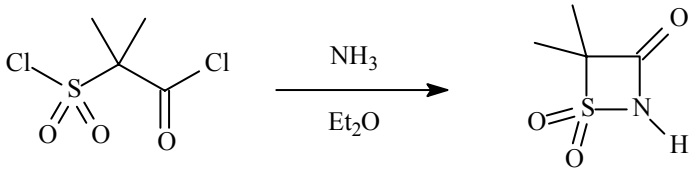
The mechanism of the reaction is described below (Scheme 2.35). The use of a catalytic amount of dimethylformamide is to activate thionyl chloride *via* a Vilsmeier-type intermediate and to dissociate the sodium cation from the sulfonate and carboxylate anions, thus increasing their nucleophilicity towards thionyl chloride.



Scheme 2.35

2.3.1.1.3 Synthesis of 4,4-dimethyl-3-oxo-*β*-sultam

The ring closure of the dichloride (**221**) with liquid ammonia proceeded in 34% yields to afford the desired four-membered ring (**215a**) (Scheme 2.36).[61]



(**221**) (**215a**)

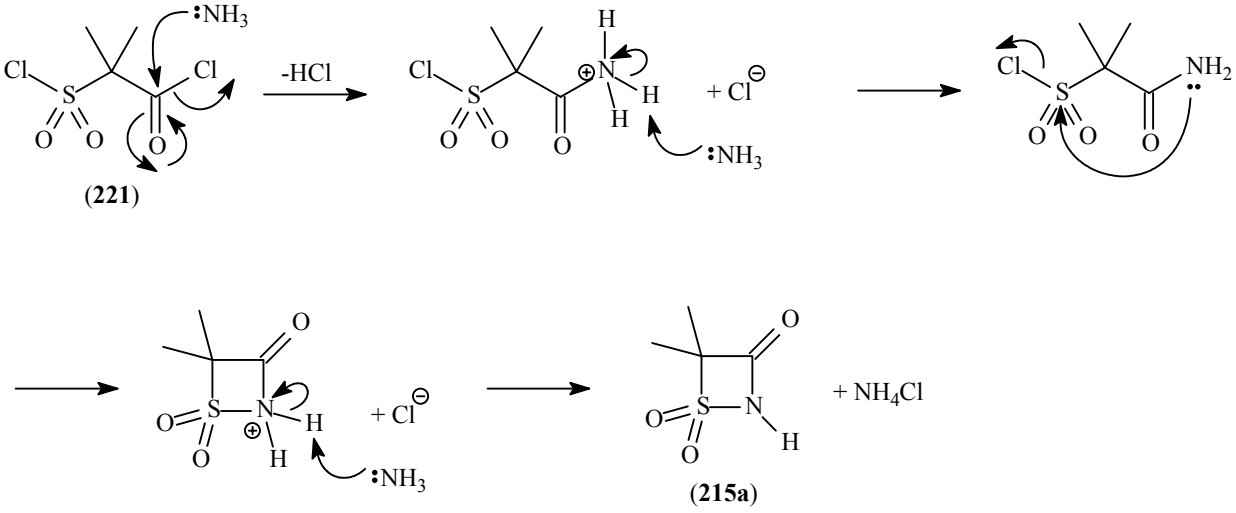
Scheme 2.36

Spectroscopic analysis provided evidence of the formation of the product. On the IR spectrum, the NH absorption appeared at 3115 cm^{-1}, the carbonyl appeared at 1748cm^{-1}, and the sulfonamide appeared at 1328 and 1157 cm^{-1}.

The ^{1}H NMR was consistent with the structure of the product with a broad singlet integrating to one proton at 8.27 ppm for the NH, and a singlet integrating to six protons at 1.76 ppm for the two CH_3s.

The ^{13}C NMR spectrum also confirmed the structure with a peak at 163.87, 82.36 and 18.55 ppm for the carbonyl, the quaternary sp^3 carbon and the two CH_3s, respectively.

The mechanism of the ring closure is described below (Scheme 2.37). Ammonia undergoes a nucleophilic attack on the carbonyl of the acyl chloride. Then, the amide is deprotonated and undergoes a nucleophilic attack on the sulfonyl chloride to form the 4-membered ring.

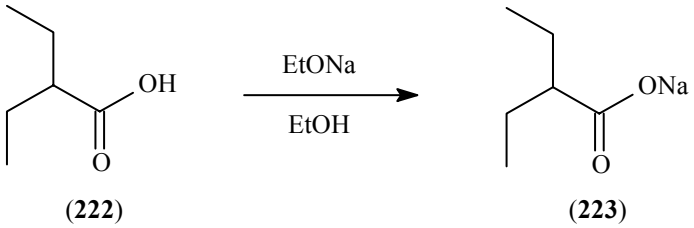


Scheme 2.37

2.3.1.2 Synthesis of 4,4-diethyl-3-oxo-*β*-sultam

2.3.1.2.1 Synthesis of sodium 2-ethylbutyrate (sodium 2-ethylbutanoate)

Treatment of 2-ethylbutyric acid (**222**) with sodium ethoxide in ethanol gave the corresponding sodium carboxylate (**223**) (Scheme 2.38).



Scheme 2.38

Spectroscopic data are in accordance with the structure. The IR spectrum shows strong absorptions at 1548 cm^{-1} and 1412 cm^{-1} for the carboxylate ion (C=O).

The ^{1}H NMR spectrum displays a triplet of triplets with J=8.3 and 6.5 Hz at 2.04 ppm for the methine proton, a multiplet at 1.44 ppm integrating to four protons for the two CH_2s, and a triplet at 0.86 ppm integrating to six protons for the two CH_3s.

The ^{13}C NMR spectrum is consistent with the structure, displaying a quaternary carbon at 186.44 ppm, a CH at 53.02 ppm, a CH_2 at 25.79 ppm, and a CH_3 at 11.71 ppm.

The surprisingly complex pattern for the methine proton suggests a restricted rotation around the CH-CH_2 bond due to steric hindrance. Assuming this hypothesis, it is possible to explain the triplet of triplets for the CH from the analysis of the Newman projections of the molecule, looking down the CH-CH_2 bond (Figure 2.1). By looking at those projections, we can see that the molecule is most likely to favour conformation (b) or (c) to minimise the steric hindrance between the methyl and both the carboxylate and the ethyl. Therefore, the two protons H_a and $H_{a'}$ are never in the same environment at any one time. Thus, the methine proton coupled to them with J=8.3 and 6.5 Hz, depending on the dihedral angle with H_a and $H_{a'}$.

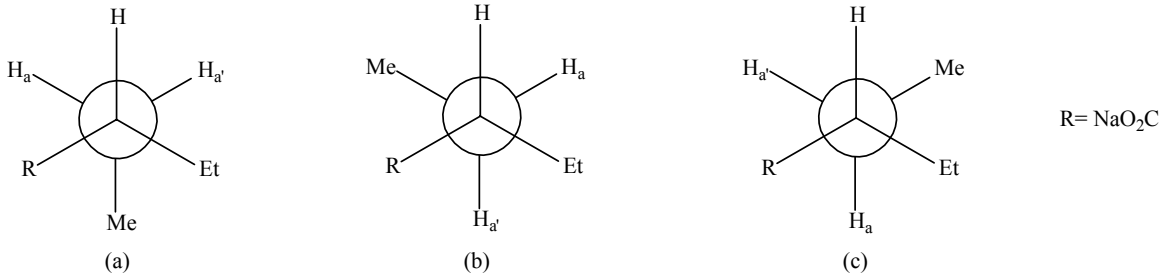


Figure 2.1 Newman projections of sodium 2-ethylbutyrate (**223**) along the CH-CH_2 bond

The same argument can be applied to the two protons H_b and $H_{b'}$ on the second ethyl group (Figure 2.2). The fact that H_a / H_b are the same and $H_{a'}$ / $H_{b'}$ are the same, but H_a is different to $H_{a'}$ and H_b is different to $H_{b'}$ gives a triplet of triplets.

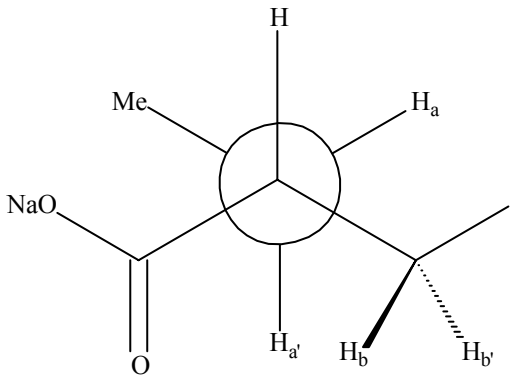
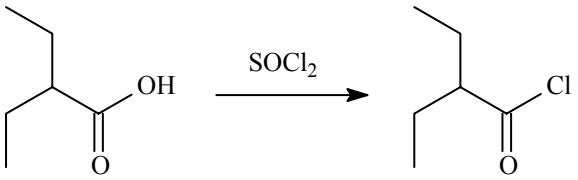


Figure 2.2 Newman projection of sodium 2-ethylbutyrate (**223**)

2.3.1.2.2 Synthesis of 2-ethylbutyryl chloride (2-ethylbutanoyl chloride)

The chlorination of 2-ethylbutyric acid (**222**) was performed using thionyl chloride to afford the corresponding acyl chloride (**224**) (Scheme 2.39).



(**222**) (**224**)

Scheme 2.39

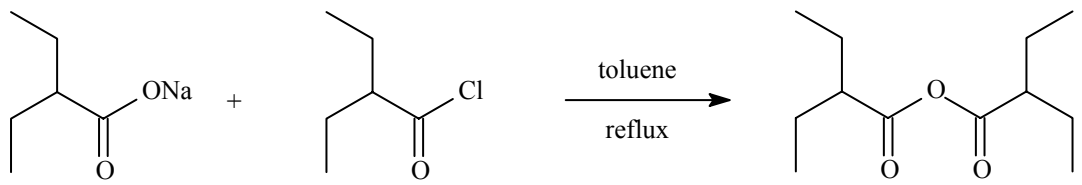
Spectroscopic analysis confirmed the structure of the product. The ^{1}H NMR again displayed a triplet of triplets with J=8.2 and 5.5 Hz for the methine proton. The two CH_2s appeared as a multiplet at 1.80 ppm integrating to two protons and two doublets of quartets at 1.69 and 1.65 ppm integrating to one proton each with J=5.5 and 7.5 Hz. The two CH_3s appeared as a triplet at 0.99 ppm with J=7.5 Hz.

The ^{13}C NMR spectrum was also consistent with the structure of the molecule.

As mentioned above, the unexpected complex pattern observed on ^{1}H NMR could be explained by a steric hindrance, which could restrict the rotation around the CH-CH_2 bond.

2.3.1.2.3 Synthesis of 2-ethylbutyric anhydride (2-ethylbutanoic anhydride)

The coupling of sodium 2-ethylbutyrate (**223**) and 2-ethylbutyryl chloride (**224**) was carried out in refluxing toluene to afford the corresponding anhydride (**225**) (Scheme 2.40).



(**223**) (**224**) (**225**)

Scheme 2.40

The spectroscopic data were consistent with the formation of the product. The IR spectrum showed two bands at 1811 and 1744 cm^{-1}, characteristic of the C=O absorptions for a carboxylic anhydride.

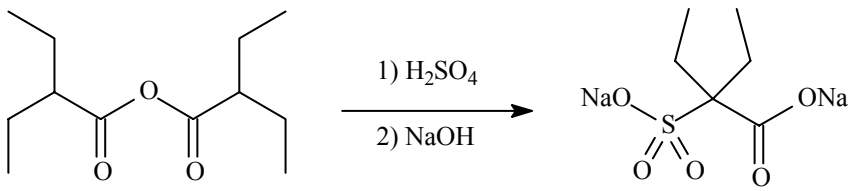
The ^{1}H NMR spectrum displayed a triplet of triplets at 2.31 ppm with *J*=8.2 and 5.5 Hz integrating to two protons for the two methine protons, two multiplets at 1.68 and 1.58 ppm integrating to four protons each for the four CH_2, and a triplet at 0.96 ppm with *J*=7.5 Hz integrating to twelve protons for the four CH_3.

The ^{13}C NMR spectrum displayed a quaternary carbon at 171.79 ppm (C=O), a CH at 49.68 ppm, a CH_2 at 24.34 ppm, and a CH_3 at 11.53 ppm.

Once again, the pattern shown for the four CH_2 might be explained by a possible restricted rotation in the CH-CH_2 bond due to steric hindrance. Subsequently, the two protons for each CH_2 would not be in the same environment at any one time as shown in the Newman projection in Figure 2.1 (Section 2.3.1.2.1), and as discussed previously.

2.3.1.2.4 Synthesis of disodium 2-ethyl-2-sulfonatobutyrate (disodium 2-ethyl-2-sulfonatobutanoate)

Hydrolysis of 2-ethylbutyric anhydride (**225**) under strong acidic conditions gave disodium 2-ethyl-2-sulfonatobutyrate (**226**) in 63% yield (Scheme 2.41).



(**225**) (**226**)

Scheme 2.41

Spectroscopic data were consistent with the structure. On the IR spectrum, a strong absorption at 1578 cm^{-1} acknowledged the presence of the carboxylate (C=O), and the two absorptions at 1385 and 1160 cm^{-1} confirmed the presence of the sulfonate (SO_2).

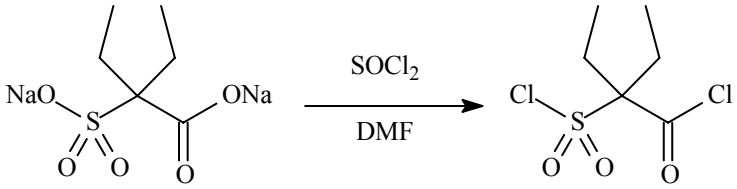
The ^{1}H NMR displayed two quartets at 1.97 ppm integrating to two protons each with *J*=7.5 Hz for the two methylenes, and a triplet at 0.96 ppm integrating to six protons with *J*=7.5 Hz for the two methyls.

In the ^{13}C NMR spectrum, the carbonyl appeared at 176.27, the sp^3 quaternary carbon appeared at 73.81, the CH_2 signal appeared at 25.35, and the CH_3 signal appeared at 9.01 ppm.

Again, the pattern for the four methylene protons suggested a restricted rotation around the C-CH_2 bond, in the same fashion as previously described in Figure 2.1 (section 2.3.1.2.1). The mechanism of this reaction is the same as the one previously described in Scheme 2.33 (section 2.3.1.1.1).

2.3.1.2.5 Synthesis of 2-chlorosulfonyl-2-ethylbutyroyl chloride (2-chlorosulfonyl-2-ethylbutanoyl chloride)

Chlorination of the disodium salt (**226**) with thionyl chloride in presence of dimethylformamide yielded 2-chlorosulfonyl-2-ethylbutyroyl chloride (**227**) in 53% yield (Scheme 2.42).



(**226**) (**227**)

Scheme 2.42

The structure of the product was determined by spectroscopic analysis. The IR spectrum provides the evidence of the chlorination with absorption at 1790 and 1765 cm^{-1} for the carbonyl of the acyl chloride, and two bands at 1371 and 1171 cm-^{1} for the sulfonyl chloride (SO_2).

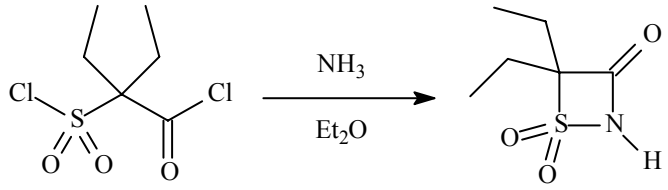
The ^1H NMR displayed a quartet at 2.48 ppm integrating to four protons and a triplet at 1.22 ppm integrating to six protons with J=7.4 Hz.

The ^{13}C NMR showed two peaks at 169.10 and 94.09 ppm for the carbonyl and the sp^3 quaternary carbon, respectively, and two other peaks at 26.98 and 8.82 ppm for the CH_2 and CH_3, respectively.

The mechanism of the chlorination has already been described in Scheme 2.35 (section 2.3.1.1.2).

2.3.1.2.6 Synthesis of 4,4-diethyl-3-oxo-*β*-sultam

The ring closure of the dichloride (**227**) was performed in liquid ammonia to give 4,4-diethyl-3-oxo-*β*-sultam (**215b**) in 33% yield (Scheme 2.43).



(**227**) (**215b**)

Scheme 2.43

Evidence of the formation of the desired product was provided by spectroscopic analysis. The IR spectrum confirmed the presence of NH with a broad band at 3237cm^{-1}. It also showed an absorption at 1772cm^{-1} for C=O (~1745cm^{-1} for *β*-lactams) and two absorptions at 1339 and 1145 cm^{-1} for SO_2.

The ^{1}H NMR spectrum displayed a broad singlet at 9.00 ppm, indicating the presence of the NH, and hence the ring closure of the dichloride. It also displayed a quartet at 2.18 ppm integrating to four protons and a triplet at 1.14 ppm integrating to six protons for the two CH_2s and the two CH_3s, respectively.

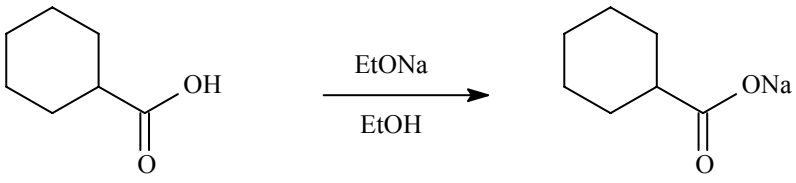
The ^{13}C NMR further supported the structure and the data are consistent with those available from previous work.[168]

The mechanism of the ring closure has already been discussed in Scheme 2.37 (section 2.3.1.1.3).

2.3.1.3 Synthesis of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam

2.3.1.3.1 Synthesis of sodium cyclohexanecarboxylate

Treatment of cyclohexane carboxylic acid (**228**) with sodium ethoxide afforded the corresponding carboxylate (**229**) (Scheme 2.44).



(**228**) (**229**)

Scheme 2.44

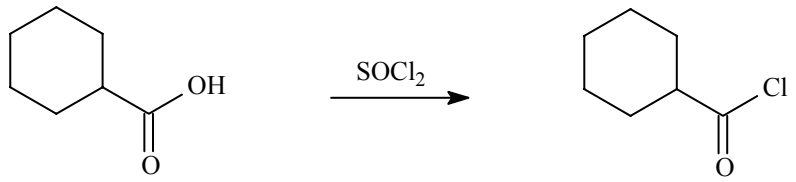
Spectroscopic analysis was consistent with the structure of the product. The IR spectrum exhibited the antisymmetrical and symmetrical stretching absorptions in the 1550 cm^{-1} range and at 1412 cm^{-1}, respectively, for the carboxylate carbonyl.

The ^{1}H NMR displayed an expected triplet of triplets at 2.14 ppm with J=11.3 and 3.4 ppm for the methine proton, and four multiplets at 1.81, 1.72, 1.64, and 1.26 ppm for the five CH_2s of the cyclohexyl ring.

The ^{13}C NMR was also consistent with the structure by displaying a quaternary carbon at 186.60 ppm (C=O), a CH at 46.86 ppm, and three CH_2s at 29.78, 25.59 and 25.44 ppm.

2.3.1.3.2 Synthesis of cyclohexanecarbonyl chloride

Chlorination of cyclohexane carboxylic acid (**228**) gave the corresponding chloride (**230**) in good yields (Scheme 2.45).



(**228**) (**230**)

Scheme 2.45

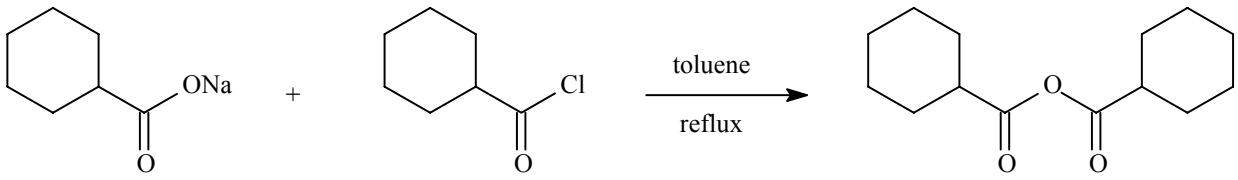
Spectroscopic data were consistent with the structure of compound (**230**). The IR spectrum showed a strong absorption at 1794 cm^{-1} for the acyl chloride carbonyl group.

On the ^{1}H NMR spectrum, the integration of a triplet of triplets with J=11.0 and 3.6 Hz at 2.66 ppm, and five multiplets in the range 2.10-1.20 ppm was matching the number of protons in the cyclohexyl ring.

The ^{13}C NMR spectrum was also supporting the product displaying a quaternary carbon at 176.86 ppm (C=O), a CH at 54.91 ppm, and three CH_2s at 28.96, 25.35, and 24.93 ppm.

2.3.1.3.3 Synthesis of cyclohexanecarboxylic anhydride

Coupling of sodium cyclohexanecarboxylate (**229**) and cyclohexanecarbonyl chloride (**230**) yielded the corresponding anhydride (**231**) (Scheme 2.46).



(**229**) (**230**) (**231**)

Scheme 2.46

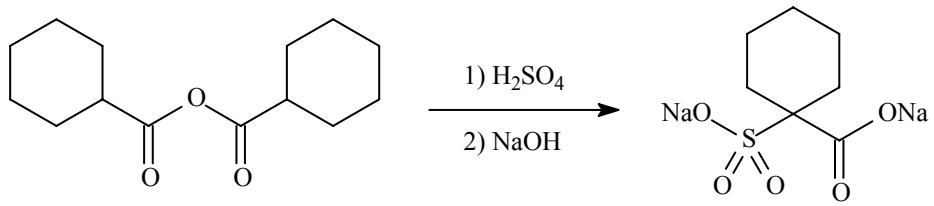
Spectroscopic analysis confirmed the structure of the product. In the IR spectrum, the two strong absorptions at 1810 and 1742 cm^{-1} supported the presence of the anhydride carbonyl.

In the ^{1}H NMR, the methine proton appeared at 2.40 ppm as a triplet of triplets with J=11.1 and 3.6 Hz, and five multiplets integrating to ten protons appeared between 2.00 and 1.20 ppm for the five CH_2s of the cyclohexyl ring.

In the ^{13}C NMR spectrum, the carbonyl appeared at 171.84 ppm, the CH appeared at 43.91 ppm, and the three CH_2s appeared at 28.35, 25.53, and 25.12 ppm, which is consistent with the structure of compound (**231**).

2.3.1.3.4 Synthesis of disodium 1-sulfonylcyclohexanecarboxylate

Acid hydrolysis of cyclohexanecarboxylic anhydride (**231**) followed by alkaline work-up gave the disodium salt (**232**) (Scheme 2.47).



(**231**) (**232**)

Scheme 2.47

Spectroscopic data were consistent with the structure of the expected product. On the IR spectrum, a strong band appeared at 1581 cm^{-1} for the carboxylate carbonyl. The presence of the sulfonate was supported by two absorptions at 1386 and 1169 cm^{-1}.

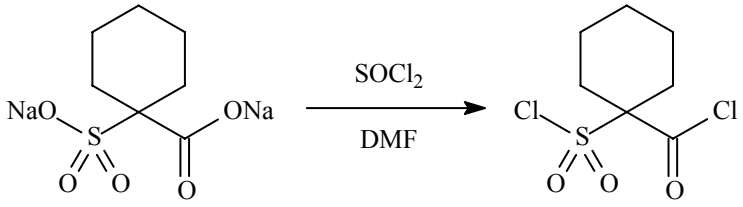
The ^{1}H NMR spectrum displays four multiplets integrating to ten protons at 2.39, 1.72, 1.61, and 1.21 ppm.

In the ^{13}C NMR, the carbonyl appeared at 175.24 ppm, the quaternary sp^3 carbon appeared at 70.83 ppm, and the three different CH_2s appeared at 30.51, 25.28, and 23.83 ppm.

The mechanism of this reaction has already been described in Scheme 2.33 (section 2.3.1.1.1).

2.3.1.3.5 Synthesis of 1-chlorosulfonylcyclohexanecarbonyl chloride

The chlorination of the disodium salt (**232**) was performed in thionyl chloride in the presence of DMF to afford the corresponding dichloride (**233**) (Scheme 2.48).



(**232**) (**233**)

Scheme 2.48

Spectroscopic analysis provided the evidence of the formation of the desired product. The IR spectrum displayed a strong absorption at 1767 cm^{-1} for the acyl chloride carbonyl, and two

strong bands at 1376 and 1169 cm^{-1}, supporting the presence of the sulfonyl chloride in the molecule.

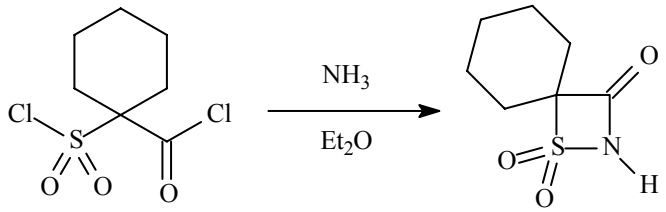
The ^{1}H NMR spectrum showed five multiplets integrating to ten protons between 2.90 and 1.30 ppm.

In the ^{13}C NMR spectrum, the carbonyl appeared at 169.64 ppm, the quaternary sp^3 carbon appeared at 90.30 ppm, and the three CH_2s appeared at 30.73, 23.89, and 22.95 ppm.

The mechanism of this chlorination reaction is the same as the one already described in scheme 2.35 (section 2.3.1.1.2).

2.3.1.3.6 Synthesis of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam

The ring closure of the dichloride (**233**) was carried out in liquid ammonia to afford 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam (**215c**) (Scheme 2.49).



(**233**) (**215c**)

Scheme 2.49

Spectroscopic data were consistent with the data available from the previous work done in the laboratory[169] and with the structure of the product. On the IR spectrum, a broad absorption at 3099 cm^{-1} attested the presence of the NH. The strong absorption at 1759 cm^{-1} for the carbonyl is consistent with the absorption of the strained carbonyl in *β*-lactams (~1745 cm^{-1}). The two strong bands at 1331 and 1161 cm^{-1} confirmed the presence of the sulfonamide (SO_2).

The ^{1}H NMR spectrum displayed a broad singlet at 8.42 ppm for the amide / sulfonamide NH, and six multiplets between 2.40 and 1.35 ppm for the ten protons of the cyclohexyl ring.

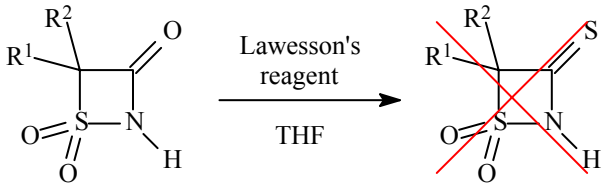
In the ^{13}C NMR spectrum, the usual peaks were shown with the carbonyl at 163.50 ppm, the quaternary sp^3 carbon at 86.79 ppm, and the three different CH_2s at 28.05, 24.01, and 22.60 ppm.

2.3.2 Reactivity of 1,2-thiazetidin-3-on-1,1-dioxides: towards the synthesis of 1,2-thiazetin-1,1-dioxides

2.3.2.1 Attempted thionations of 1,2-thiazetidin-3-on-1,1-dioxides

2.3.2.1.1 With Lawesson's reagent

The thionation reaction with Lawesson's reagent in THF (Scheme 2.50) was attempted with 4,4-diethyl-3-oxo-*β*-sultam (**215b**) and 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam (**215c**) for the simple reason that they were expected to be more stable compounds than 4,4-dimethyl-3-oxo-*β*-sultam (**215a**)[170] which is susceptible to hydrolytic ring opening. The presence of bulky substituents on the 4-position decreases the distortion of the 4-membered ring (Thorpe-Ingold effect[171-173] or *gem*-dialkyl effect), which makes it less likely to release its strain by ring opening, and therefore increases its stability. Other work in the group had shown that the 4,4-dimethyl compound (**215a**) was resistant to thionation.



(**215b**) $R^1 = R^2$ = Et
(**215c**) $R^1 = R^2$ = *spiro*-cyclohexyl

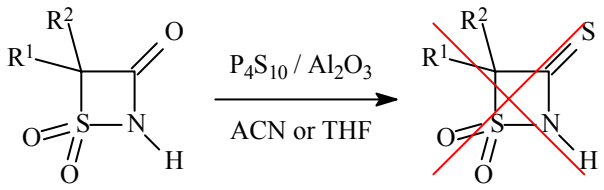
(**216b**)
(**216c**)

Scheme 2.50

The reactions were monitored by TLC, but unfortunately, no change seemed to occur, and neither the product nor the starting material could be isolated after chromatography on neutral alumina with both 3-oxo-*β*-sultams (**215b**) and (**215c**). The requirement to use chromatography in order to remove the by-products derived from Lawesson's reagent itself is probably not suitable for 3-oxo-*β*-sultams due to their sensitivity to ring opening. It was concluded that no reaction had occurred, or the product and the starting material had degraded during chromatography. Hence, two other methods previously outlined (section 2.2.1.1.2) have been attempted and are described below.

2.3.2.1.2 With phosphorus pentasulfide and alumina

The combination of P_4S_{10}/Al_2O_3 can be used to thionate ketones and amides.[99,100] This method, which does not require chromatography to separate the product from organic side products, was attempted to convert 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam (**215c**) into its thioxo analogue (**216c**) (Scheme 2.51).



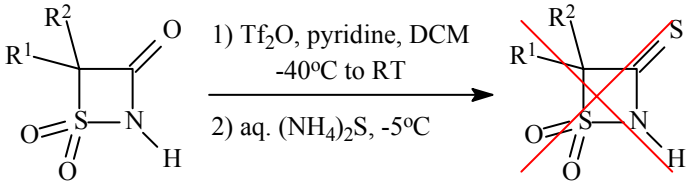
(**215c**) $R^1 = R^2$ = *spiro*-cyclohexyl (**216c**)

Scheme 2.51

The procedure was carried out in both acetonitrile and THF. On TLC, no reaction seemed to have occurred in both cases. In acetonitrile, the presence of the starting material and the appearance of another compound on TLC were confirmed by the ^{1}H NMR spectrum of the crude product. Purification by chromatography on basic alumina afforded only thioacetamide, as a result of the hydrolysis of acetonitrile followed by thionation of its carbonyl group. The starting material was not recovered.

2.3.2.1.3 With pyridine, trifluoromethane sulfonic anhydride, and aqueous ammonium sulfide

A mild method has been developed by Charette[110] for the conversion of amides to thioamides by prior activation of the amide with an electrophilic reagent (Scheme 2.52).



(**215b**) $R^1 = R^2 =$ Et
(**215c**) $R^1 = R^2 =$ *spiro*-cyclohexyl

(**216b**)
(**216c**)

Scheme 2.52

This method was first tested on pyrrolidin-2-one to perform the reaction described in Scheme 2.27 (section 2.2.2.1). Unfortunately, the yields published could not be reproduced in our laboratory and were much lower than the ones produced with Lawesson's reagent. Moreover, this method also requires purification by chromatography. Furthermore, this procedure requires the use of aqueous ammonium sulfide, a medium that 3-oxo-*β*-sultams will not withstand due to hydrolysis. For all those reasons, this method was abandoned and not explored further. Other possible methods for use in future work might be attempted (section 2.2.1.1.2).

2.3.2.2 Alkylation of 3-oxo-*β*-sultams: synthesis of 4,4-dialkyl-3-ethoxy-1,2-thiazetin-1,1-dioxides

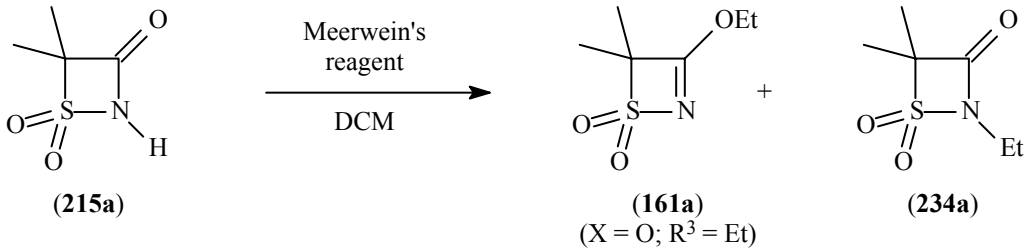
Having failed to thionate 3-oxo-*β*-sultams, we decided to try direct *O*-alkylation using Meerwein's reagent.

2.3.2.2.1 Alkylation of 4,4-dimethyl-3-oxo-*β*-sultam

In the first place, the alkylation was attempted with Meerwein's reagent (Scheme 2.53) using the same procedure as the one used for 1-azetines. The reaction was monitored by TLC, which indicated the disappearance of the starting material. On the IR spectrum of the crude product, the absence of a broad absorption in the region 3100-3500 cm^{-1} suggested alkylation had occurred. A strong band at 1774 cm^{-1} was suggesting the carbonyl was still present in the sample, but a medium band at 1584 cm^{-1} was also suggesting the presence of a C=N bond. From this spectrum, we concluded that both *O*- and *N*-alkylation could have occurred, and that we

were dealing with a mixture of compounds (**161a**) and (**234a**), a feature confirmed by $^{1}H/^{13}C$ NMR analysis.

In a second attempt, the alkylation was performed with dimethyl sulfate. The reaction was monitored by TLC and IR, but no reaction took place at all. On the IR spectrum, no band at 1584 cm^{-1} for the C=N appeared, indicating no *O*-methylation occurred, and the absorption for C=O remained at 1750 cm^{-1}, whereas it should have shifted to ~1775 cm^{-1} if *N*-methylation had occurred as suggested above with Meerwein's reagent.

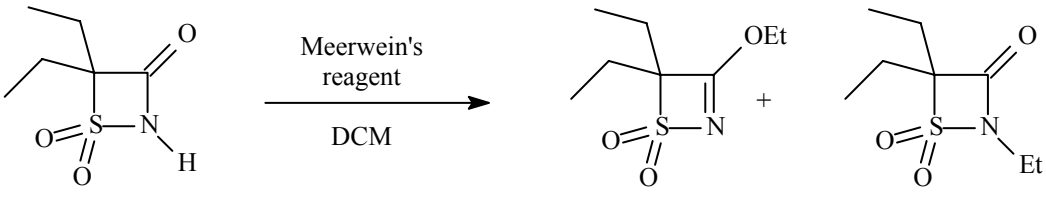


(**215a**) (**161a**) (X = O; R^3 = Et) (**234a**)

Scheme 2.53

2.3.2.2.2 Alkylation of 4,4-diethyl-3-oxo-*β*-sultam

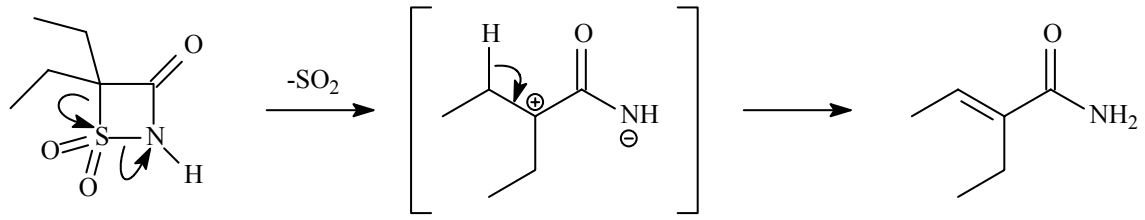
In order to confirm the suspicions of *O*- and *N*-alkylation, ethylation of 4,4-diethyl-3-oxo-*β*-sultam (**215b**) with Meerwein's reagent was carried out (Scheme 2.54).



(**215b**) (**161b**) (X = O; R^3 = Et) (**234b**)

Scheme 2.54

Interestingly, as well as the expected products (**161b**) and (**234b**), after purification by gravity silica chromatography, 2-ethylcrotonamide (**235**) was isolated as a side-product in 8 % yield. It is believed to form through a SO_2 extrusion of the starting material (**215b**) (Scheme 2.55). Compounds (**161b**) and (**234b**) were found to be inseparable.



(**215b**) (**235**)

Scheme 2.55

Spectroscopic analysis confirmed the presence of the *O*- and *N*-alkylated compounds (**161b**) and (**234b**). First, on the IR spectrum, the alkylation was confirmed by the absence of the NH absorption between 3100 and 3500 cm^{-1}. The two bands at 1766 and 1579 cm^{-1} suggested the presence of both C=O and C=N, respectively, in the molecule.

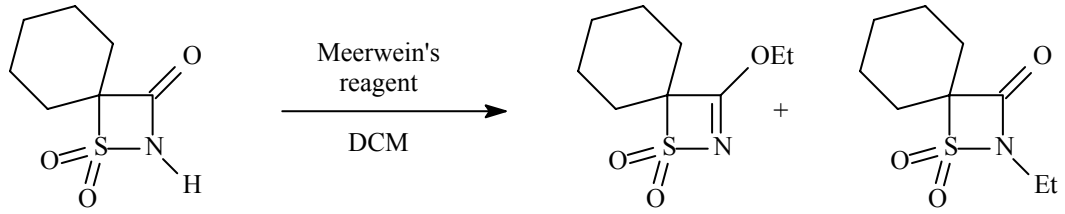
The ^{1}H NMR spectrum clearly confirmed the formation of *O*- and *N*-alkylated products. It displayed one quartet at 4.50 ppm with *J*=7.1 Hz for the CH_2 attached to the oxygen in the *O*-ethylated compound (**161b**) and a quartet at 3.54 ppm with *J*=7.4 Hz for the CH_2 attached to the nitrogen in the *N*-ethylated compound (**234b**). The four CH_2s for the ethyl groups present overall in the two products at the 4-position appeared as a quartet at 2.18 ppm with *J*=7.5 Hz, a quartet at 2.17 ppm with *J*=7.5 Hz, and a multiplet at 2.14 ppm. The two CH_3s of the *O*- and *N*-ethyl groups appeared at 1.47 ppm with *J*=7.1 Hz, and 1.40 ppm with *J*=7.4 Hz, respectively. Finally, a triplet at 1.16 ppm with *J*=7.5 Hz appeared for the two CH_3s at the 4-position of the *N*-alkylated product (**234b**), and a triplet at 1.12 ppm with *J*=7.5 Hz for the two CH_3s at the 4-position of the *O*-alkylated product (**161b**).

The ^{13}C NMR spectrum confirmed the presence of C=O and C=N bonds with peaks at 180.98 and 163.63 ppm, respectively. Two quaternary sp^3 carbons appeared at 93.85 and 90.55 ppm. The CH_2 attached to the oxygen appeared at 68.38 ppm, whereas the one attached to the nitrogen appeared at 35.72 ppm. The two CH_2s and the two CH_3s of the ethyl groups at the 4-position appeared at 23.08, 22.53, 8.44, and 8.43 ppm, respectively. The two CH_3s for the *O*- and *N*-ethyl groups appeared at 13.90 and 13.39 ppm, respectively.

The spectroscopic data supported the formation of the *O*- and *N*-alkylated products (**161b**) and (**234b**) in a 1:2 ratio, reinforcing the observation made with the alkylation of 4,4-dimethyl-3-oxo-*β*-sultam (**215a**).

2.3.2.2.3 Alkylation of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam

Alkylation of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam (**215c**) was performed with Meerwein's reagent to afford the *O*-alkylated product (**161c**) and the *N*-alkylated product (**234c**) as an inseparable mixture (Scheme 2.56).



(**215c**) (**161c**) (X = O; R^3 = Et) (**234c**)

Scheme 2.56

Spectroscopic analysis confirmed the formation of 4-*spiro*-cyclohexyl-3-ethoxy-1,2-thiazetin-1,1-dioxide (**161c**) and 4-*spiro*-cyclohexyl-2-ethyl-1,2-thiazetidin-3-on-1,1-dioxide (**234c**). The IR spectrum showed the two characteristic bands for C=O and C=N at 1768 and 1581 cm^{-1}, respectively, and the absence of the NH broad absorption over 3000 cm^{-1}.

The ^1H NMR spectrum displayed a quartet at 4.43 ppm with *J*=7.1 Hz for the ethoxy CH_2, and another quartet at 3.49 ppm with *J*=7.4 Hz for the CH_2 attached to the nitrogen, integrating to four protons overall. A complex series of multiplets appeared between 2.60 and 1.50 ppm, integrating to twenty protons overall, indicating the presence of the two cyclohexyl rings. Finally, the ethoxy CH_3 appeared as a triplet at 1.42 with *J*=7.1 Hz, and the CH_3 attached to the nitrogen appeared as a triplet at 1.35 ppm with *J*=7.4 Hz, with an overall integration of six protons.

On the ^{13}C NMR, two peaks appeared at 180.91 and 163.71 ppm for the C=O and the C=N bonds, respectively. The two quaternary sp^3 carbons appeared at 91.62 and 87.53 ppm. The ethoxy CH_2 appeared at 68.25 ppm, whereas the one attached to the nitrogen appeared at 35.73 ppm. Six CH_2s for the two cyclohexyl rings appeared between 28.54 and 22.65 ppm. The two CH_3s resulting from the *O*- and *N*-ethylation appeared at 13.76 and 13.22 ppm, respectively.

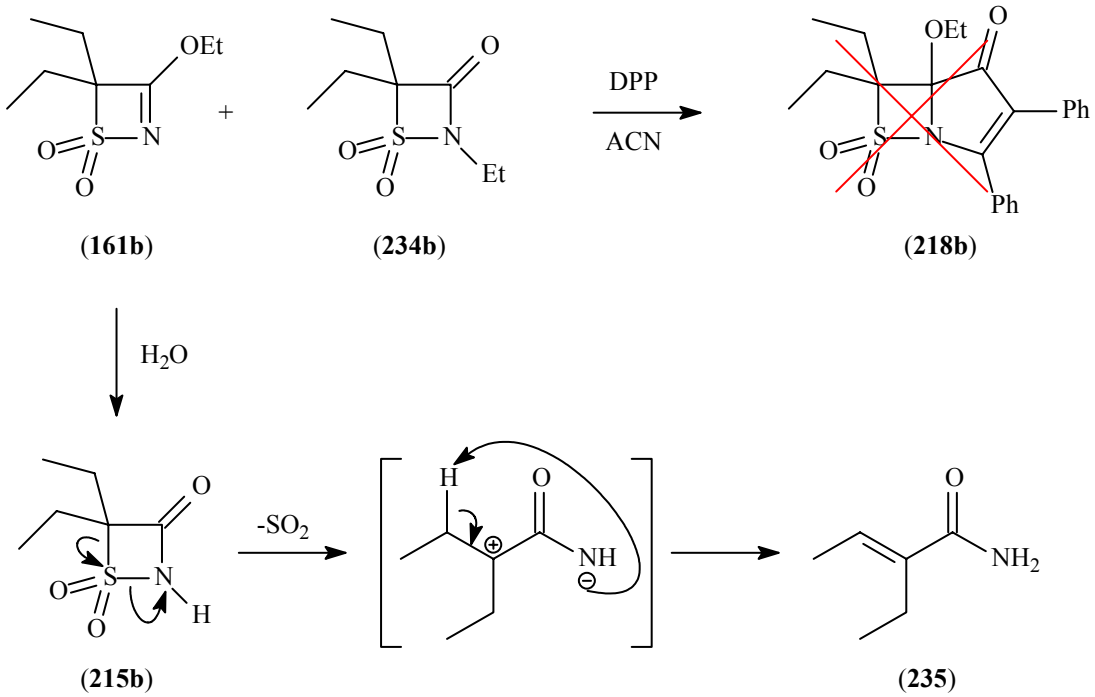
Once again, the spectroscopic data supported the formation of both *O*- and *N*-alkylated products (**161c**) and (**234c**), in a 1:2.75 ratio.

In order to overcome this problem of reactivity and regioselectivity, other alkylating reagents could be used, as previously discussed in the case of the alkylation of 1-azetines (section 2.2.1.1.3). However, before embarking on a detailed and time consuming study, it was decided to explore the reactivity of the 3-alkoxy-1,2-thiazetin-1,1-dioxides present in the above mixtures.

2.3.3 Reactivity of 3-alkoxy-1,2-thiazetin-1,1-dioxide towards cycloadditions

2.3.3.1 Attempted trapping of 4,4-diethyl-3-ethoxy-1,2-thiazetin-1,1-dioxide with diphenylcyclopropenone

The mixture of *O*- and *N*-alkylated compounds (**161b**) and (**234b**) was dissolved in dry acetonitrile and heated under reflux with dicyclopropenone for 22 hours (Scheme 2.56). After purification by column chromatography, the starting materials were mostly recovered. However, 2-ethylcrotonamide (**235**) was isolated as a side-product and a mechanism for its formation is proposed (Scheme 2.57). None of the desired bicyclic product (**218b**) was present.



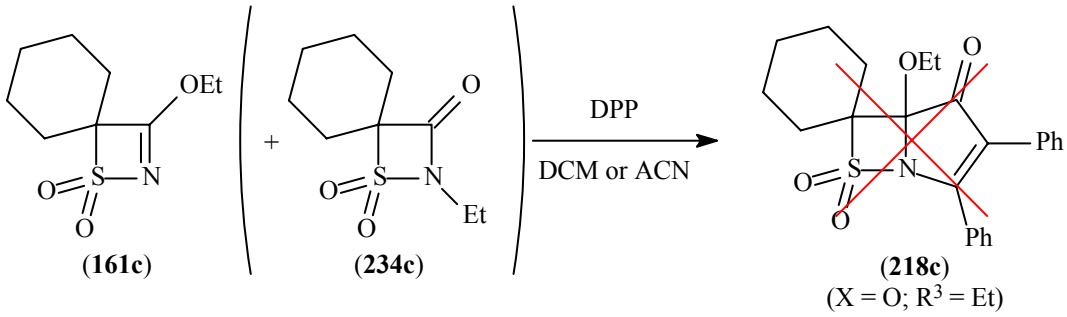
(**161b**) (**234b**) (**218b**)

(**215b**) (**235**)

Scheme 2.57

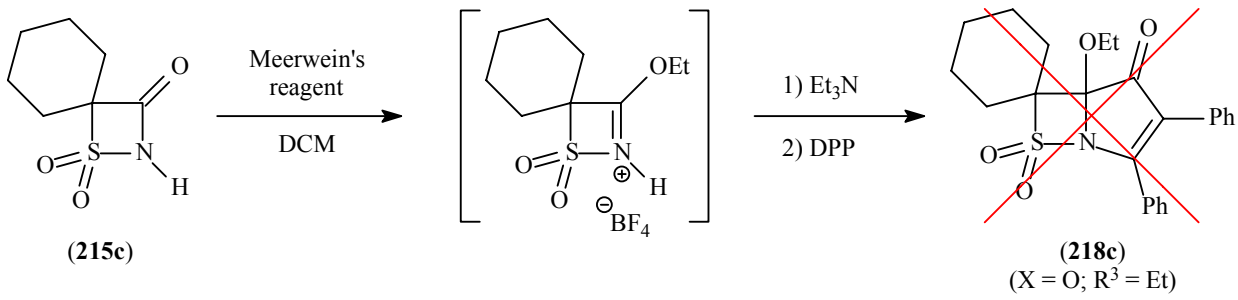
2.3.3.2 Attempted trapping of 4-*spiro*-cyclohexyl-3-ethoxy-1,2-thiazetin-1,1-dioxide with diphenylcyclopropenone

The ring expansion with diphenylcyclopropenone was attempted in DCM and in acetonitrile by dissolving the mixture of (**161c**) and (**234c**) in the solvents and stirring the whole overnight at RT (Scheme 2.58). In both cases, purification by silica chromatography recovered almost quantitatively the starting materials, with no traces of the desired target (**218c**) or any other identifiable products.



Scheme 2.58

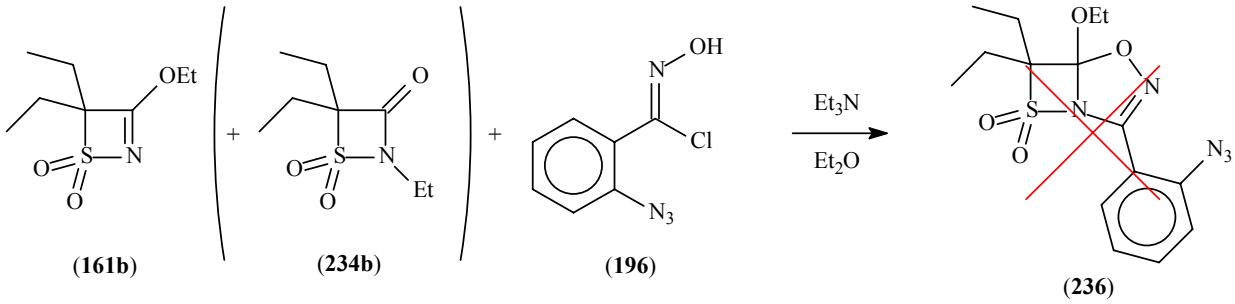
A third attempt was made by trying to alkylate 3-oxo-*β*-sultam (**215c**) with Meerwein's reagent, deprotonate the intermediate species with triethylamine without isolating the alkylated product (**161c**), and trap the alkylated intermediate *in situ* by adding diphenylcyclopropenone (Scheme 2.59). But once again, only diphenylcyclopropenone was recovered after column chromatography, and neither the starting material (**215c**) nor any new products could be detected or isolated.



Scheme 2.59

2.3.3.3 Attempted trapping of 4,4-diethyl-3-ethoxy-1,2-thiazetin-1,1-dioxide with nitrile oxides

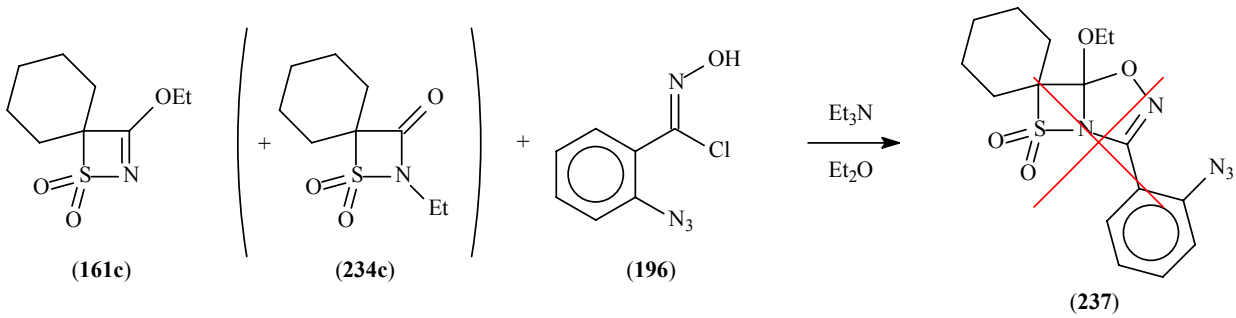
The attempted trapping of 4,4-diethyl-3-ethoxy-1,2-thiazetin-1,1-dioxide (**161b**) by the nitrile oxide generated *in situ* from 2-azidobenzohydroximoyl chloride (**196**) was performed in ether by adding a dilute ethereal solution of triethylamine over three hours (Scheme 2.60). After purification by silica chromatography, only the starting materials and the dimer of the nitrile oxide were isolated, indicating none of the desired reaction had taken place.



Scheme 2.60

2.3.3.4 Attempted trapping of 4-*spiro*-cyclohexyl-3-ethoxy-1,2-thiazetin-1,1-dioxide with nitrile oxides

The attempted trapping of 4-*spiro*-cyclohexyl-3-ethoxy-1,2-thiazetin-1,1-dioxide (**161c**) was performed, as discussed above, by generating the nitrile oxide *in situ* in the presence of triethylamine in ether (Scheme 2.61). Purification by column chromatography on silica afforded the dimer of the nitrile oxide as the only isolated product. The starting compound (**161c**) was not recovered.

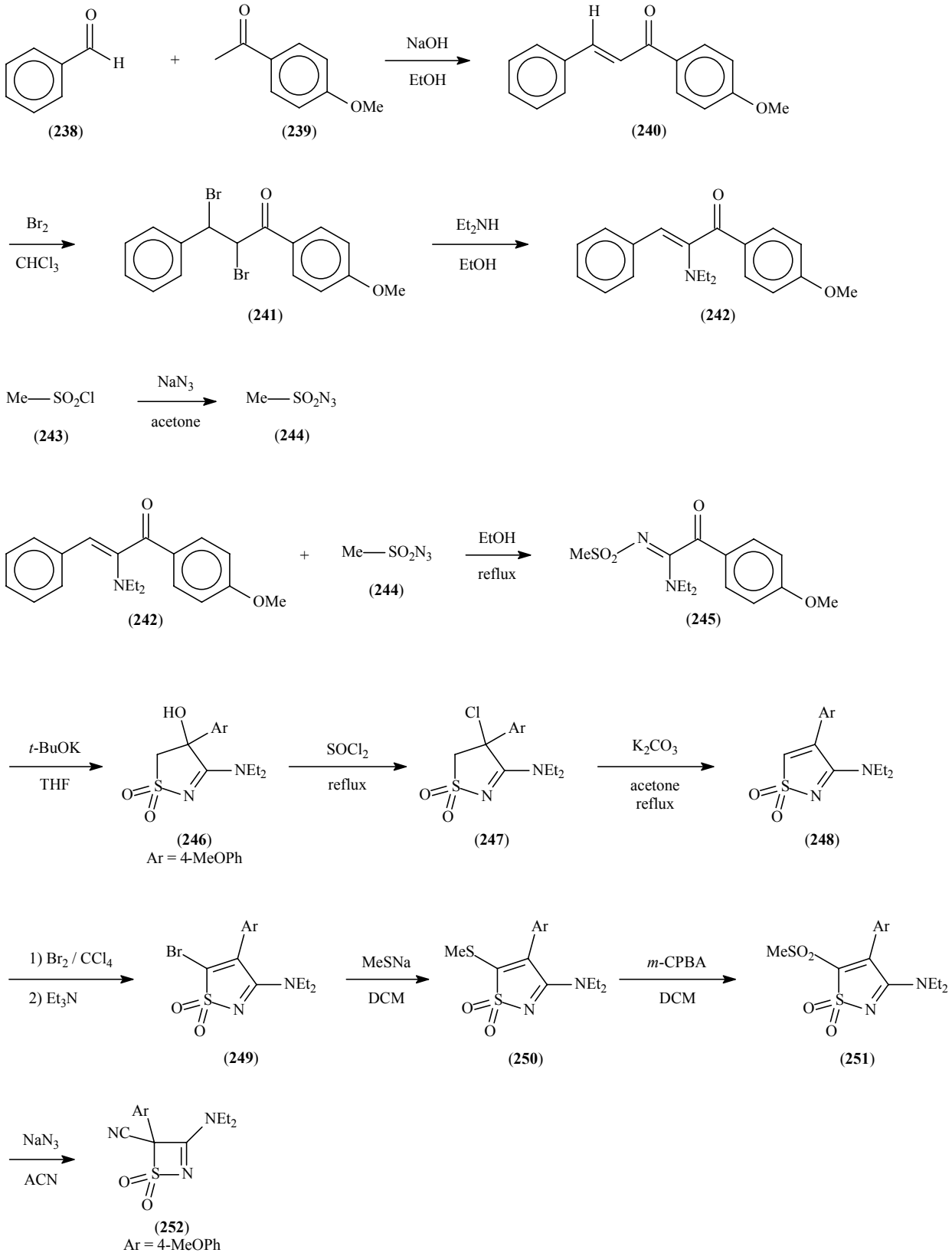


Scheme 2.61

These results indicate that 3-alkoxy-1,2-thiazetin-1,1-dioxides (**161b**) and (**161c**) are not reactive towards diphenylcyclopropenone and nitrile oxides. Further efforts to prepare 3-alkoxy systems were not made. However, a 3-amino-1,2-thiazetin-1,1-dioxide was prepared as described below. It is noteworthy that 2-amino-1-azetines are reactive towards diphenylcyclopropenone.[141]

2.3.4 Synthesis of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide

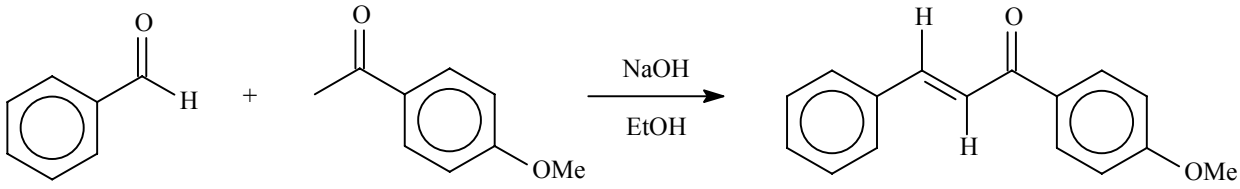
In the literature, only a few papers mention the formation of 1,2-thiazetin-1,1-dioxide systems, as discussed in the introduction (section 1.2). However, recently, Clerici *et al.*[174] isolated 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide (**252**) through an unexpected ring contraction of 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**251**) (Scheme 2.62). In our quest to investigate the reactivity of these 4-membered ring systems towards cycloaddition reactions, we embarked upon the synthesis of this compound. This synthesis gave some interesting observations and is discussed in full below.


NaOH
EtOH
OMe
(238)
(239)
(240)
Br2
CHCl3
Et2NH
EtOH
NEt2
(241)
(242)
Me— SO2Cl
NaN3
acetone
Me— SO2N3
(243)
(244)
EtOH
reflux
MeSO2
(245)
t-BuOK
THF
HO
Ar
NEt2
(246)
Ar = 4-MeOPh
SOCl2
reflux
Cl
(247)
K2CO3
acetone
reflux
(248)
1) Br2 / CCl4
2) Et3N
Br
(249)
MeSNa
DCM
MeS
(250)
m-CPBA
DCM
MeSO2
(251)
NaN3
ACN
NC
(252)
Ar = 4-MeOPh

Scheme 2.62

2.3.4.1 Synthesis of 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one

The aldol condensation of benzaldehyde (**238**) with 4'-methoxyacetophenone (**239**) in the presence of sodium hydroxide in ethanol occurred in the expected manner to give the desired *α,β*-unsaturated ketone (**240**) in 85% yield (Scheme 2.63).



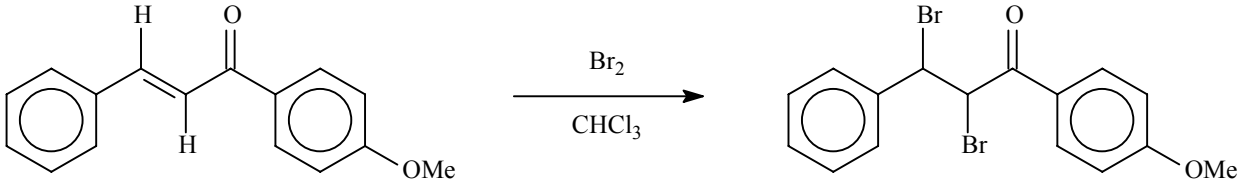
(**238**) (**239**) (**240**)

Scheme 2.63

The spectroscopic data were fully consistent with the formation of the expected product.

2.3.4.2 Synthesis of 2,3-dibromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one

The bromination of the *α,β*-unsaturated ketone (**240**) was performed in chloroform to yield the corresponding dibromo compound (**241**) in 85% yield (Scheme 2.64).



(**240**) (**241**)

Scheme 2.64

The bromination of the *α,β*-unsaturated ketone was confirmed by spectroscopic analysis. The IR spectrum showed the absorption of the carbonyl at 1667 cm^{-1}.

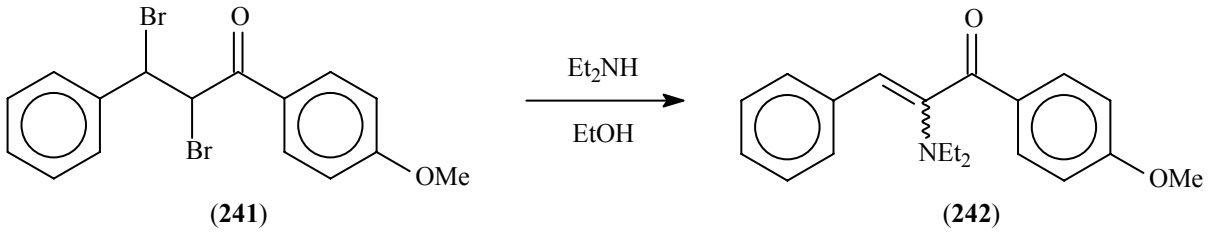
Evidence of the bromination was given by NMR spectroscopy. On the ^{1}H NMR spectrum, the shift of the two doublets of the ethylenic CH from 7.83 and 7.58 ppm to 5.84 and 5.68 ppm with

J=11.3 Hz indicated the bromination of the double bond. The other signals confirmed that the rest of the molecule remained unchanged.

The ^{13}C NMR spectrum also confirmed the bromination of the double bond by showing a shift of the two CH signals from 143.96 and 121.83 ppm to 49.99 and 46.72 ppm, which is consistent with a transformation from two ethylenic CHs to two sp^3 CHs. The remaining signals remained unchanged and are consistent with the structure of the product.

2.3.4.3 Synthesis of 2-diethylamino-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one

The formation of the enamine (**242**) from the *α,β*-dibromoketone (**241**) was carried out in ethanol in the presence of diethylamine (81% yield) (Scheme 2.65).[175]



(**241**) (**242**)

Scheme 2.65

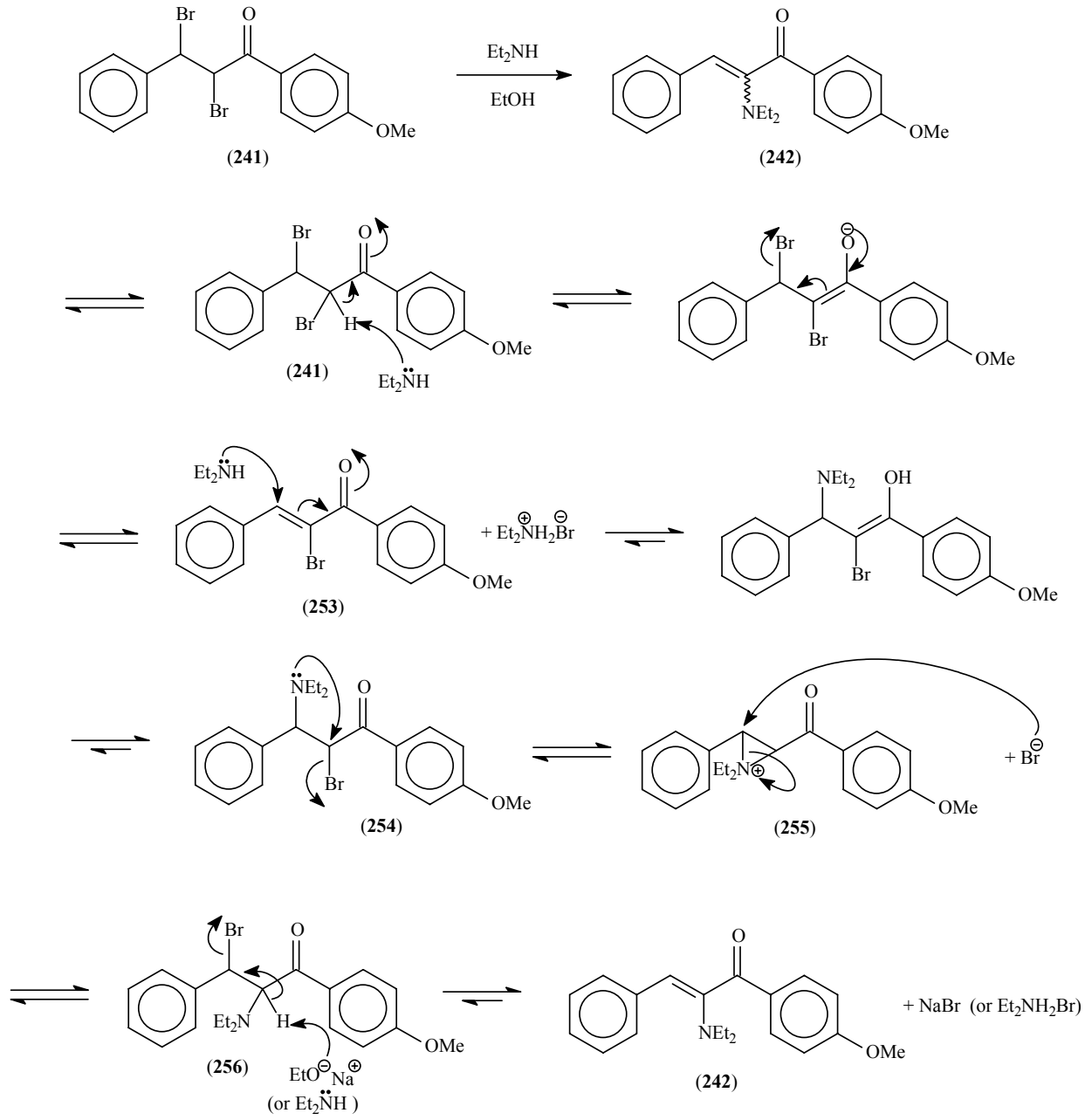
Spectroscopic analysis gave the evidence of the proposed structure of the product. The IR spectrum exhibited a band at 1708 cm^{-1} for the carbonyl, and a band at 1657 cm^{-1} suggesting the presence of the enamine grouping.

In the ^1H NMR spectrum, the four aromatic protons from the AB system of the para-substituted aromatic ring are present at 8.06 and 6.89 ppm as two doublets with *J*=8.8 Hz. The five other aromatic protons were also present at 7.05 and 6.93 ppm as two multiplets. The olefinic proton appeared at 5.60 ppm as a singlet and the three protons from the methoxy group appeared at 3.85 ppm as a singlet. A quartet integrating to four protons at 3.15 ppm and a triplet integrating to six protons at 1.16 ppm with *J*=7.0 Hz gave the evidence of the presence of the diethylamino group.

The ^{13}C NMR spectrum displayed the five quaternary carbons and the five different aromatic CH groups. The olefinic CH appeared at 102.16 ppm, the methyl of the methoxy group appeared at 55.48 ppm, and the CH_2 and the CH_3 of the diethylamino group were shown at 43.51 and 12.39 ppm, respectively.

A possible mechanism of formation of the enamine (**242**) is described in Scheme 2.66. First, diethylamine acts as a base to deprotonate the starting material to form the corresponding *α*-bromo-*α,β*-unsaturated ketone (**253**). Second, the diethylamine acts as a nucleophile in a Michael addition on compound (**253**) to afford the *β*-diethylamino-*α*-bromoketone (**254**), which undergoes an intramolecular nucleophilic attack to give the aziridinium salt (**255**). The released bromide anion then attacks the aziridinium salts, resulting in the formation of the *β*-bromo-*α*-diethylaminoketone (**256**). The bromide is now in the correct position so that compound (**256**) can undergo a *β*-elimination under the action of sodium ethoxide (or, as in the original procedure, a third equivalent of diethylamine) to reset the conjugated system and form the desired *α*-diethylamino-*α,β*-unsaturated ketone (**242**). The formation of *α*-dialkylamino-*α,β*-unsaturated ketones has already been reported in the literature.[175,176]

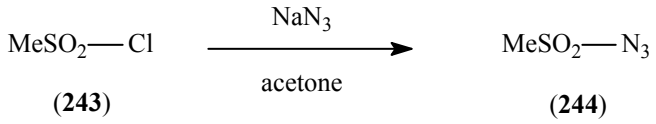
It is noteworthy to mention that, on TLC and HPLC, the reaction always showed a mixture of two or three spots very close to each other which were hard to separate, correlating with the complex equilibrium described in this mechanism. The *α*-bromo-*α,β*-unsaturated ketone (**253**) formed during the course of the reaction was isolated once after silica chromatography and was fully characterised by NMR, IR and HRMS. Usually, however, the product was used as crude without further purification to avoid a difficult separation, and without affecting the next step of the synthesis.



Scheme 2.66

2.3.4.4 Synthesis of methanesulfonyl azide

Methanesulfonyl azide (**244**) was prepared in 88% yield by mixing commercially available methanesulfonyl chloride (**243**) with sodium azide in dry acetone (Scheme 2.67).[177]



(**243**) (**244**)

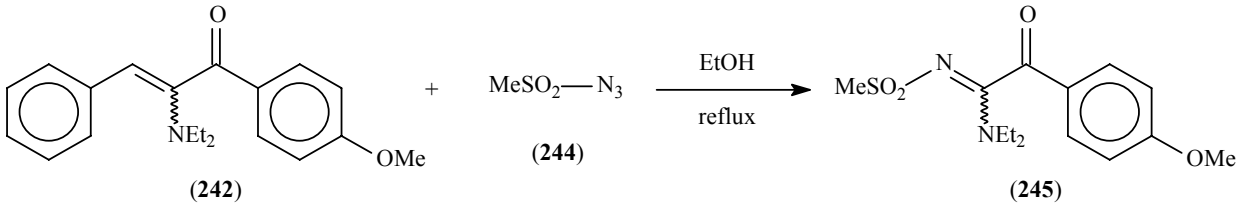
Scheme 2.67

Spectroscopic analysis gave the necessary evidence for the formation of the product. The IR spectrum displayed the absorption of the azide at 2132 cm^{-1}, and the two absorptions of the sulfonyl at 1349 and 1148 cm^{-1}.

The ^{1}H NMR spectrum showed a singlet at 3.29 ppm, and the ^{13}C NMR spectrum showed a CH_3 at 42.75 ppm.

2.3.4.5 Synthesis of *N*-methanesulfonylamidine (245)

N-Methanesulfonylamidine (**245**) was preprared in 82% yield by refluxing the enamine (**242**) with methanesulfonyl azide (**244**) in ethanol overnight (Scheme 2.68).[178]



(**242**) (**244**) (**245**)

Scheme 2.68

The structure of the desired product was confirmed by spectroscopic analysis. The IR spectrum showed absorptions at 1674, 1596 and 1544 cm^{-1}, for C=O, C=N and the aromatic ring, respectively. Two other bands appeared at 1288 and 1129 cm^{-1} for SO_2.

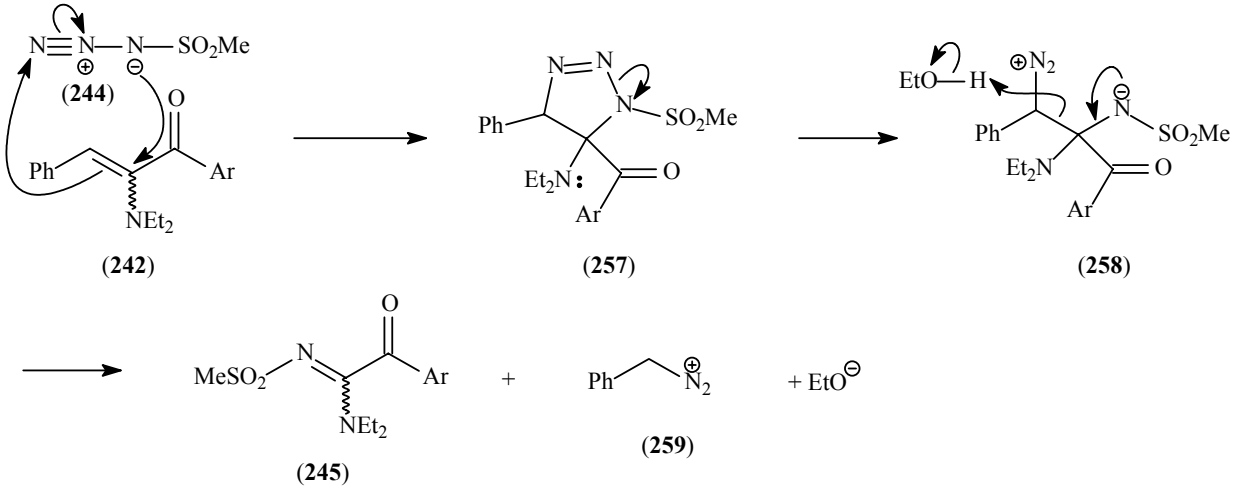
In the ^{1}H NMR spectrum, two pairs of aromatic protons appeared at 7.87 and 7.00 ppm, one as a broad doublet with J=7.2 Hz and the other one as a doublet with J=9.1 Hz. The three protons of the methoxy group appeared at 3.89 ppm as a singlet. The two CH_2s of the diethylamino group were present at 3.73 and 3.53 ppm as two doublets of quartets with J=13.5 and 7.1 Hz, and at 3.20 and 3.17 ppm as two doublets of quartets with J=14.2 and 7.1 Hz, integrating to one proton each. This suggested the four protons were in a different environment, indicating the double bond character of the C-NEt_2 bond due to resonnance with the zwitterionic form of the

amidine. The two CH_3s appeared as two triplets with J=7.1 Hz at 1.33 and 1.10 ppm. The methyl of the methanesulfonyl group appeared at 2.98 ppm as a singlet.

In the ^{13}C NMR spectrum, the two peaks at 190.58 and 162.24 ppm gave evidence of the presence of the carbonyl and the amidine carbon, respectively. The four signals at 164.88, 131.40, 127.68 and 114.54 ppm were consistent with the four expected resonances of the aromatic ring. The methoxy CH_3 was present at 55.63 ppm, and the methanesulfonyl CH_3 appeared at 42.57 ppm. The two ethyl groups were displayed as two CH_2 at 44.12 and 42.46 ppm, and two CH_3 at 13.71 and 11.90 ppm.

The NMR data were consistent with the proposed structure, which was further confirmed by HRMS with a measured accurate mass (m/z) for the $[M+Na]^+$ ion of 335.1033 for 335.1036 required.

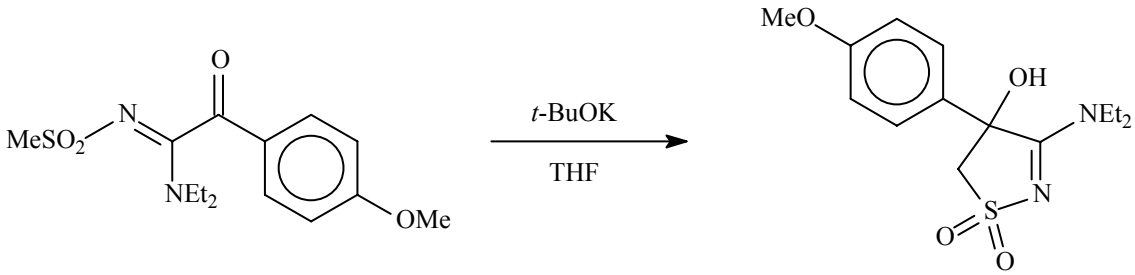
The formation of the *N*-methanesulfonylamidine (**245**) is produced by 1,3-dipolar cycloaddition of the azide on the enamine double bond to form the unstable 5-amino-1,2,3-triazoline (**257**), which undergoes a cycloreversion *via* the intermediate (**258**) to afford the desired product (**245**) and phenyldiazomethane (**259**) (Scheme 2.69).[179,180]



Scheme 2.69

2.3.4.6 Synthesis of 3-diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

The intramolecular cyclisation of *N*-methanesulfonylamidine (**245**) was performed in THF in the presence of potassium *tert*-butoxide acting as a base to give the desired cyclised product (**246**) in 89% yield (Scheme 2.70).[178]



(**245**) (**246**)

Scheme 2.70

Spectroscopic analysis gave the evidence of the formation of the cyclised product. In the IR spectrum, the disappearance of the absorption for the carbonyl at 1674 cm^{-1} and the appearance of a band at 3384 cm^{-1} for the hydroxyl group suggested that the intramolecular cyclisation had occurred. The C=N absorption was present at 1582 cm^{-1}, as well as the two bands of the sulfonyl group at 1297 and 1125 cm^{-1}.

In the ^{1}H NMR spectrum, a broad singlet appeared at 5.54 ppm for the OH proton. The disappearance of the singlet at 2.98 ppm for the methane sulfonyl group confirmed the loss of the methyl and the appearance of two doublets integrating to one proton each at 3.93 and 3.65 ppm with J=14.0 Hz confirmed the presence of a methylene group in the molecule, further indicating the cyclisation of the starting material.

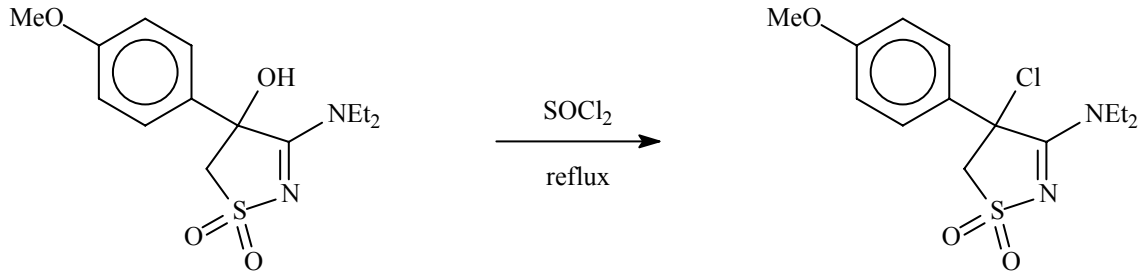
This cyclisation was further confirmed by the ^{13}C NMR spectrum with the disappearance of the peak in the region 180-190 ppm, indicating the loss of C=O, and the appearance of a quaternary sp^3 carbon and a CH_2 at 83.47 and 64.68 ppm, respectively, indicating the presence of the quaternary carbon bearing the hydroxyl group and the methylene adjacent to the sulfonyl group. The C=N carbon appeared at 168.84 ppm, and the aromatic carbon bearing the methoxy group appeared at 159.47 ppm. The aromatic CHs in *meta* position relative to the methoxy group appeared more downfield at 125.27 ppm, whereas those in *ortho* position were more

upfield at 114.31 ppm. The methoxy carbon, the diethylamino methylene and methyl carbons appeared at 55.31, 44.88, 43.36, 12.73, and 11.33 ppm, respectively.

The structure of the product was further confirmed by HRMS with a measured accurate mass (*m/z*) for $[M+Na]^+$ of 335.1028 for 335.1036 required.

2.3.4.7 Synthesis of 4-chloro-3-diethylamino-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

The chorination of the cyclic alcohol (**246**) was performed in thionyl chloride at reflux to afford the corresponding chlorinated compound (**247**) in 95% yield (Scheme 2.71).[178]



(**246**) (**247**)

Scheme 2.71

The structure of the product was assigned on the basis of spectroscopic data. The IR spectrum displayed a strong absorption at 1578 cm^{-1} for the C=N bond, and two strong bands at 1310 and 1137 cm^{-1} for the sulfonyl group.

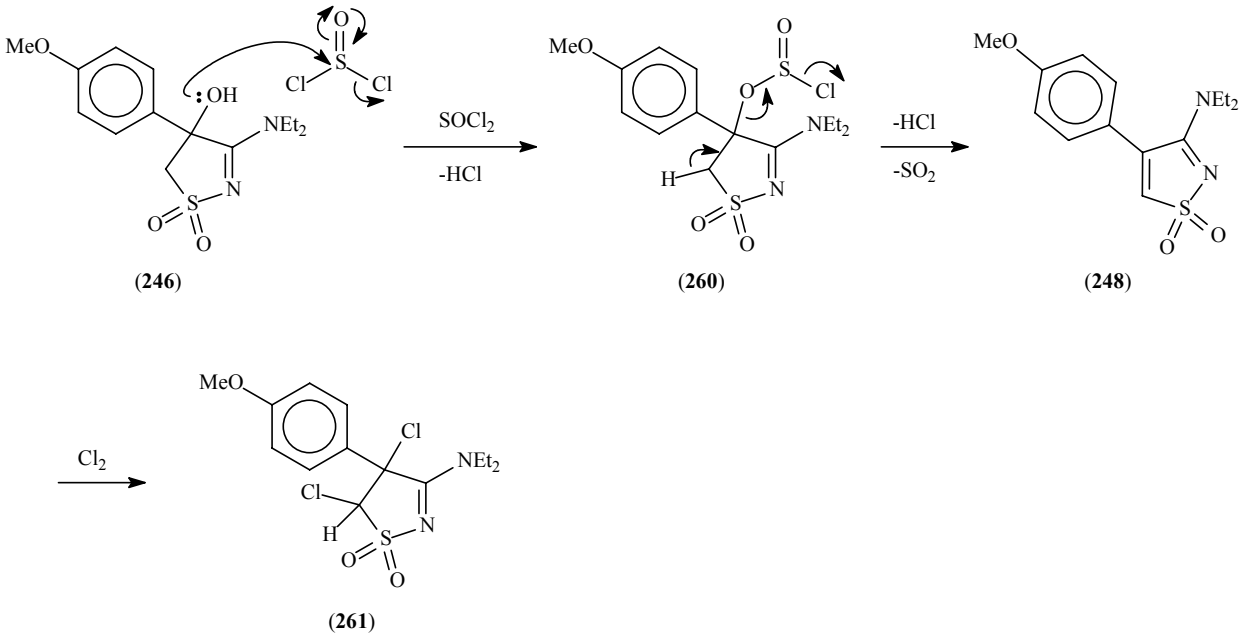
In the ^1H NMR spectrum, the two protons adjacent to the sulfonyl group appeared more downfield than in the starting material at 4.17 and 3.82 ppm as doublets with *J*=14.5 Hz. The pattern for the four protons of the two CH_2s from the diethylamino group was also different from that of the starting material. They appeared as two sets of two doublets of quartets at 3.67 and 3.51 ppm with *J*=13.5 and 7.0 Hz, and at 3.21 and 3.08 ppm with *J*=14.4 and 7.1 Hz. The two methyls appeared as triplets at 1.30 and 0.90 ppm with *J*=7.0 Hz and *J*=7.1 Hz, respectively. The two sets of aromatic protons were displayed at 7.42 and 6.93 ppm as doublets with *J*=8.9 Hz, and the three protons of the methoxy group occurred at 3.85 ppm.

On the ^{13}C NMR spectrum, the C=N carbon appeared at 164.59 ppm, and the aromatic carbon bearing the methoxy group appeared at 160.09 ppm. The aromatic CHs in *meta* position relative

to the methoxy group appeared more downfield at 126.08 ppm compared to those in *ortho* position, which was more upfield at 114.74 ppm. The quaternary sp^3 carbon and the CH_2 adjacent to the sulfonyl group appeared at 71.03 and 67.81 ppm, respectively. The methoxy carbon, and the diethylamino methylene and methyl carbons appeared at 55.43, 44.97, 43.98, 12.30, and 11.06 ppm, respectively.

Finally, the chlorination was confirmed by HRMS with a measured accurate mass (*m/z*, ^{35}Cl) for $[M+Na]^+$ of 353.0690 for 353.0697 required. The desired product (**247**) was formed in very high yield (95%).

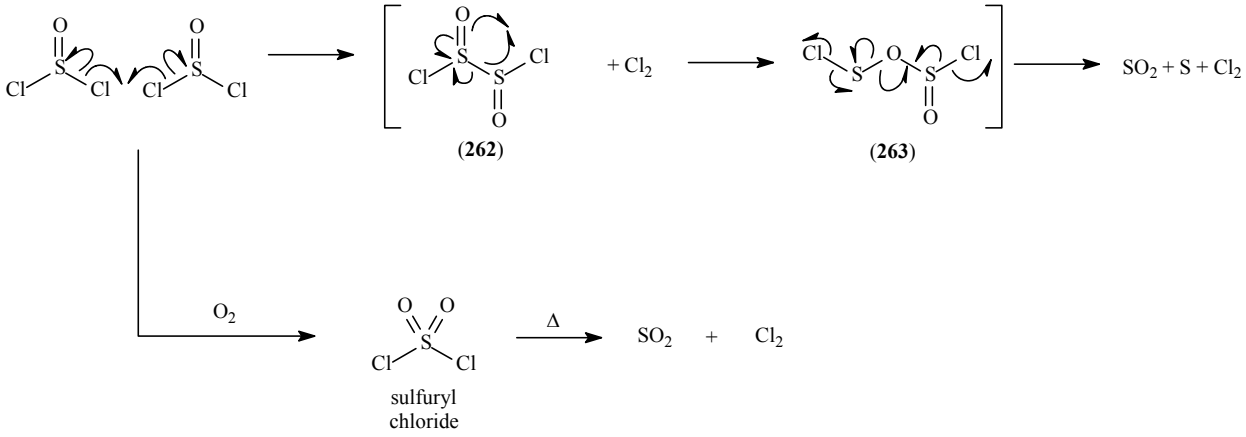
Interestingly, two side products (**261**) and (**248**) could, on occasion, be isolated from the reaction mixture. It is possible that under the reaction conditions, compound (**260**) was formed and underwent a *β*-elimination to give the conjugated isothiazole (**248**) (**431mg, 10%**), which in turn was chlorinated to afford the dichlorinated isothiazolin-1,1-dioxide (**261**) as an impurity (**225 mg, 4%**) (Scheme 2.72).



Scheme 2.72

This mechanism involves the electrophilic addition of chlorine to the olefinic double bond of the isothiazole (**248**). Obviously the question of the generation of chlorine in the reaction mixture arises. A possible explanation is that thionyl chloride is the source of chlorine either directly by thermal decomposition,[181] or indirectly by oxidation to sulfuryl chloride[182] which is

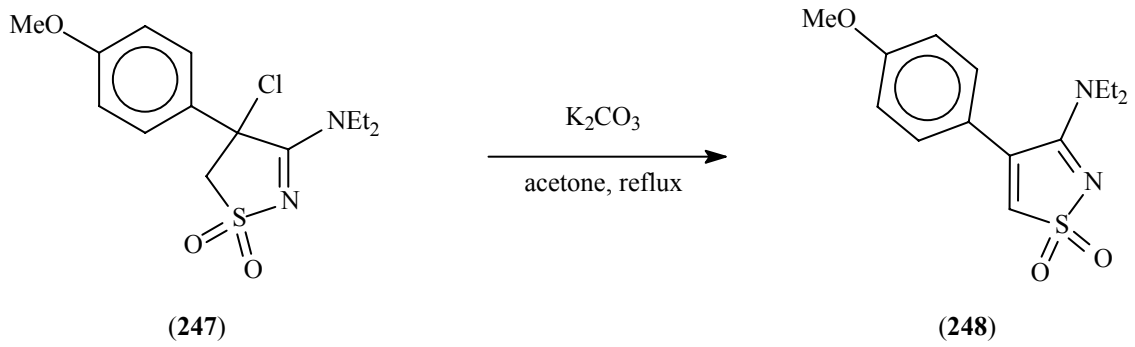
known to be a source of chlorine. Thus, under the conditions of the reaction (reflux), chlorine could have formed through a radical dimerisation of thionyl chloride to form chlorine and the intermediate (**262**), which then underwent a concerted reduction and oxidation of the two adjacent sulfur atoms to give the species (**263**), which in turn released sulfur dioxide, elemental sulfur and further chlorine *via* another radical pathway (Scheme 2.73). Thionyl chloride could also have been oxidised to sulfuryl chloride, which decomposed upon heating to generate chlorine and sulfur dioxide.



Scheme 2.73

2.3.4.8 Synthesis of 3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

The dehydrohalogenation of the chlorinated isothiazoline (**247**) was performed in refluxing acetone using potassium carbonate as a base to undergo a *β*–elimination and form the corresponding isothiazole (**248**) in 86% yield (Scheme 2.74).[178]



Scheme 2.74

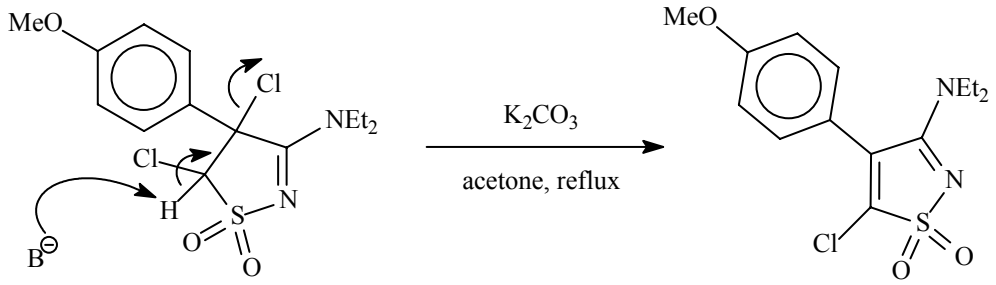
The structure of the product was assigned on the basis of spectroscopic data. The IR spectrum displayed the absorption of the C=N at 1603 cm^{-1}, and the absorption of the sulfonyl group at 1288 and 1189 cm^{-1}.

In the ^{1}H NMR spectrum, the disappearance of the two protons of the methylene adjacent to the sulfonyl group at 4.17 and 3.82 ppm from the starting material, and the appearance of the deshielded olefinic proton at 7.17 ppm as a singlet gave the evidence of the occurance of the *β*–elimination. The *meta* aromatic protons relative to the methoxy group appeared at 7.24 ppm as a doublet with *J*=8.8 Hz, whereas those in the *ortho* position appeared at 6.97 ppm. The three protons of the methoxy group occurred at 3.86 ppm as a singlet. The two CH_2s and the two CH_3s from the diethylamino group appeared at 3.64 and 3.14 ppm as broad doublets with *J*=6.3 Hz, and at 1.31 and 0.93 ppm as broad singlets, respectively. The splitting of the two methylenes and the two methyl groups indicated the double bond character of the C-NEt_2 bond, but the unexpected broadening of the signals could be related to the loss of the stereogenic center adjacent to the carbon bearing the diethylamino group, after the occurance of the *β*–elimination. By losing the chiral center, the two protons of the methylenes lose their diastereotopic relationship.

In the ^{13}C NMR spectrum, the olefinic CH was displayed at 142.94 ppm, whereas the olefinic quaternary carbon was displayed at 139.67 ppm. The disappearance of the characteristic quaternary sp^3 carbon and CH_2 from the starting material at 71.03 and 67.81 ppm, respectively, further confirmed the dehydrohalogenation had taken place.

The evidence of the *β*–elimination was completed by HRMS with a measured accurate mass (*m/z*) for $[M+Na]^+$ of 317.0931 for 317.0930.

During this process, the side product (**264**) was isolated. It is believed that this product must be formed easily from the dehydrochlorination of the dichloroisothiazoline (**261**), which was isolated in the previous step (Scheme 2.72). A small amount of compound (**261**) must have been carried through this step, and its dehydrochlorination in refluxing acetone under the action of potassium carbonate afforded 5-chloro-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**264**) (Scheme 2.75).



(**261**) (**264**)

Scheme 2.75

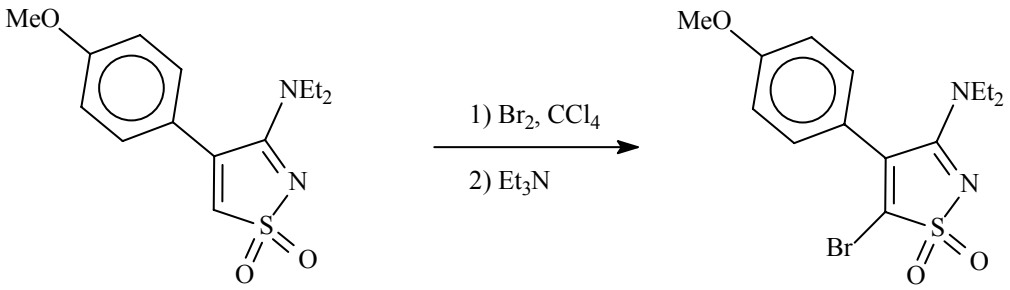
Spectroscopic analysis gave the evidence of the formation of the product (**264**). The IR spectrum showed the usual characteristic bands at 1624 cm^{-1} for the C=N bond, and at 1306 and 1153 cm^{-1} for the sulfonyl group.

The ^{1}H NMR and the ^{13}C NMR spectra were very similar to that of the 5-bromoisothiazol-1,1-dioxide (**249**) described below, as expected.

The identification of the chlorinated product (**264**) was confirmed by HRMS with a measured accurate mass (*m/z* for ^{35}Cl) for $[M+H]^{+}$ of 329.0719 for 329.0721 required.

2.3.4.9 Synthesis of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

The bromination of compound (**248**) was carried out by treatment of the olefinic double bond with bromine in carbon tetrachloride followed by dehydrobromination with triethylamine to give the brominated isothiazole (**249**) in 93% yield (Scheme 2.76).[183] The use of sodium metabisulfite during the work-up removed any trace of bromine left in the reaction mixture.



(**248**) (**249**)

Scheme 2.76

Spectroscopic analysis gave the evidence for the formation of the product. In the IR spectrum, the band at 1603 cm^{-1} confirmed the continued presence of a C=N bond, and the two bands at 1306 and 1150 cm^{-1} indicated the presence of the sulfonyl group.

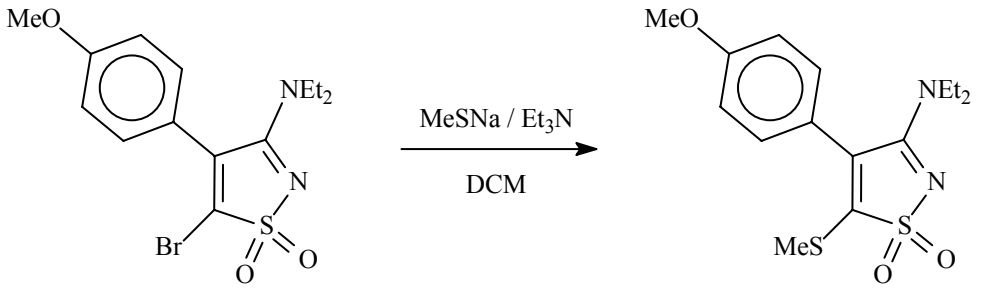
In the ^{1}H NMR spectrum, the absence of the singlet at 7.17 ppm suggested that the olefinic CH was no longer present in the molecule.

In the ^{13}C NMR spectrum, the disappearance of the CH at 142.94 ppm combined with the presence of two quaternary sp^2 carbon at 137.90 and 135.87 ppm confirmed the loss of the olefinic CH present in the starting material.

The bromination was further confirmed by HRMS with a measured accurate mass (*m/z* for ^{79}Br) for $[M+Na]^+$ of 395.0038 for 395.0035 required.

2.3.4.10 Synthesis of 3-diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

The substitution of the bromide in compound (**249**) by the methansulfanyl group was performed using sodium thiomethoxide in dichloromethane to give the desired product (**250**) in 97% yield (Scheme 2.77).[184] The nucleophilic substitution was carried out in the presence of triethylamine, in order to maintain the nucleophilicity of sodium methoxide in case of a possible protonation.



(**249**) (**250**)

Scheme 2.77

The spectroscopic data gave the evidence of the formation of the desired product. The IR spectrum showed the usual absorptions at 1583 cm^{-1} for the C=N bond, with further peaks at 1286 and 1145 cm^{-1} for the sulfonyl group.

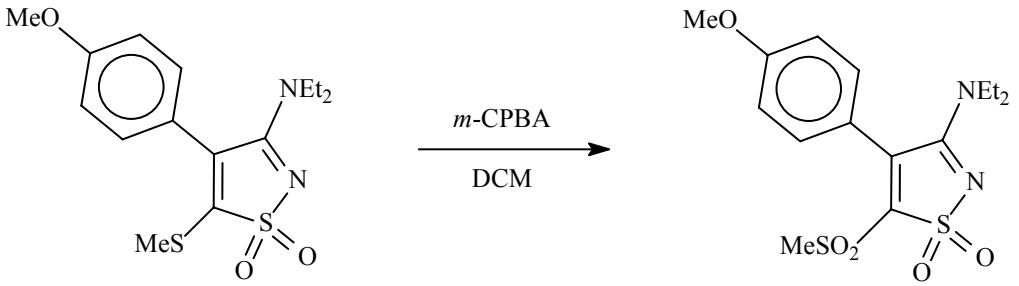
In the ^{1}H NMR spectrum, the three protons of the methanesulfonyl group appeared at 2.79 ppm as a singlet.

In the ^{13}C NMR spectrum, the methyl of the methanesulfanyl group appeared at 12.92 ppm. The carbon on which the nucleophilic substitution took place shifted from 137.90 to 157.02 ppm.

The nucleophilic substitution was further confirmed by HRMS with a measured accurate mass (*m/z*) for $[M+H]^+$ of 341.0992 for 341.0988 required.

2.3.4.11 Synthesis of 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

The oxidation of the methanesulfanyl group in compound (**250**) to the methanesulfonyl group was carried out with two equivalents of *meta*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane to afford compound (**251**) in 51% yield (Scheme 2.78).[174]



(**250**) (**251**)

Scheme 2.78

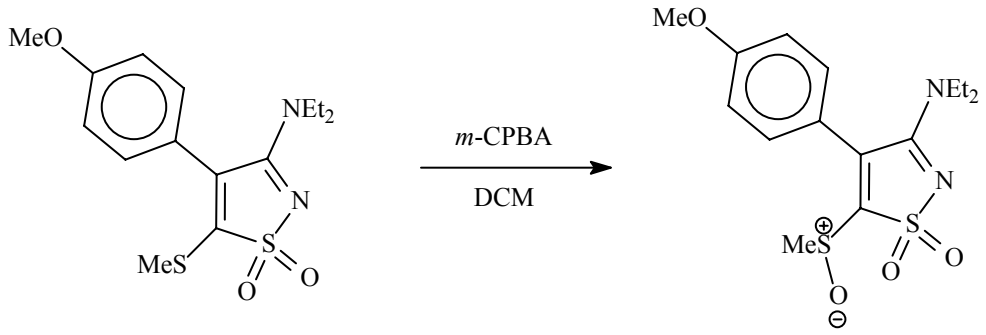
Spectroscopic analysis provided the evidence of the formation of the product. On the ^{1}H NMR spectrum, the singlet for the three protons of the methanesulfonyl group appeared at 3.17 ppm, whereas they were appearing at 2.79 ppm in the methanesulfanyl group.

In the ^{13}C NMR spectrum, the chemical shift of the methyl group was even more significant by moving from 12.92 ppm in the methanesulfanyl group to 43.93 ppm in the methanesulfonyl group, confirming the oxidation of the sulfur atom.

The structure of the product was confirmed by HRMS with a measured accurate mass (*m/z*) for $[M+Na]^+$ of 395.0710 for 395.0706 required.

2.3.4.12 Synthesis of 3-diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

The oxidation of the methanesulfanyl group in compound (**250**) to the methanesulfinyl group was carried out with one equivalent of *m*-CPBA in dichloromethane to afford compound (**265**) in 67% yield (Scheme 2.79), which, although not needed here, would be used in the 1,3-dipolar cycloadditions described later in this thesis.



(**250**) (**265**)

Scheme 2.79

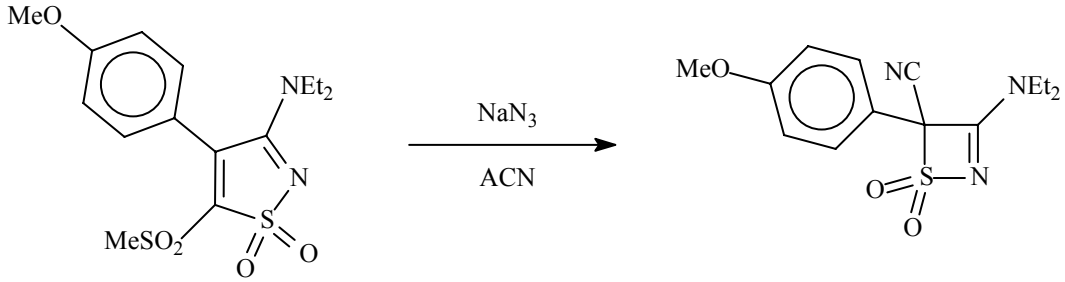
Spectrosocopic analysis provided the evidence of the formation of the product. On the ^{1}H NMR spectrum, the singlet for the three protons of the methanesulfinyl group appeared at 3.16 ppm as a sinlet. The four aromatic protons appeared unexpectedly as three broad singlets integrating to four at 7.41, 7.15 and 7.02 ppm.

In the ^{13}C NMR spectrum, the chemical shift of the methyl of the sulfinyl group appeared at 38.34 ppm.

The structure of the product was confirmed by HRMS with a measured accurate mass (*m/z*) for $[M+NH_4]^+$ of 374.1198 for 374.1203 required.

2.3.4.13 Ring contraction of 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide: synthesis of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide

The ring contraction of the five-membered ring (**251**) to the four-membered ring (**252**) was performed with sodium azide in acetonitrile in 57% yield (Scheme 2.80), using an adaptation of a procedure previously described in the literature.[174]



(**251**) (**252**)

Scheme 2.80

Spectroscopic analysis confirmed the proposed structure of the product, and was consistent with the spectroscopic data described in the literature. In the IR spectrum, the weak absorption at 2241 cm^{-1} confirmed the presence of the cyano group. The C=N bond appeared as a strong band at 1641 cm^{-1}, as well as the SO_2 showing with two strong absorptions at 1336 and 1158 cm^{-1}.

In the ^{1}H NMR, the four aromatic protons appeared at 7.40 and 7.00 ppm with *J*=8.9 Hz. The methoxy CH_3 is shown at 3.81 ppm as a singlet. The two CH_2s of the diethylamino group are displayed as four doublets of quartets at 3.61 and 3.43 ppm with *J*=13.9 and 7.2 Hz integrating to one proton each on one hand, and at 3.12 and 3.09 ppm with *J*=14.4 and 7.2 Hz integrating to one proton each on the other hand. The two methyls appeared at 1.28 and 1.06 ppm with *J*=7.2 Hz.

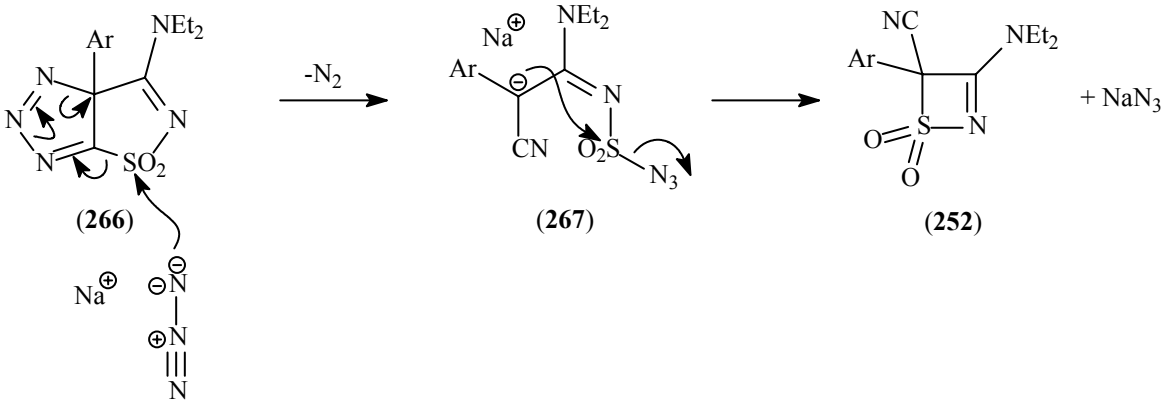
The differentiation of the two ethyl groups indicates the double bond character of the enamine bond, meaning that the two ethyl groups are in a different environment. The differentiation between the two protons in each CH_2 is due to their diastereotopic relationship.

In the ^{13}C NMR spectrum, the quaternary aromatic carbon bearing the methoxy group appeared at 161.68ppm, and the quaternary carbon bearing the diethylamino group appeared at 160.58 ppm. The remaining quaternary aromatic carbon appeared at 116.45 ppm, and the two

types of aromatic CHs resonated at 128.37 and 115.08 ppm. The cyano carbon appeared at 111.14 ppm, whereas the quaternary sp^3 carbon of the 4-membered ring appeared at 86.23 ppm. The methoxy methyl appeared at 55.38 ppm, and the two CH_2s and the two CH_3s of the diethylamino group appeared at 45.31, 42.19, 12.63, and 11.32 ppm, respectively.

The structure of the product was further confirmed by a measured accurate mass (*m/z*) of 330.0888 for 330.0883 required.

The mechanism of this expected but surprising ring contraction must involve some unusual rearrangement of the intermediates formed during the reaction course. The mechanism is described below (Scheme 2.81). It should be noted that the structure of compound (**252**) was confirmed unequivocally by X-ray crystallography.[174]



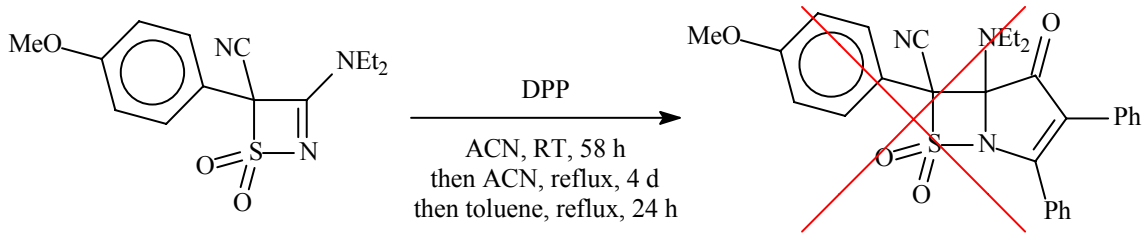
Scheme 2.81

The mechanism proposed in the literature implies, after the loss of sodium methanesulfonate, the ring opening of the bicyclic triazole (**266**) initiated by the nucleophilic attack of the sulfonyl moiety by the azide with loss of nitrogen to form a stablised anion (**267**). The latter undergoes a nucleophilic substitution on the sulfonyl group to release the azide anion, forming the 4-membered ring (**252**) (Scheme 2.81).

2.3.5 Reactivity of 3-diethylamino-1,2-thiazetin-1,1-dioxide towards cycloadditions

2.3.5.1 Attempted trapping of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide with diphenylcyclopropenone

The addition of diphenylcyclopropenone to the 1,2-thiazetin-1,1-dioxide **(252)** was attempted in acetonitrile (Scheme 2.82). The reaction was monitored by TLC, and after 58 hours at RT, no reaction seemed to occur. The reaction mixture was then heated at reflux for four days, but again no new product appeared on TLC. Acetonitrile was evaporated under reduced pressure and the mixture was dissolved and refluxed in toluene for 24 hours, at which point the reaction was stopped and the crude product was purified. Silica chromatography afforded an unidentified product and the starting material. The ^{1}H NMR spectrum of the unidentified compound displayed only protons in the aromatic region between 7.69 and 7.03 ppm, but no protons for the methoxy group at ~3.80 ppm nor for the CH_2 at ~3.50 ppm and for the CH_3 at ~1.00 ppm for the diethylamino group, indicating the loss of both the methoxyphenyl and the diethylamino moeity.

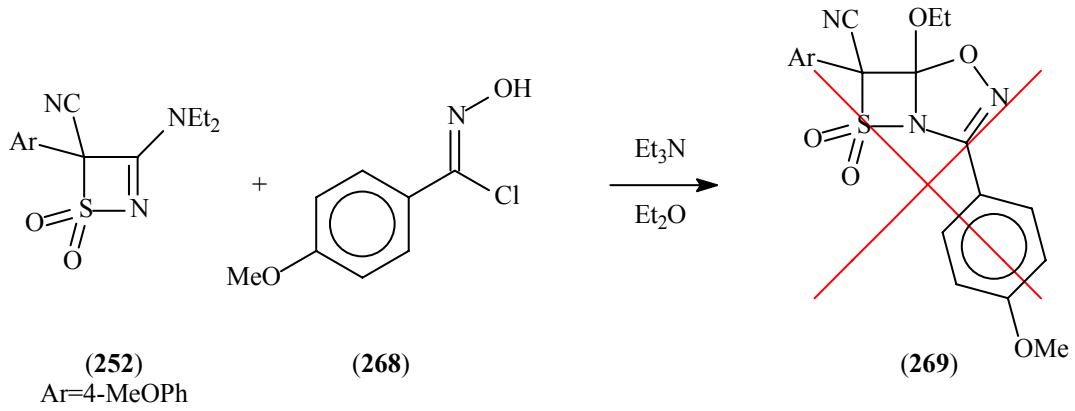


(252) **(268)**

Scheme 2.82

2.3.5.2 Attempted trapping of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide with nitrile oxides

The 1,3-dipolar cycloaddition was attempted by slow addition of a dilute ethereal solution of triethylamine to a mixture of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide (**252**) and 4-methoxybenzohydroximoyl chloride (**268**) in ether (Scheme 2.83). Purification on silica gel allowed almost quantitative recovery of the starting material together with formation of the dimer of the nitrile oxide as the major product, indicating that the desired 1,3-dipolar cycloaddition had failed.



(**252**)
Ar=4-MeOPh

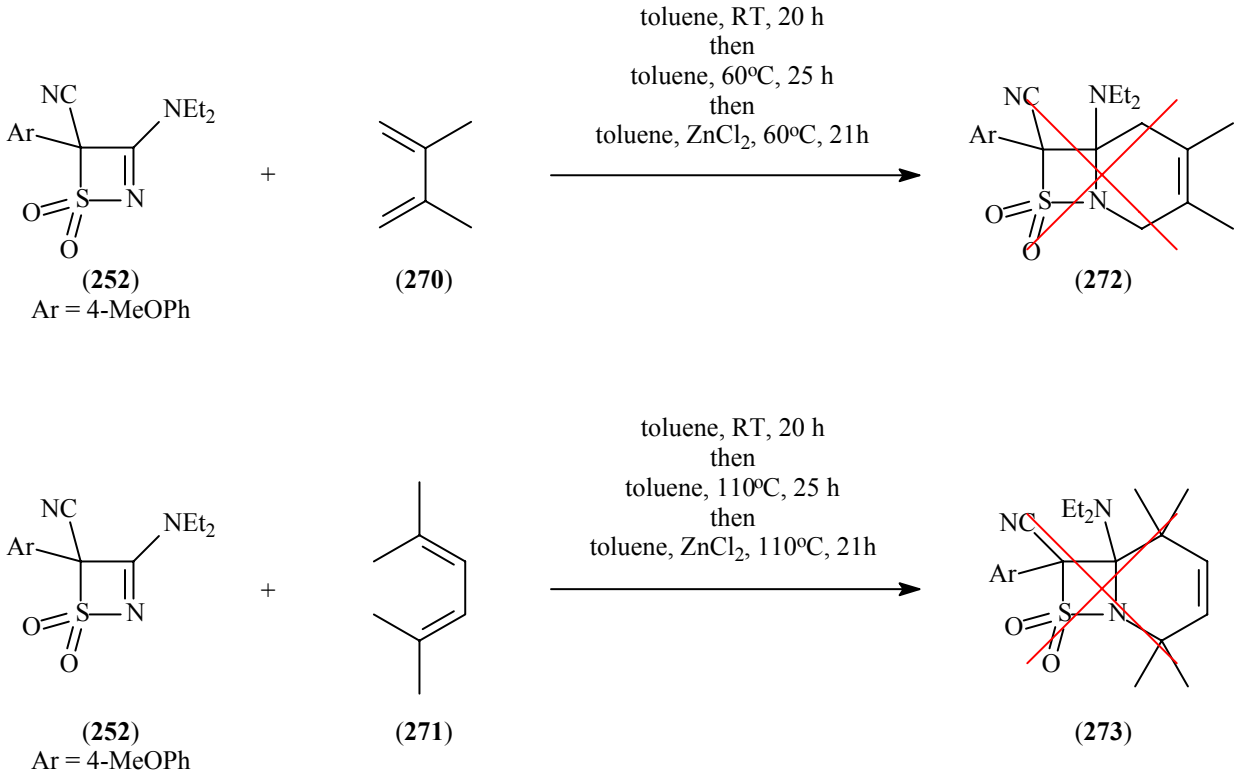
(**268**)

(**269**)

Scheme 2.83

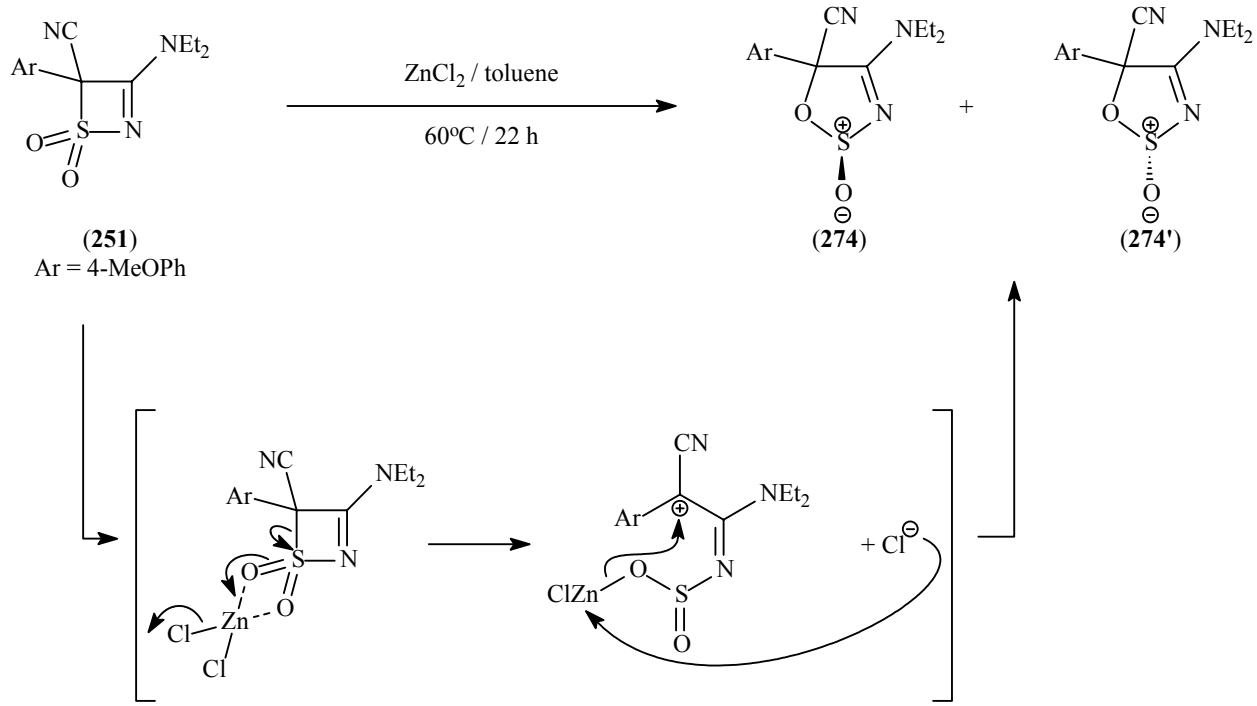
2.3.5.3 Attempted trapping of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide with dienes

The Diels-Alder cyclisation of 1,2-thiazetin-1,1-dioxide (**252**) with both 2,3-dimethylbutadiene (**270**) and 2,5-dimethyl-2,4-hexadiene (**271**) was attempted (Scheme 2.84). Under the conditions used, none of the dienes reacted with the four-membered ring to form compounds (**272**) and (**273**). Instead, in the presence of zinc chloride, two isomers of the starting material were isolated, products of a zinc promoted rearrangement as discussed below.



Scheme 2.84

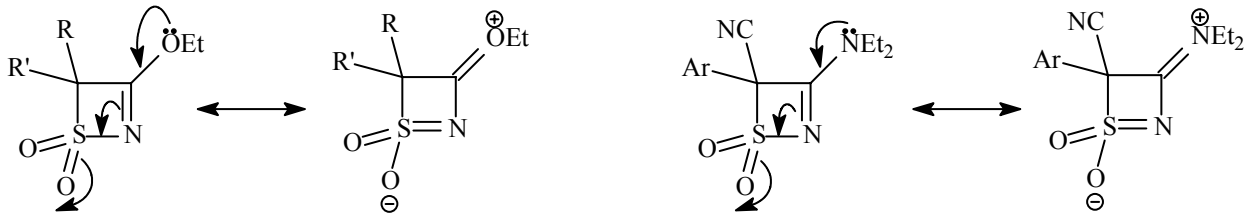
Possibly, the formation of these two isomers could be the result of a ring opening of the four-membered ring under the catalysis of the Lewis acid followed by ring closure to the less strained and more stable five-membered diastereomeric 1,2,3-oxathiazolin-2-oxides (**274**) and (**274'**) in ~20% yield (Scheme 2.85). A similar ring expansion of 1,2-thiazetidin-1,1-dioxides catalysed by Lewis acids has already been reported.[49,62]



Scheme 2.85

2.3.6 Conclusion

In the light of all the reactions performed with 1,2-thiazetin-1,1-dioxides, it can be concluded that they are not reactive towards 1,3-dipolar cycloaddition with nitrile oxides, or the formal [3+2] cycloaddition with diphenylcyclopropenone, or Diels-Alder cyclisation with dienes. By comparing these results with those previously described with 1-azetines (sections 2.2.1.3.1 and 2.2.1.3.3), it seems sensible to suggest that the sulfonyl group is responsible for the difference of reactivity. Indeed, the ring expansion of DPP, the mechanism involves the nucleophilicity of the nitrogen (Scheme 2.12). Hence, it is possible that the presence of the sulfonyl in 1,2-thiazetin-1,1-dioxides reduces the nucleophilicity of the nitrogen to such an extent that no reaction occurred (Scheme 2.86). Thus, the electron-donating effect of the 3-ethoxy or 3-diethylamino groups would be deviated by the sulfonyl group, resulting in an electron-poor double bond involved in the cyclisation reaction and a reduction of the nucleophilicity of the nitrogen.



(**161b**) $R^1 = R^2 = Et$
(**161c**) $R^1 = R^2 =$ *spiro*- cyclohexyl
(X = O; $R^3 = Et$)

(**252**)
Ar = 4-MeOPh

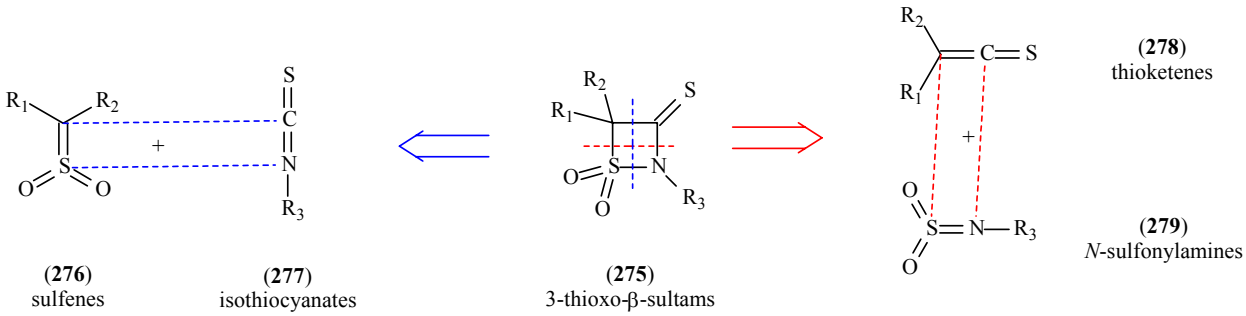
Scheme 2.86

In concerted cycloadditions driven by frontier molecular orbitals (FMO), the presence of the electron-donating substituents OEt or NEt_2 on the imine double bond should raise the energy of LUMO and HOMO of the dipolarophile, whereas the electron-withdrawing SO_2 group should lower energy. Hence, the ethoxy or diethylamino groups favour the interaction of the LUMO of the dipole with the HOMO of the dipolarophile, whereas the sulfonyl group favours the interaction of the LUMO of the dipolarophile with the HOMO of the dipole. Thus, in the case of the 1-azetines (**180**) and (**185**) studied in section 2.2.1 which are reactive towards 1,3-dipoles and where only an electron-donating substituent (SEt) is present, it is possible to assume that the molecular orbitals interacting are the dipole's LUMO and the dipolarophile's HOMO. In the case of the 1,2-thiazetin-1,1-dioxides, where the sulfonyl group is present, it is likely that the dipolarophile's HOMO is lowered and the gap between the latter and the dipole's LUMO is enhanced, thus accounting for the difference of reactivity of those systems towards dipoles compared to that of 1-azetines.

Another possible explanation is that the orientation of the molecular orbitals of the two S=O double bonds of the sulfonyl group does not allow the sulfonyl group to act as an electron-withdrawing substituent due to a lack of overlapping with the molecular orbitals of the C=N bond. However, this unsuitable orientation of the orbitals could create repulsive secondary interactions with the dipole's orbitals during the approach.

2.4 Attempted [2+2] cycloadditions as routes to 3-thioxo-*β*-sultams

In order to overcome the problem of the thionation and the alkylation of 3-oxo-*β*-sultams, we thought to try [2+2] cycloaddition reactions to form directly 3-thioxo-*β*-sultams (**275**), which, after deprotection of the nitrogen, should be easier to alkylate to produce the desired 1,2-thiazetin-1,1-dioxides (**161**; X=S). A simple retrosynthetic analysis gives two obvious pathways to reach this target (Scheme 2.87): on one hand, the [2+2] cycloaddition of sulfenes (**276**) with isothiocyanates (**277**), and on the other hand, the [2+2] cycloaddition of thioketenes (**278**) with *N*-sulfonylamines (**279**). The former was attempted and the latter was not but both of them will be discussed in this section, as the latter will be attempted in the future.

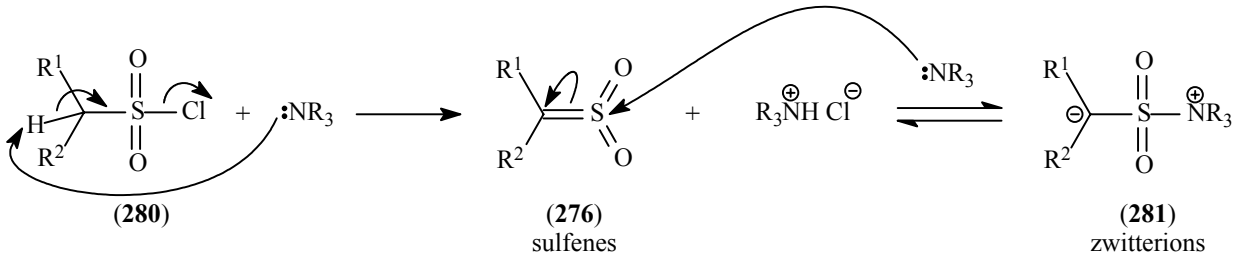


Scheme 2.87

Sulfenes[185] have been used as intermediates in the construction of a wide range of heterocyclic four-membered rings such as thietane 1,1-dioxides,[186-189] thiete 1,1-dioxides,[42,190,191] *β*-sultones,[192] and *β*-sultams.[44,45,193] They have also been used in [3+2][194,195] and [4+2][196,197] cycloadditions for the construction of bigger heterocycles.

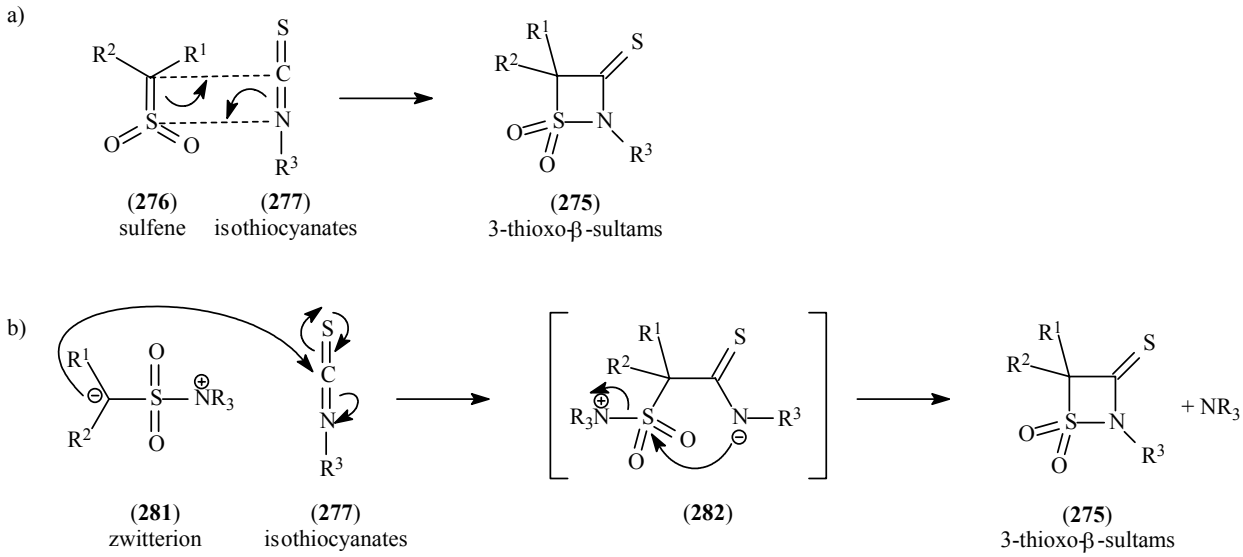
2.4.1 [2+2] Cycloadditions of sulfenes with isothiocyanates

Sulfenes are generally generated *in situ*[185,198,199] from sulfonyl chlorides (**280**) in the presence of a base. Depending on the base used, it is possible to generate as an intermediate either the electrophilic sulfenes (**276**) or the corresponding nucleophilic zwitterions (**281**) (Scheme 2.88).[200,201]



Scheme 2.88

The equilibrium between the sulfene and the zwitterion depends on several parameters such as the base size or the polarity of the solvent. According to the species predominantly formed, the mechanism involved in the potential formation of 3-thioxo-*β*-sultams (**275**) and the reactivity towards isothiocyanates can be hugely different (Scheme 2.89a and b). The base size will affect the nucleophilicity of the trialkylamine, and the polarity of the solvent will affect the formation of the zwitterion. Hence, with a bigger size of the tertiary amine and a less polar solvent, the formation of the sulfene (**276**) should be favoured (Scheme 2.89a), whereas with a smaller size of the tertiary amine and a more polar solvent, the formation of the zwitterion (**281**) should be favoured (Scheme 2.89b).

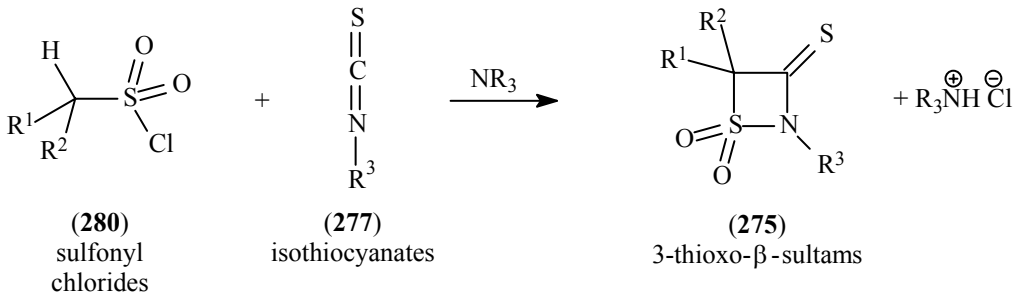


Scheme 2.89

The first mechanism involves the formation of the electrophilic sulfene (**276**), which undergoes a concerted [2+2] cycloaddition with the isothiocyanate (**277**) (Scheme 2.89a), whereas the second one involves the nucleophilic addition of the zwitterion (**281**) on the

thiocarbonyl of the isothiocyanate (**277**) to form the intermediate (**282**), which undergoes an intramolecular nucleophilic substitution on the sulfonyl group, with the trialkylamine as a leaving group (Scheme 2.89b).

Therefore, we embarked on the study of the reaction between sulfonyl chlorides (**280**) and isothiocyanates (**277**) (Scheme 2.90), using various sulfonyl chlorides with benzyl isothiocyanate and benzoyl isothiocyanate under various conditions as summarised in Table 2.1. All the reactions were carried out at -10ºC. During the course of the reaction, in all cases, the precipitation of the trialkylamine hydrochloride salt was observed. With benzylsulfonyl chloride, the disappearance of the starting material was also observed by TLC, indicating the reaction of the sulfonyl chloride with the base to form either the sulfene or the zwitterion. In all cases, there was no reaction observed with isothiocyanates, which were recovered as the major products.



(**280**) sulfonyl chlorides

(**277**) isothiocyanates

(**275**) 3-thioxo-β-sultams

Scheme 2.90

The aim of this work was to investigate whether this reaction would show any signs of success by changing the different parameters, and use any sign of success to drive an optimisation process. Whilst it is obvious that further work is required to conclude definitively that the formation of 3-thioxo-*β*-sultams from sulfenes and isothiocyanates cannot occur, it remains the case that no indication of even a trace of the desired product could be seen. Given the success of some other areas, further work was not pursued in this area.

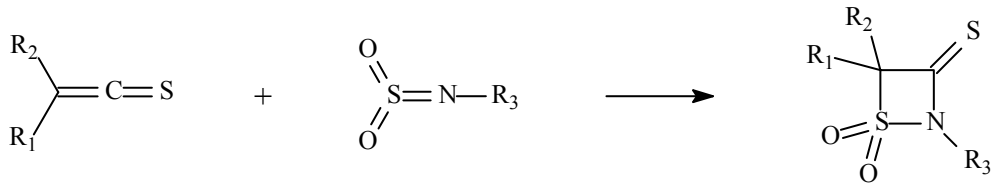
Entry	Reactants in reaction mixture				Added reactant				Solvent	Reaction time (h)	Lewis acid
	R^3	Concentration (mol/L)	Base	Eq. of base	R^1	R^2	Concentration (mol/L)	Addition time (min)			
1	$PhCH_2$	0.25	Et_3N	1	Ph	H	1.26	30	Et_2O	16	-
2	$PhCH_2$	0.15	Et_3N	1	Ph	H	0.15	60	Et_2O	21	BF_3
3	$PhCH_2$	0.15	Et_3N	1	Ph	H	0.15	60	Et_2O	21	$ZnCl_2$
4	$PhCH_2$	0.15	Et_3N	1	Ph	H	0.15	60	DCM	22	-
5	$PhCH_2$	0.075	Me_3N	large xs	Ph	H	0.037	90	Et_2O	overnight	-
6	$PhCH_2$	0.075	Me_3N	large xs	Ph	H	0.075	30	DCM	1	-
7	$PhCH_2$	0.075	Me_3N	large xs	Ph	H	0.075	90	ACN	1	-
8	$PhCH_2$	0.075	Me_3N	large xs	Me	H	0.037	90	Et_2O	1	-
9	$PhCH_2$	0.075	Me_3N	large xs	Me	H	0.075	15	DCM	1	-
10	$PhCH_2$	0.075	Me_3N	large xs	Me	H	0.075	60	ACN	1	-
11	$PhCH_2$	0.25	Et_3N	1	H	H	1.26	30	Et_2O	16	-
12	$PhCH_2$	0.075	Me_3N	large xs	H	H	0.075	60	ACN	1	-
13	PhCO	0.25	Et_3N	1	Ph	H	1.24	30	Et_2O	19	-
14	PhCO	0.74	Me_3N	xs	Ph	H	1.48	30	DCM	18	-
15	PhCO	0.74	Me_3N	xs	Me	H	1.48	30	DCM	18	-
16	PhCO	0.25	Et_3N	1	H	H	1.24	30	Et_2O	19	-
17	PhCO	0.74	Me_3N	xs	H	H	1.48	30	DCM	18	-

Entry	R^1	R^2	Concentration (mol/L)	Base	Eq. of base	R^3	Conc. (mol/L)	Addition time (min)	Solvent	Reaction time (h)	Lewis acid
18	Ph	H	0.15	Me_3N	xs	$PhCH_2$	0.15	10	Et_2O	overnight	-
19	Ph	H	0.15	Me_3N	1 drop	$PhCH_2$	0.075	90	Et_2O	19	-
20	Ph	H	0.075	Et_3N + Me_3N	1 eq. + 2 drops	$PhCH_2$	0.075	60	Et_2O	overnight	-

Table 2.1 Reaction conditions for the reaction between sulfonyl chlorides (**280**) and isothiocyanates (**277**)

2.4.2 [2+2] Cycloadditions of *N*-sulfonylamines with thioketenes

As stated above, the other obvious route to 3-thioxo-*β*-sultams (**275**) is the [2+2] cycloaddition of *N*-sulfonylamines (**279**) with thioketenes (**278**) (Scheme 2.91).



(**278**) thioketenes (**279**) *N*-sulfonylamines (**275**) 3-thioxo-β-sultams

Scheme 2.91

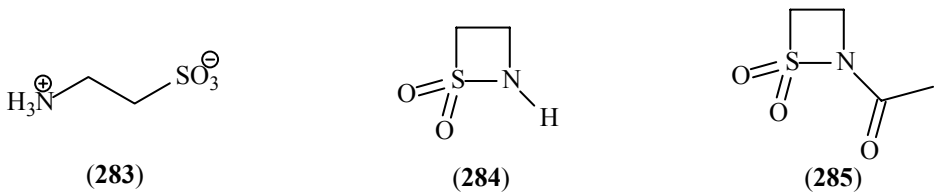
N-Sulfonylamines can be generated *in situ* from the corresponding sulfamoyl chlorides and have been used in [2+2] cycloadditions for the synthesis of *β*-sultams[202-206] and in [4+2] cycloadditions.[207] They can also be generated from sulfonyl azides in a similar fashion to the Curtius, Lossen and Wolff rearrangements.[208]

The synthesis of thioketenes is difficult due to their high tendency to dimerise or oligomerise. Introduction of bulky or strongly electron-withdrawing groups has a stabilising effect. Synthetic methods involving pyrolysis, generation at low temperature or trapping have been reviewed.[209] An interesting preparation under milder conditions from diazoalkanes and carbon monosulfide has been reported.[210] However, there is no general thioketene synthesis since the instability of thioketenes renders their synthesis very specific and often of narrow synthetic applications. But once again, this area was not explored in order to focus on other successful areas.

2.5 Synthesis of unsubstituted *β*-sultams and *γ*-sultams

The purpose of this work was to synthesise some *β*-sultams and *γ*-sultams in order that they could be studied as taurine and homotaurine pro-drugs. Taurines (**283**) (Figure 2.3) and their derivatives have been recently reviewed.[211] They are involved in various therapeutic treatments such as epilepsy,[212] cardiovascular diseases, congestive heart failure,[213,214] myocardial infarction,[215] anti-hypertension,[216] diabetes,[217,218] ischemia,[219] obesity,[220] alleviation of the noxious effects of smoking,[221] treatment of alcoholic craving after detoxification,[222] and prevention of neurodegeneration in the elderly.[223] Taurines, despite their high potential for activity against various diseases, are poorly absorbed and the ratio between doses administered orally and the corresponding levels which reach the target are very unfavourable.[211] *β*-Sultam (**284**) (Figure 2.3) is a taurine pro-drug, it leads to taurine *via* a simple hydrolysis step and could

potentially be used in the place of taurines. The addition of an acyl group to this molecule also delays its hydrolysis, thereby enhancing intracellular concentrations of taurines.



(**283**) (**284**) (**285**)

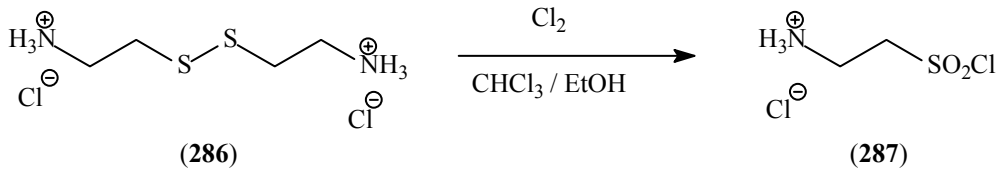
Figure 2.3

As a part of a collaboration with a Belgian research group, and because of their obvious relationship to the chemistry discussed in this thesis, unsubstituted *β*-sultam (**284**) and *N*-acyl-*β*-sultam (**285**) have been synthesised. These compounds were required in order to assess their validity as taurine pro-drugs in laboratory Alzheimer and alcohol detoxification models.

2.5.1 Synthesis of unsubstituted *β*-sultam and *N*-acyl *β*-sultam

2.5.1.1 Synthesis of taurine sulfonyl chloride

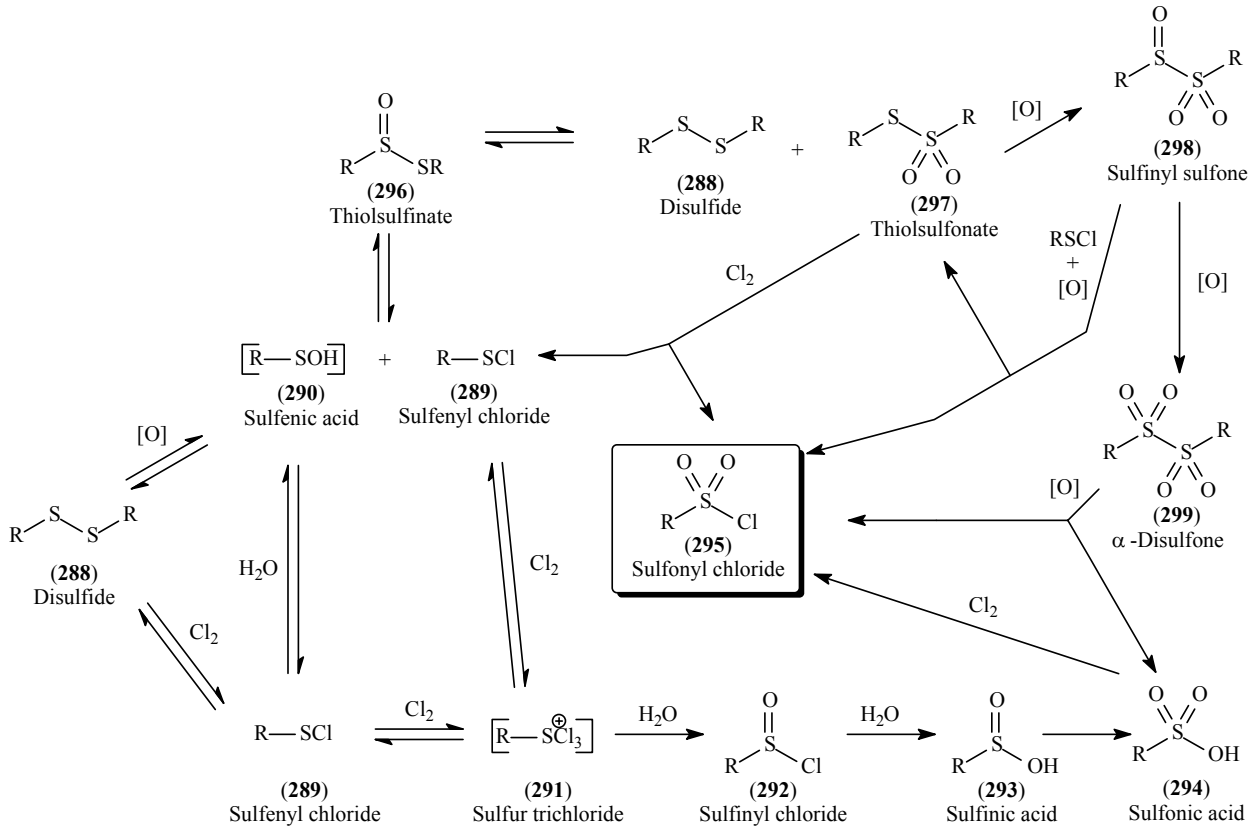
Oxidative chlorination was performed by bubbling chlorine through a suspension of cystamine dihydrochloride (**286**) in chloroform and ethanol to give taurine sulfonyl chloride (**287**) in quantitative yield (Scheme 2.92).



(**286**) (**287**)

Scheme 2.92

Disulfides are known to produce the corresponding sulfonyl chlorides by oxidative chlorination in water.[224-228] The mechanism of oxidation is very complex and remains unclear due to the potential presence of a large amount of species in the mixture (Scheme 2.93).

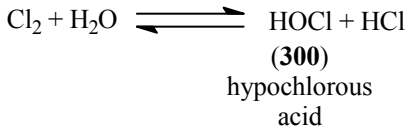


Scheme 2.93

Disulfides (**288**) can be cleaved by chlorine into sulfenyl chlorides (**289**), which, on one hand, can be converted to sulfur trichlorides (**291**).[224,226,229] These intermediates (**291**) can be hydrolysed to the corresponding sulfinyl chlorides (**292**) and sulfinic acids (**293**).[224,229,230] Sulfinic acids decompose to yield the corresponding sulfonic acids (**294**), which can be chlorinated in the presence of chlorine to afford sulfonyl chlorides (**295**).[226] On the other hand, sulfenyl chlorides (**289**) can react with water to form sulfenic acids (**290**), which can react with another molecule of sulfenyl chloride to form thiolsulfinates (**296**).[231] It has also been suggested that thiolsulfinates (**296**) can be formed by disproportionation of sulfenic acids (**290**).[232] Easy disproportionation of thiolsulfinates (**296**) leads to disulfides (**288**) and thiolsulfonates (**297**).[233-235] Chlorination of thiolsulfonates (**297**) leads to sulfonyl chlorides (**295**) and organosulfur trichlorides (**291**).[224,236]

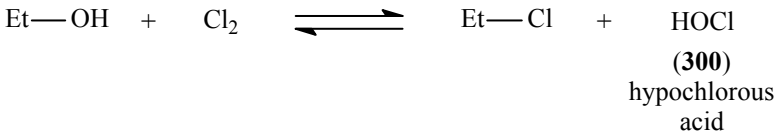
Another mechanistic suggestion is the direct oxidation of the disulfides (**288**) to sulfenic acids (**290**) under the action of a strong oxidising agent. Aqueous chlorine generates hypochlorous acid (**300**) (Scheme 2.94), a strong oxidising agent, which has been extensively reported to react with sulfur-containg compounds.[237,238] Thus, hypochlorous acid (**300**) could possibly be the actual oxidant in the oxidative chlorination of disulfides (Scheme 2.93, [O] = HOCl). If this is

the case, oxidation of thiolsulfonates (**297**) to α-disulfones (**299**) *via* sulfinyl sulfones (**298**) can't be excluded.[226,239] It is then possible to suggest the subsequent oxidation of these compounds to sulfonyl chlorides (**295**).[240]



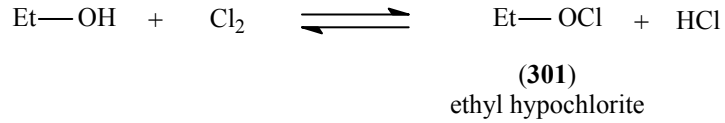
Scheme 2.94

Nevertheless, the generation of hypochlorous acid (**300**) with chlorine occurs in water, whereas the reaction was performed in chloroform and ethanol. It is noteworthy that the reaction was achieved in both laboratory grade and pre-dried solvents without affecting the yield of the reaction. It is possible to suggest that hypochlorous acid is generated either from water contained in the solvents or produced *in situ* during the course of the reaction (Scheme 2.93), but these suggestions are unlikely since the reaction has been carried out in pre-dried solvent and the reaction requires 4 moles of water per mole of disulfide. It is also possible to suggest that hypochlorous acid is generated from ethanol (Scheme 2.95) by analogy to the reaction of water with chlorine described above. However, the generation of hypochlorous acid from the reaction of alcohols with chlorine has never to our knowledge been reported in the literature and is, once again, very unlikely.



Scheme 2.95

The last possibility is the presence of a strong oxidising agent other than hypochlorous acid such as ethyl hypochlorite (**301**) produced from the reaction of ethanol with chlorine (Scheme (2.96). But both the formation of ethyl hypochlorite and its oxidising ability remain hypothetic since no example of such reactions has been reported in the literature to the best of our knowledge.



(**301**)
ethyl hypochlorite

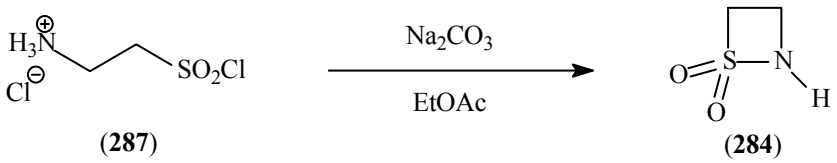
Scheme 2.96

Thus, the mechanism of oxidative chlorination in ethanol and chloroform remains unexplained and would require a much more detailed investigation which was not necessary for the course of this work.

The IR spectrum of the spectrum (**287**) showed two strong absorptions at 1371 and 1159 cm^{-1}, indicating the presence of the sulfonyl group.

2.5.1.2 Ring closure of taurine sulfonyl chloride: synthesis of unsubstituted *β*-sultam

Treatment of taurine sulfonyl chloride (**287**) with sodium carbonate in ethyl acetate afforded unsubstituted *β*-sultam (**284**) in 14 to 60% yield (Scheme 2.97). But the scale of the reaction was sufficient to provide enough material for the next step and biological tests.



(**287**) (**284**)

Scheme 2.97

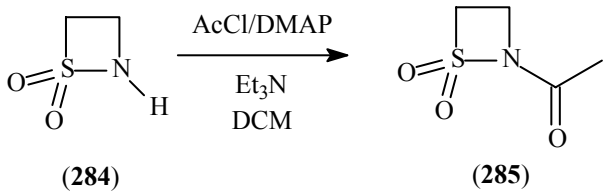
The ring closure of taurine sulfonyl chloride was confirmed by spectroscopic analysis. The IR spectrum displayed a broad absorption at 3297 cm^{-1} for the NH, and two other strong absorptions at 1300 and 1150 cm^{-1} for the sulfonyl group.

The ^{1}H NMR spectrum displayed a broad singlet at 5.33 ppm for the NH, and two doublets of triplets at 4.25 and 3.33 ppm for the methylenes.

The ^{13}C NMR spectrum displayed two CH_2 signals at 60.93 and 28.14 ppm.

2.5.1.3 *N*-acylation of *β*-sultam: synthesis of *N*-acyl-*β*-sultam

N-acylation of *β*-sultam (**284**) was performed in DCM with acetyl chloride in the presence of triethylamine and a catalytic amount of DMAP to produce the *N*-acyl-*β*-sultam (**285**) (Scheme 2.98).



(**284**) (**285**)

Scheme 2.98

The *N*-acylation was confirmed by spectroscopic analysis. In the IR, the disappearance of broad absorption in the 3300 cm^{-1} region indicated the absence of NH in the molecule, and the appearance of a strong band at 1695 cm^{-1} provided the evidence of the presence of the carbonyl.

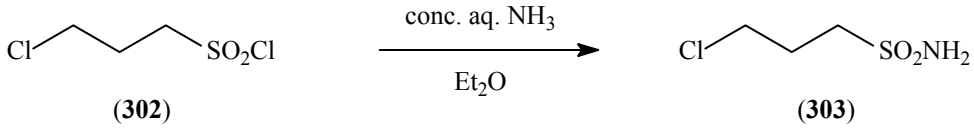
The acylation was further confirmed by the presence, on ^{1}H NMR, of a singlet at 2.25 ppm integrating to three protons for the methyl of the acyl group. The ^{13}C NMR spectrum showed an additional peak at 167.34 ppm for the carbonyl and another one at 23.33 ppm for the methyl, confirming the presence of the acyl group.

2.5.2 Synthesis of unsubstituted *γ*-sultam and *N*-acyl-*γ*-sultam

One of the issues identified during pharmacological assays of the *β*-sultams was a relatively poor absorption caused by low lipophilicity. One possibility to enhance the absorption of taurines is to increase their lipophilicity without ignoring the water solubility. Thus, the synthesis of the five-membered ring analogue of the *β*-sultam (*γ*-sultam or propanesultam) was identified as a strategy to increase their lipophilicity by adding an extra carbon to the ring chain. Hence, the synthesis of the parent *γ*-sultam, propanesultam, and its *N*-acyl analogue was undertaken. The *γ*-sultam is also much more resistant to hydrolysis than the *β*-sultam and may therefore give further advantages.

2.5.2.1 Synthesis of 3-chloropropanesulfonamide

3-chloropropanesulfonamide (**303**) was prepared by amination of commercially available 3-chloropropanesulfonyl chloride (**302**) with concentrated aqueous ammonia (Scheme 2.99).[241]



(**302**) (**303**)

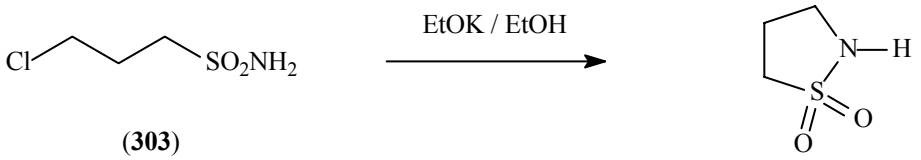
Scheme 2.99

Spectroscopic analysis confirmed the formation of the product. The IR displayed broad absorptions in the 3200-3400 cm^{-1} region for the stretching of N-H suggesting the presence of NH_2. The two strong bands at 1302 and 1120 cm^{-1} confirmed the presence of the sulfonyl group.

The ^1H NMR confirmed the presence of the NH_2 with a broad singlet integrating to two protons at 4.90 ppm. The presence of the three methylenes was provided by three signals integrating to two protons each at 3.71, 3.33, and 2.35 ppm. The ^{13}C NMR further confirmed their presence with three CH_2 signals at 52.52, 42.63, and 27.04 ppm.

2.5.2.2 Ring closure of 3-chloropropanesulfonamide: synthesis of unsubstituted *γ*-sultam

The ring closure of the sulfonamide (**303**) was performed using an ethanolic solution of potassium ethoxide to give the desired product (**304**) (Scheme 2.100).[241]



(**303**) (**304**)

Scheme 2.100

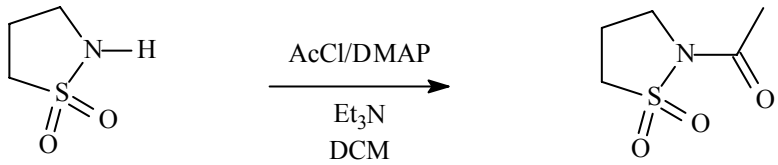
Spectroscopic analysis confirmed the ring closure of 3-chloropropanesulfonamide. On the IR spectrum, a broad absorption appeared at 3269 cm^{-1} for the N-H stretching. Two strong absorptions at 1289 and 1130 cm^{-1} confirmed the presence of the sulfonyl group.

On the ^{1}H NMR spectrum, the occurance of a broad singlet integrating to one proton at 4.39 ppm gave the evidence of the presence of NH in the molecule. Three signals integrating to two protons at 3.43, 3.09, and 2.48 ppm confirmed the presence of the three methylenes. This was further confirmed by three CH_2 peaks on the ^{13}C NMR spectrum.

The structure of the product was further confirmed by a consistent MS analysis.

2.5.2.3 *N*-Acylation of *γ*-sultam: synthesis of *N*-acyl-*γ*-sultam

As for *β*-sultam (**284**), the acylation of *γ*-sultam (**304**) was performed in DCM with acetyl chloride in the presence of triethylamine and a catalytic amount of DMAP to give compound (**305**) (Scheme 2.101).



(**304**) (**305**)

Scheme 2.101

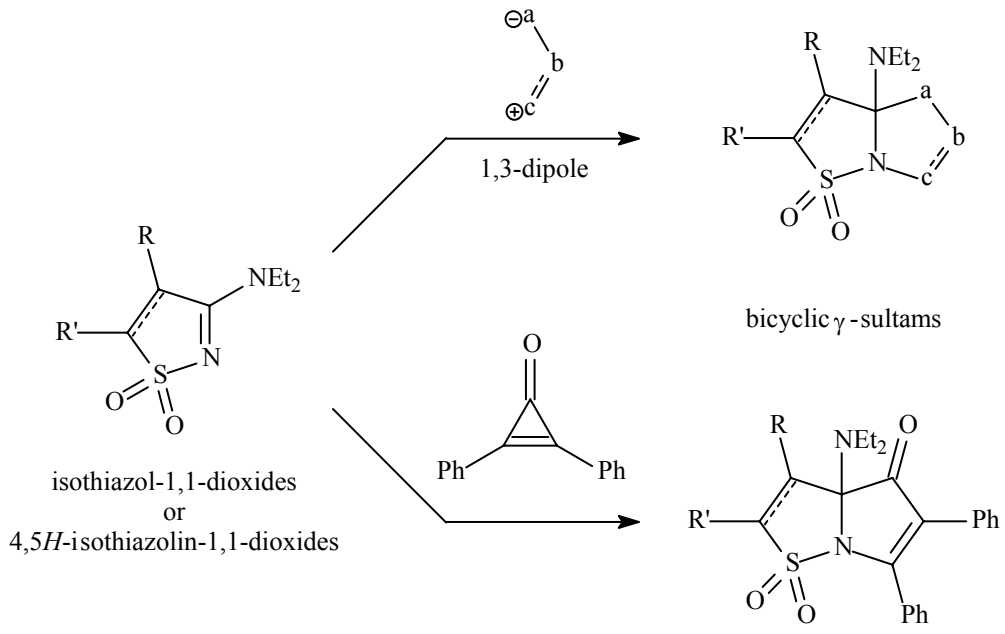
Spectroscopic analysis provided the evidence of the formation of the product. On the IR spectrum, the disappearance of the NH strectching absorption and the appearance of a strong stretching C=O absorption suggested the success of the *N*-acylation.

This was confirmed by the ^{1}H NMR spectrum, with the appearance of a singlet integrating to three protons at 2.43 ppm, and by ^{13}C NMR with the appearance of a quaternary carbon at 167.77 ppm for C=O and a CH_3 signal at 22.82 ppm, both indicating the presence of the acyl group.

The structure of the product was further confirmed by HRMS analysis with an accurate measured mass (*m/z*) for $[M+NH_4]^+$ of 181.0642 for 181.0641 required.

2.6 Cycloaddition reactions with 4,5*H*-isothiazolin-1,1-dioxides and isothiazol-1,1-dioxides: attempted syntheses of bicyclic *γ*-sultams

The initial and ultimate aim of this research was to synthesise bicyclic *β*-sultams through the use of 1,2-thiazetin-1,1-dioxides. As discussed above, we had failed to do so, but on our way to make the 3-diethylamino-1,2-thiazetin-1,1-dioxide (**252**), we had several isothiazol-1,1-dioxides in hand, which are the 5-membered ring analogues of 1,2-thiazetin-1,1-dioxides, and we thought they were interesting molecules for several reasons. First, these molecules contain the sulfonimine moiety, which is the key structural feature in our strategy to synthesise bicyclic systems. The investigation of their chemical behaviour towards cycloadditions would allow us to conclude whether the sulfonimine moiety is able or not to form bicyclic heterocycles. Second, in case of positive results, it would provide some bicyclic *γ*-sultams (Scheme 2.102), which would be made available for biological testing as discussed above (section 2.5). Third, these products constitute in some cases hitherto unreported heterocycles. For these reasons, we embarked upon the exploration of cycloadditions with the isothiazolin-1,1-dioxides and isothiazol-1,1-dioxides, the synthesis of which has been discussed earlier in this thesis (section 2.3.4).

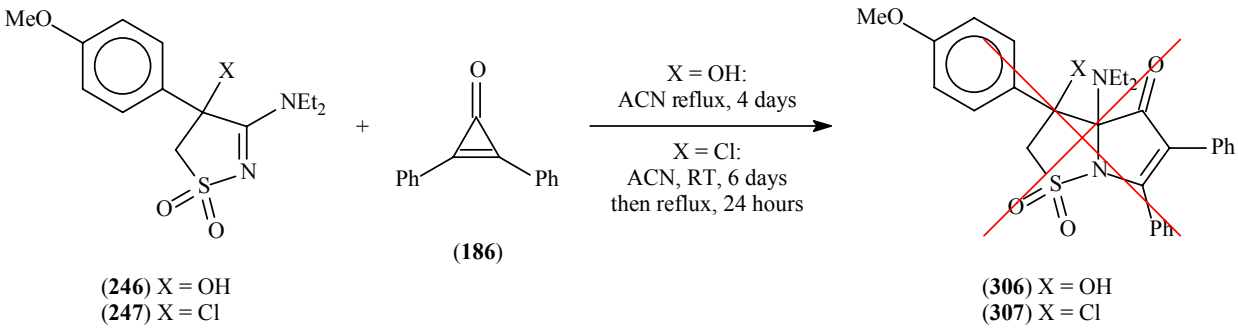


Scheme 2.102

2.6.1 Cycloaddition with diphenylcyclopropenone (DPP)

2.6.1.1 Reactivity of 4,5*H*-isothiazolin-1,1-dioxides

The attempted formal [2+2] cycloadditions of 4-hydroxy-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**246**) and 4-chloro-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**247**) with DPP (**186**) to give the corresponding bicyclic compounds (**306**) and (**307**) were unsuccessful (Scheme 2.103).



(**246**) X = OH
(**247**) X = Cl

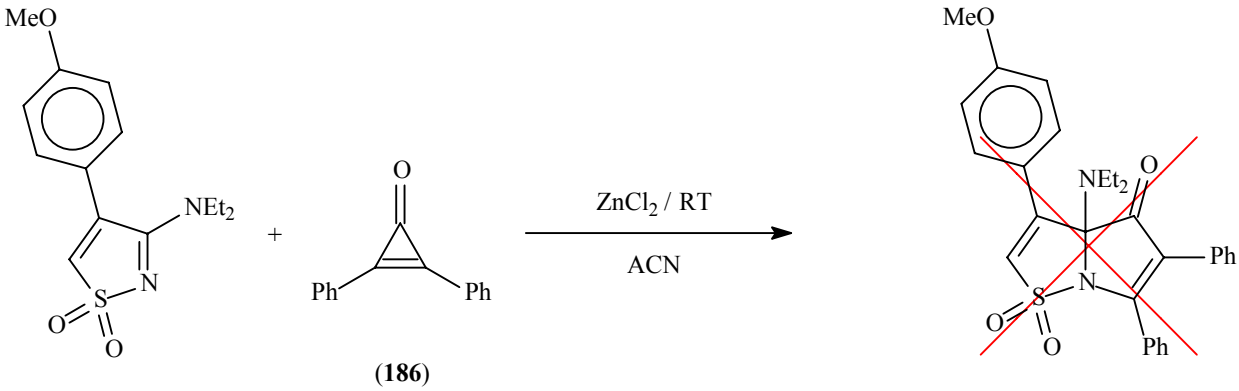
(**186**)

(**306**) X = OH
(**307**) X = Cl

Scheme 2.103

2.6.1.2 Reactivity of isothiazol-1,1-dioxides

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) did not react with DPP to form the cycloadduct (**308**) (Scheme 2.104). The reaction was carried out in acetonitrile at RT and was monitored by TLC. After 50 hours, no sign of reaction could be observed, and a catalytic amount of zinc chloride (8% mol.) was added to the mixture, which was stirred for a further 54 hours, but no formation of any new product could be seen on TLC and the reaction was stopped.



(**248**)

(**186**)

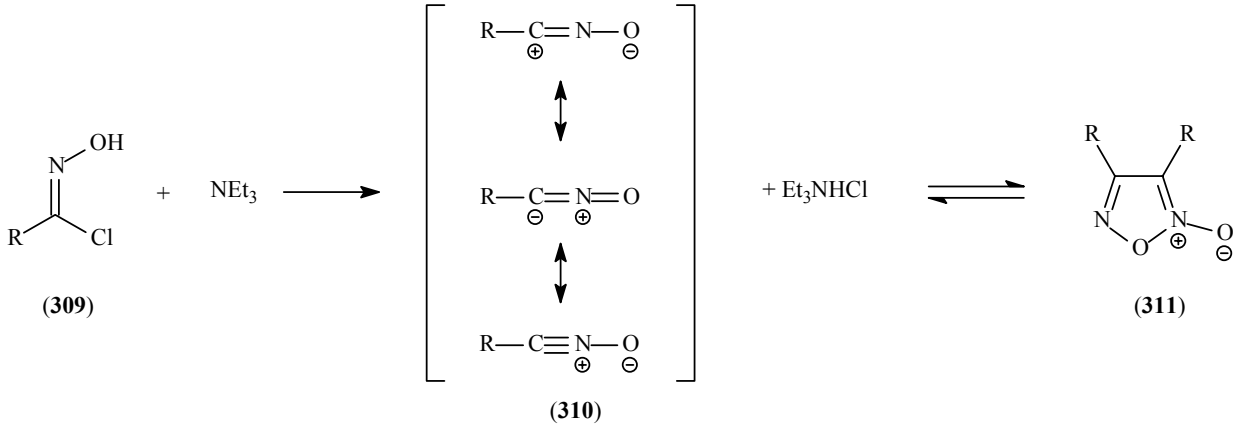
(**308**)

Scheme 2.104

2.6.2 1,3-Dipolar cycloaddition with nitrile oxides

[3+2] Cycloadditions are a useful tool to access a wide range of five-membered heterocyclic compounds by addition of a dipole to a multiple bond.[154,155,242,243]

Nitrile oxides (**310**) are usually generated *in situ* from the corresponding hydroximoyl chlorides (**309**) using triethylamine as a base to perform the dehydrochlorination.[152,153,155] Being highly reactive species, nitrile oxides tend to dimerise in the absence of a dipolarophile to give the corresponding oxadiazole *N*-oxide (**311**) (Scheme 2.105).[152,154] But even in the presence of a dipolarophile, the dimer is still able to form, depending on the reactivity of the dipolarophile relative to that of the nitrile oxide itself. In order to minimise the formation of this dimer, the addition of triethylamine was performed very slowly over several hours using a syringe pump and a dilute ethereal solution.

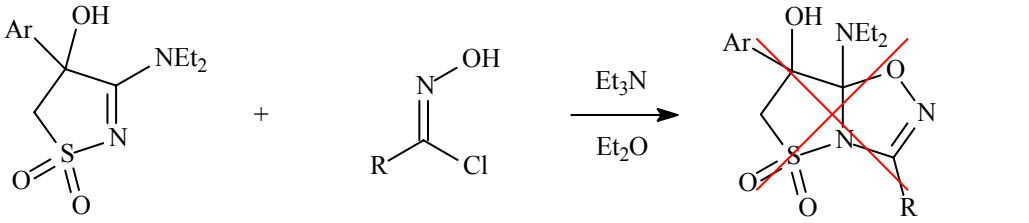


Scheme 2.105

2.6.2.1 Reactivity of 4,5*H*-isothiazolin-1,1-dioxides

2.6.2.1.1 Reactivity of 3-diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

The cycloadditions of 3-diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**246**) with different nitrile oxides generated *in situ* from the corresponding hydroximoyl chlorides (**196**), (**268**) and (**312a-c**) to give the corresponding isothiazolidino-oxazolines (**313a-e**) were all unsuccessful (Scheme 2.106). The only isolated compounds after column chromatography were the starting material and the oxadiazole-*N*-oxides from the dimerisation of the nitrile oxides.



(**246**)
Ar = 4-MeOPh

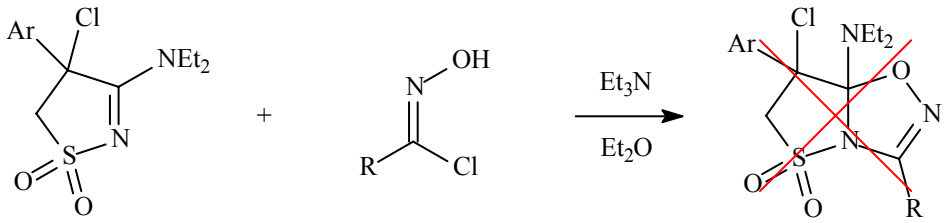
(**196**) R = 2-N_3Ph
(**268**) R = 4-MeOPh
(**312a**) R = EtO_2C
(**312b**) R = Ph
(**312c**) R = 4-O_2NPh

(**313a**) R = 2-N_3Ph
(**313b**) R = 4-MeOPh
(**313c**) R = EtO_2C
(**313d**) R = Ph
(**313e**) R = 4-O_2NPh

Scheme 2.106

2.6.2.1.2 Reactivity of 3-diethylamino-4-chloro-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

The cycloaddition of 3-diethylamino-4-chloro-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**247**) with 2-azidobenzohyroximoyl chloride (**196**) in the presence of triethylamine was attempted, but it was revealed to be unsuccessful and did not afford the corresponding cycloadduct (**314**) (Scheme 2.107). Given the failure of 4-hydroxy-4,5*H*-isothiazolin-1,1-dioxide (**246**) to react with nitrile oxides, no further attempts of 1,3-dipolar cycloaddition of 4-chloro-4,5*H*-isothiazolin-1,1-dioxide (**246**) with nitrile oxides was made.



(**247**)
Ar = 4-MeOPh

(**196**)
R = 2-N_3Ph

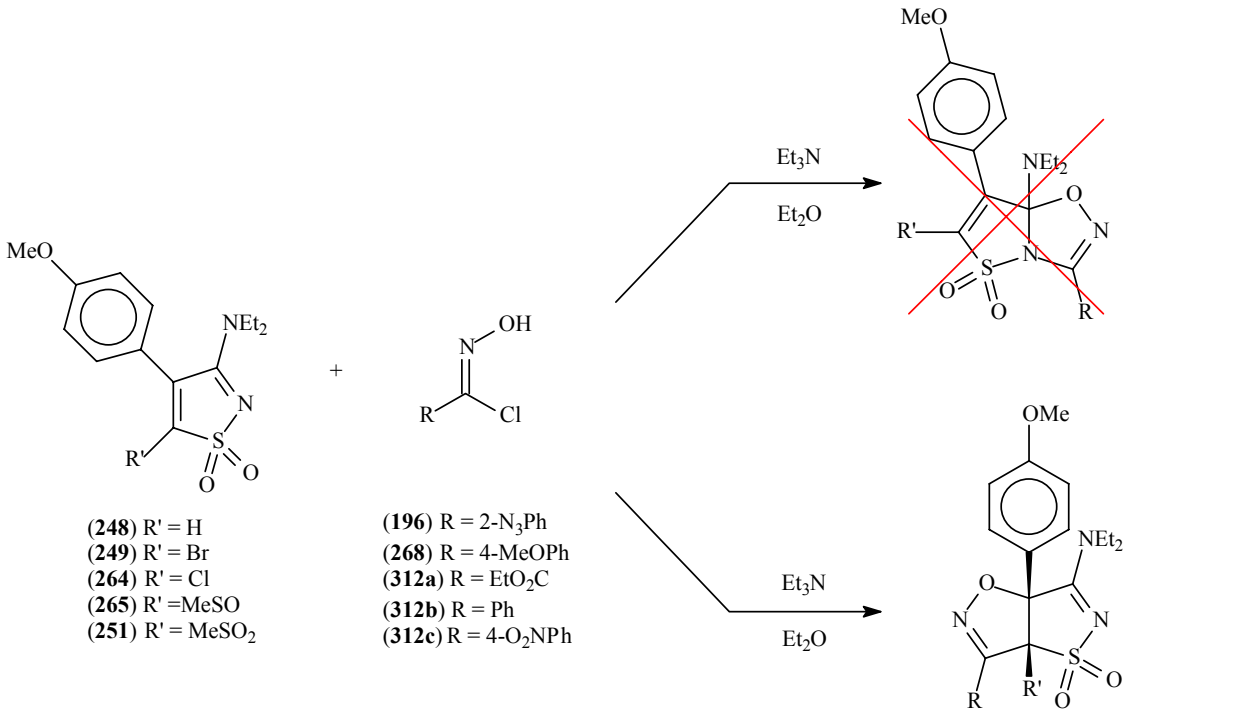
(**314**)
Ar = 4-MeOPh
R = 2-N_3Ph

Scheme 2.107

Given the failure of the corresponding four-membered ring to react, these results are perhaps not surprising.

2.6.2.2 Reactivity of isothiazol-1,1-dioxides

The next set of reactions explored were those of the fully conjugated isothiazole system with compounds (**248**), (**249**), (**251**), (**264**) and (**265**). Instead of occurring on the imine double bond, as described above (Scheme 2.101), the addition of the nitrile oxides occurred, in all cases, on the olefinic double bond to give the corresponding isothiazolino[5,4-*d*]isoxazolin-4,4-dioxides (**315a-i**), hence forming two new stereogenic centres (Scheme 2.108). In all cases, only a single diastereoisomer was formed, *i.e.* the reaction was diastereospecific, typical of the concerted 1,3-dipolar cycloaddition[152,155,242,244-247] . It is interesting to note that there are examples of two-step 1,3-dipolar cycloadditions[248,249] and that there is much lively debate on the mechanism of such reactions.[250-253] It is notable that only a single regioisomer was formed in these reactions. A summary of the results is shown in Table 2.2. The result of these reactions is not a surprise given the failure of the isothiazol-1,1-dioxides (**246**) and (**247**) (which lack the alkene) to react.



(**248**) R' = H
(**249**) R' = Br
(**264**) R' = Cl
(**265**) R' =MeSO
(**251**) R' = $MeSO_2$

(**196**) R = 2-N_3Ph
(**268**) R = 4-MeOPh
(**312a**) R = EtO_2C
(**312b**) R = Ph
(**312c**) R = 4-O_2NPh

(**315a**) R = EtO_2C ; R' = H
(**315b**) R = Ph ; R' = H
(**315c**) R = 2-N_3Ph ; R' = H
(**315d**) R = 4-O_2NPh ; R' = H
(**315e**) R = 4-MeOPh ; R' = H
(**315f**) R = 4-MeOPh ; R' = Cl
(**315g**) R = 4-MeOPh ; R' = Br
(**315h**) R = 4-MeOPh ; R' = MeSO
(**315i**) R = 4-MeOPh ; R' = $MeSO_2$

Scheme 2.108

Determination of structures

The structure of the products was, in each case, assigned on the basis of ^{1}H NMR, ^{13}C NMR, HSQC, HMBC, MS, and IR analysis.

When R'=H (entry 1-5), the proton of the ring junction appeared in the range of 4.97-5.70 ppm as a characteristic singlet on ^{1}H NMR.

With ethyl chlorooximidoacetate (entry 1), the presence of the carbonyl in the product was given by the appearance of an IR absorption at 1742 cm^{-1}. In the ^{1}H NMR spectrum, the appearance of a quartet at 4.42 ppm and a triplet at 1.38 ppm with J=7.1 Hz confirmed the presence of the ethyl group from the ethoxy carbonyl moiety in the molecule. The addition of the nitrile oxide was further confirmed by ^{13}C NMR with the appearance of two quaternary sp^2 carbons at 157.97 and 147.65 ppm for C=O and C=N, respectively, and also the appearance of a CH_2 and a CH_3 at 62.92 and 13.85 ppm, respectively.

In each other case (entry 2-9), the evidence of the cycloaddition was provided by the appearance of the appropriate number of protons in the aromatic region on ^{1}H NMR. Cycloaddition was further confirmed by the appearance, on ^{13}C NMR, of the new C=N bond carbon in the range of 151.00-155.44 ppm, and the appearance of the appropriate number of additional aromatic CH and quaternary carbons.

The HMBC analysis was in accordance with the expected regioselectivity of the cycloaddition on the olefinic double bond. However, it is noteworthy to highlight that the expected coupling between the proton and the quaternary sp^3 carbon at the ring junction was missing for compounds (**315a-c**) (appendix VI for (**315c**)) and (**315e**) (entry 1-3 and 5), and that only a weak coupling was observed for coumpound (**315d**) (entry 4, appendix IX). The lack of this coupling had thrown a slight suspicion on the exact identification of the isomer isolated, but the crystal structures of compounds (**315a**) and (**315c**) did confirm the formation of the proposed structures, confirming the regioselectivity of the cycloaddition suggested by HMBC analysis.

The structure of each product was further confirmed by HRMS analysis with a consistent accurate mass for each compound when compared to the proposed structures.

Entry	Isothiazol-1,1-dioxides (R')	Hydroximoyl chlorides (R)	Product	Yield (%)	Comment
1	H	EtO_2C	**315a**	86	single diastereoisomer

2	H	Ph	**315b**	71	single diastereoisomer
3	H	2-N_3-Ph	**315c**	28	single diastereoisomer
4	H	4-O_2N-Ph	**315d**	28	single diastereoisomer
5	H	4-MeO-Ph	**315e**	71	single diastereoisomer
6	Cl	4-MeO-Ph	**315f**	56	single diastereoisomer
7	Br	4-MeO-Ph	**315g**	54	single diastereoisomer
8	MeSO	4-MeO-Ph	**315h**	34	mixture of diastereoisomers
9	$MeSO_2$	4-MeO-Ph	**315i**	68	single diastereoisomer
10	MeS	4-MeO-Ph	**315j**	no reaction	-

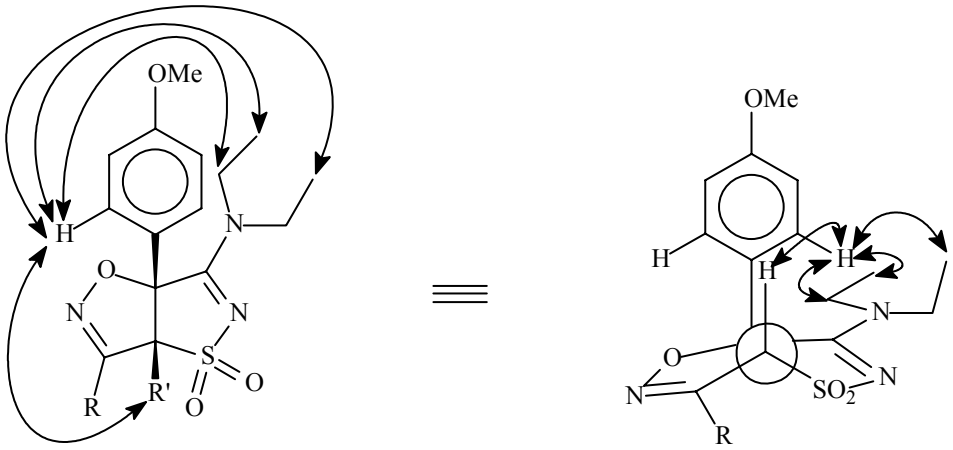
Table 2.2 Yields of the cycloaddition of nitrile oxides on isothiazol-1,1dioxides

It is interesting to note that no reaction occurred with 5-methanesulfanyl-isothiazol-1,1-dioxide (R' = MeS, entry10), indicating a dramatic change of reactivity of the fully conjugated system when the substituent at the 5-position is electron-donating compared to electron-withdrawing substituents (entry 6-9).

Determination of the *syn*-stereochemistry at the ring junction

The *syn*-stereochemistry of the ring junction of compounds (**315a**) and (**315c**) was clearly and undoubtedly established by 1D and 2D nOe experiments. The NOESY spectra showed a correlation between the hydrogen at the ring junction and the aromatic proton in the *meta* position relative to the methoxy group of the aryl group attached to the ring junction (Figure 2.4). This correlation is possible only if the hydrogen and the aromatic ring are in a *syn* configuration, which is consistent with the concerted mechanism of the cycloaddition of nitrile oxides on double bonds. The crystal structures of compounds (**315a**) and (**315c**) further confirmed, once again, the *syn* configuration of the aryl group and the hydrogen at the ring junction. It was therefore assumed by correlation that the stereochemistry of the ring junction should be *syn* for the other products.

The NOESY spectrum also showed correlations between the two aromatic hydrogens closer to the ring junction with one CH_2 and the two CH_3s of the diethylamino group, indicating the close relationship in space between those hydrogens.



(**315a**) R = EtO_2C; R' = H
(**315c**) R = 2-N_3Ph; R' = H

Figure 2.4 NOE correlations for compounds (**315a**) and (**315c**)

This assumption about the *syn* configuration at the ring junction was further suggested by unexpected stereoelectronic effects observed on the ^{1}H NMR spectrum for the aromatic protons of the aryl group on the ring junction of compounds (**315f-i**). Those effects would not be observed if the aryl group and the R' group at the ring junction were in an *anti* configuration. This is explained below.

For compounds (**315f**, R'=Cl) and (**315g**, R'=Br), the AB system of the two pairs of aromatic protons of the aryl group was expected to give two doublets. Instead, the four protons appeared, on ^{1}H NMR, as broad singlets (appendix X and XI) with significantly different chemical shifts (δ), indicating they are in a very different electronic environment. Unfortunately the broadening, flattening and coalescence of the signals did not allow a proper observation of this discrimination.

For compound (**315h**, R'=MeSO) isolated as a mixture of diastereoisomers, the AB system of the two pairs of aromatic protons of the aryl group appeared as four multiplets, which, in fact, looked like broad unresolved doublets (appendix XII and XIII). The broadening and coalescence of the signals was stronger for one stereoisomer compared to the other one. Once again, this indicated those four protons are in a different electronic environment, suggesting a restricted rotation of the aromatic ring at the ring junction.

For compound (**315i**, R'=$MeSO_2$), the broadening of the signals on ^{1}H NMR disappeared but the four aromatic protons gave four dinstinct doublets of doublets (appendix XIV), indicating, once again, a possible restricted rotation of the aromatic ring resulting in a blocked conformation of the ring and a discrimination of the electronic environment for each proton.

It is interesting to note that, for compounds (**315f**, R'=Cl) and (**315g**, R'=Br), two flattened peaks appeared in the ^{13}C NMR spectrum for the two aromatic CH carbons closer to the stereogenic center at the ring junction, whereas no discrimination was observed between the two other aromatic CH carbons, *i.e.* those *ortho* to the methoxy group. For compound (**315h**, R'=MeSO), the two aromatic CH carbons *ortho* to the methoxy group appeared as two peaks at 114.51 and 114.16 ppm for one stereoisomer. For the other stereoisomer, they appeared at 115.02 and 114.35 ppm, and the two CH carbons closer to the ring junction were flattenened. This indicated that the four aromatic CH carbons on the ring junction were discriminated, further suggesting the restriction of the rotation of the aromatic ring. For compound (**315i**, R'=$MeSO_2$), only the two aromatic CH carbons closer to the ring junction were discriminated.

A possible explanation for a restricted rotation of the methoxyphenyl ring, resulting in the discrimination of the aromatic protons, is that of steric hindrance between the aryl group and the substituent R' at the ring junction (Figure 2.5). This steric hindrance could account for the restricted rotation of the aromatic ring by creating a vibrational/switching movement of the ring.

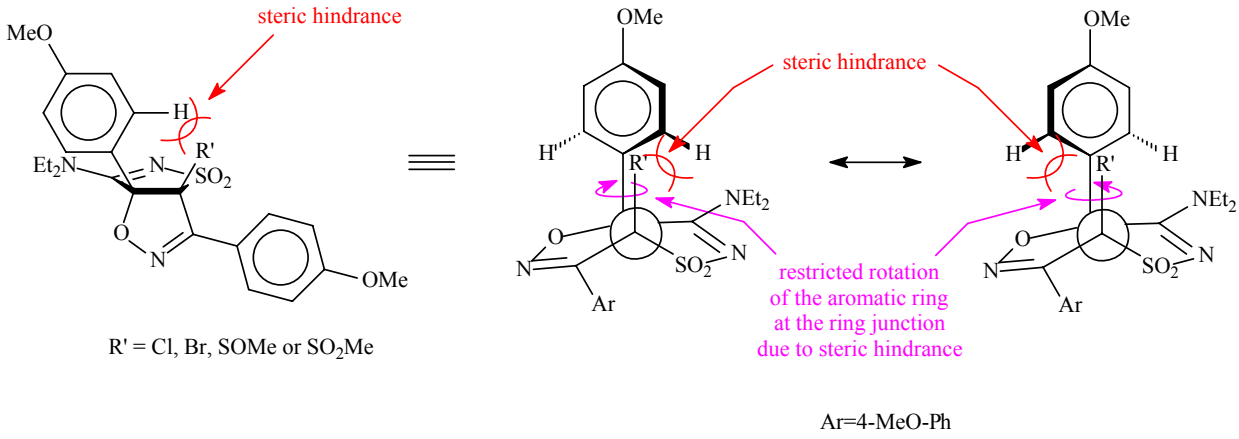


Figure 2.5 Possible restricted rotation of the aryl group at the ring junction

It is interesting to note that the broadening of the signals for these aromatic protons on ^{1}H NMR decreases from R'=halogen to R'=SO_2Me (appendix X, XI, XII, XIII and XIV). This could be explained by the amplitude of this movement. Indeed, moving from the halogens to the methanesulfonyl group, the size of the substituent increases, the amplitude of the movement decreases until the aromatic ring is blocked in a given conformation when R'=SO_2Me (Figure 2.6).

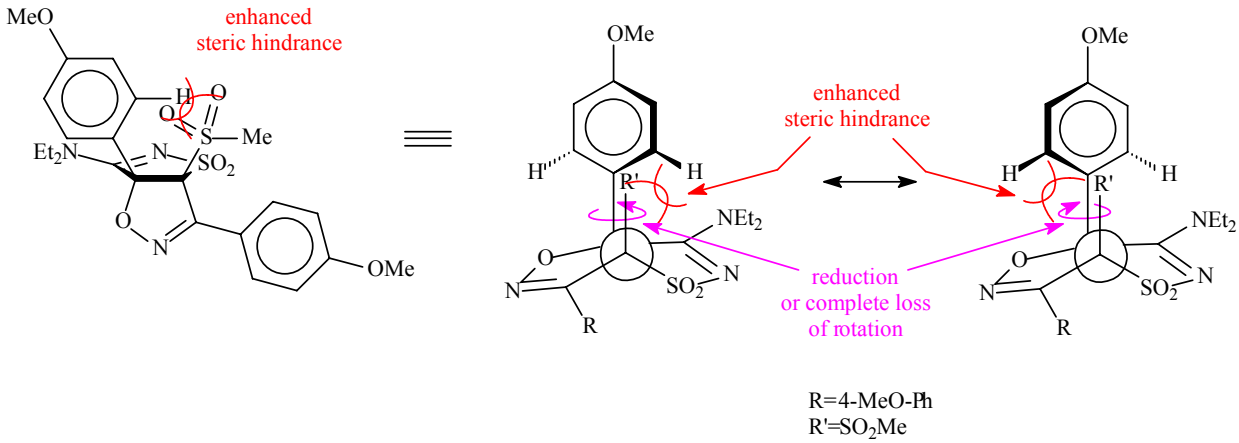


Figure 2.6 Reduction or complete loss of rotation of the aryl group with enhanced steric hindrance

The broadening of signals can be caused by efficient relaxation promoted by the fluctuation of a local magnetic field created by a vibrational movement, which restores the equilibrium Boltzmann population.[254] Hence, the bigger the substituent, the smaller is the amplitude of the rotation, the smaller is the vibrational movement, the more defined and uniform is the electronic environment, the more resolved are the signals. It is then possible to define a scale related to the size of the substituent R' (Figure 2.7). Therefore, in the case of compounds (**315f-g**, R'=halogens), this effect can take place and account for the broadening of the signals, whereas in the case of compounds (**315h**, R'=MeSO) and (**315i**, R'=$MeSO_2$), the aromatic ring is blocked and the vibrational movement cannot take place, resulting in more resolved and sharp signals.

The flattening and broadening of signals could also be caused when the rate constant for the exchange from one environment to another is greater than the frequency difference of the proton resonances in the separate environments.[254] Thus, if the rate of exchange is low, the protons will appear as separate signals, and, if the rate of exchange is fast, they will appear as a single signal. In between, if the rate constant of exchange is comparable to the frequency difference, the protons appear as broadened signals. In the case of compounds (**315f-g**), R'=halogens), it is possible to assume the occurance of this phenomenon, resulting in the broadening of the signals. In the case of compounds (**315h**, R'=MeSO) and (**315i**, R'=$MeSO_2$), there is no change of environment for the protons since the aromatic ring is in a blocked conformation, and the phenomenon cannot take place, resulting in more resolved and sharp signals.

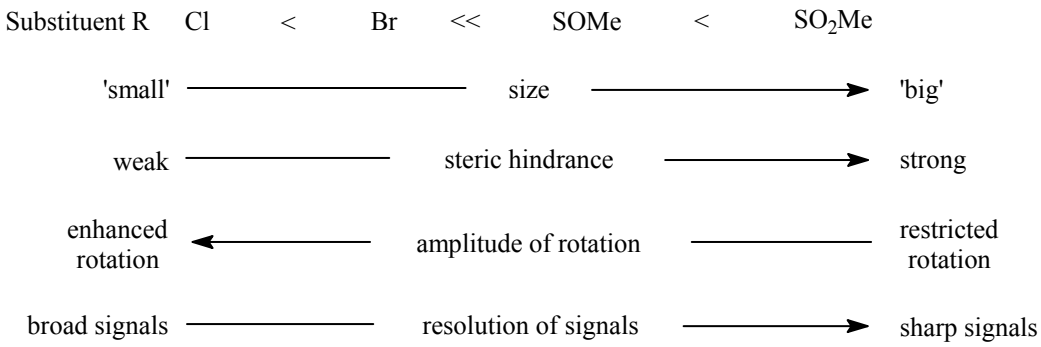


Figure 2.7 Scale relating the size of the substitutent R' to the broadening of signals on ^1H NMR for the aromatic protons

This phenomenon also accounts for the intact AB system observed when R'=H. Indeed, with R'=H, there is complete free rotation of the aromatic ring at the ring junction because there is no steric hindrance at all. Hence, the two aromatic protons in each pair are in the same environment at any time and appear as two doublets as expected. Similarly, it can be argued that the rate of exchange between all the environments during the rotation of the aromatic ring is very fast. Hence the protons appear as a single sharp signal.

In the ^{13}C NMR spectrum of compounds (**315f**) and (**315g**), the phenomena of efficient relaxation and environmental exchange described above could also account for the flattening, broadening and coalescence of some signals. For compounds (**315h**) and (**315i**), the full splitting of the four aromatic CH carbons is due to the blocked conformation of the aromatic ring closer to the ring junction caused by the steric hindrance, resulting in four distinct electronic environment for these aromatic carbons.

Selectivity between the olefinic and the imine double bond

The selectivity between the imine and the olefinic double bonds could be explained by a difference in the influence of the sulfonyl group on each double bond. The cycloaddition of nitrile oxides with alkenes is known to be more efficient with alkenes substituted by both electron-withdrawing and electron-donating groups.[152] The olefinic double bond of the starting materials are either trisubstituted (R'=H) or tetrasubstituted (R'=Br, Cl, SOMe or SO_2Me) by electron-donating or electron-withdrawing groups, a fact that should enhance the reactivity of this double bond.

It is also known that *trans* alkenes are better dipolarophiles than *cis* alkenes towards the addition of nitrile oxides.[152] The sulfonyl group is a more electron-withdrawing group than the Et_2N-C=N group, forming a *trans* substituted 'push-pull' system with the electron-donating 4-methoxyphenyl group (Figure 2.8). This structural feature should also increase the reactivity of the olefinic double bond by creating a favourable electron density on both carbons, which accounts for the regioselectivity of the reaction.

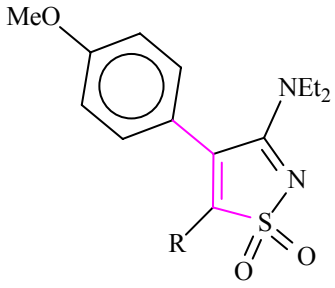
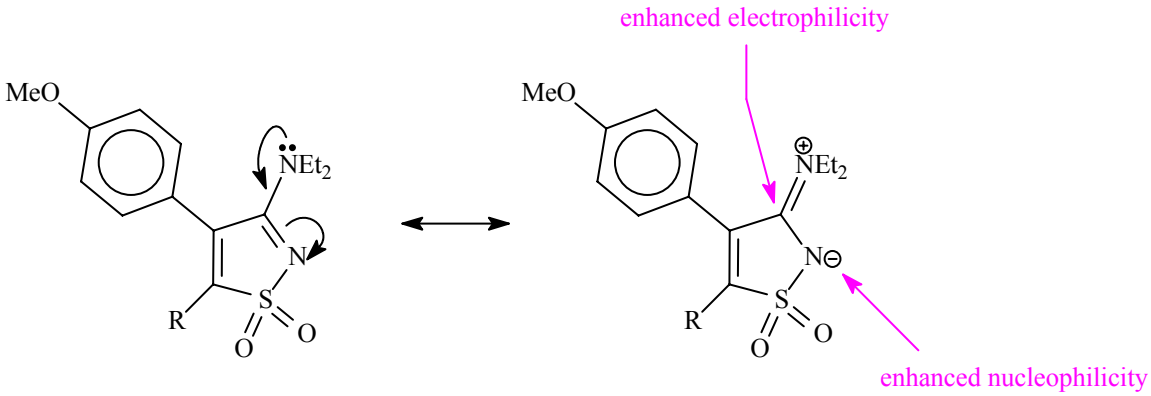


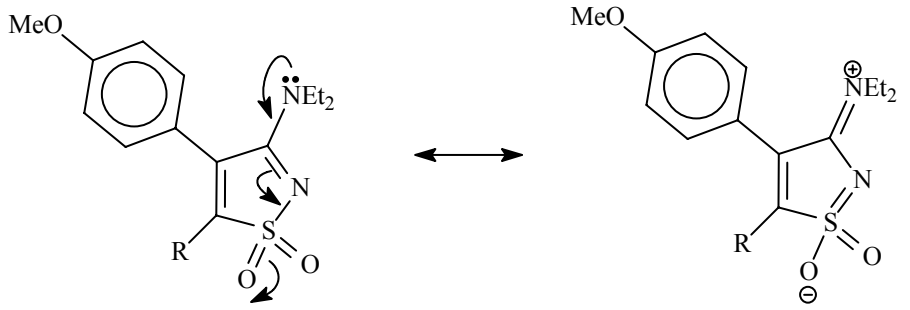
Figure 2.8 *Trans* substituted 'push-pull' system

The cycloaddition of nitrile oxides on the imine double bond should be increased by both the presence of the diethylamino group and the imine nitrogen, by creating a favourable electron density towards the HOMO/LUMO interactions. In other words, the electron-donating diethylamino group should increase both the nucleophilicity of the nitrogen and the electrophilicity of the carbon by the mesomeric effect (Scheme 2.109).



Scheme 2.109

However, the presence of the sulfonyl group attached to the imine nitrogen could lower its nucleophilicity by moderating the electron-donating effect of the diethylamino group, thus reducing its reactivity towards the cycloadditon with nitrile oxides (Scheme 2.110).

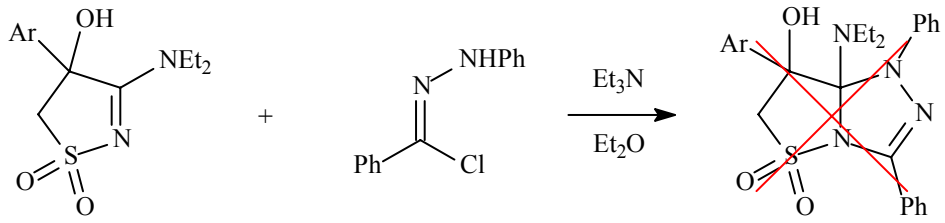


Scheme 2.110

2.6.3 1,3-Dipolar cycloaddition with a nitrile imine

2.6.3.1 Reactivity of 3-diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

The 1,3-dipolar cycloaddition of 4,5*H*-isothiazolin-1,1-dioxide (**246**) with a nitrile imine was attempted. The dipole was generated *in situ* from the corresponding *α*-chlorobenzaldehyde phenylhydrazone (**316**) in the presence of triethylamine to yield the cycloadduct (**317**) (Scheme 2.111). Unfortunately, once again, the dipolar cycloaddition was unsuccessful.



(246)
Ar = 4-MeOPh

(316)

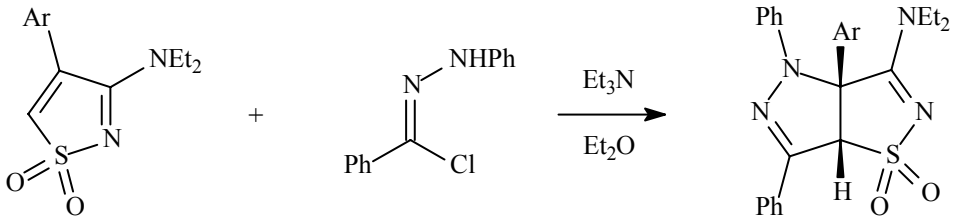
(317)

Scheme 2.111

2.6.3.2 Reactivity of 3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) was reacted with *α*-chlorobenzaldehyde phenylhydrazone (**316**) in the presence of triethylamine to give the

cycloadduct (**318**) in 27% yield (Scheme 2.112). Nitrile imines, as described earlier for nitrile oxides, react with double bonds in a concerted fashion.[154,155]



(**248**)
Ar = 4-MeOPh

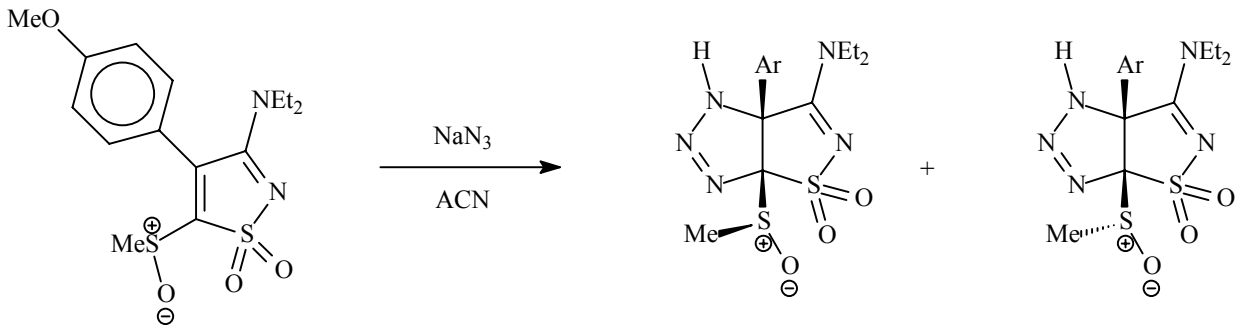
(**316**)

(**318**)
Ar = 4-MeOPh

Scheme 2.112

2.6.4 1,3-Dipolar cycloaddition with sodium azide

The proposed mechanism of the surprising ring contraction of 5-methanesulfonylisothiazol-1,1-dioxide (**251**) to afford the 3-diethylamino-1,2-thiazetine (**252**) previously described involves the loss of methanesulfinate as a leaving group (Scheme 2.80 and 2.81, section 2.3.4.13). Thus, by changing the substituent in the 5-position of the isothiazole from methanesulfonyl to methanesulfinyl, *i.e.* by putting a worse leaving group at this position, we wanted to see if the isothiazole ring would follow the same path. The reaction was carried out, the methanesulfinyl substituent did not act as a leaving group and the reaction of 5-methanesulfinylisothiazol-1,1-dioxide (**265**) with sodium azide in acetonitrile afforded the bicyclic adducts **319** and **319'** as a mixture of diastereoisomers in 22 and 27% yield, respectively (Scheme 2.113), which further confirmed the mechanism of the ring contraction, as discussed before (Scheme 2.81).



(**265**) (**319**) Ar = 4-MeOPh (**319'**) Ar = 4-MeOPh

Scheme 2.113

2.6.5 Conclusion

In the light of the results obtained with isothiazol-1,1-dioxides (**248**), (**249**), (**264**), (**265**) and (**251**), it may be concluded that the effect of the sulfonyl group is to activate the olefinic double bond and deactivate the imine double bond, a fact which is consistent with the difference of reactivity observed between 1-azetines and 1,2-thiazetin-1,1-dioxides discussed earlier in this thesis.

Moreover, the fact that 4,5*H*-isothiazolin-1,1-dioxides (**246**) and (**247**) did not react with 1,3-dipoles, nor with diphenylcyclopropenone further supports the lack of reactivity of the sulfonimine moiety.

Conclusion

Some 1-azetines have been synthesised and reacted successfully with diphenylcyclopropenone and nitrile oxides to afford the corresponding bicyclic compounds. The thermolysis of the strained cycloadducts (or their reaction with dimethylacetylene dicarboxylate where appropriate) released the strain of the four-membered ring to afford five- and six-membered heterocycles such as 1,2,4-oxadiazoles, a pyridine, and a pyrimidine.

In the same fashion, one example of 3,4-dihydro-2*H*-pyrrole was synthesised and reacted with diphenylcyclopropenone to open a new route to pyrrolizidines, a five-fused heterocycle present in a wide range of alkaloids.

1,2-Thiazetin-1,1-dioxides, the sulfonyl analogues of 1-azetines, were also synthesised *via* the alkylation of 3-oxo-*β*-sultams and *via* the ring contraction of an isothiazol-1,1-dioxide. Unfortunately, they failed to react with DPP, nitrile oxides or dienes. The introduction of the sulfonyl group in the four-membered ring changed dramatically the reactivity of the double bond, thus impeding the access to bicyclic *β*-sultams through a new route. The presence of the sulfonyl group also affected the reactivity of the carbonyl in 3-oxo-*β*-sultams since the thionation of those molecules remained unsuccessful whereas that of 1-azetines was smoothly performed. However, 3-diethylamino-1,2-thiazetin-1,1-dioxide reacted with a Lewis acid, zinc chloride, to undergo a ring enlargement yielding a 1,2,3-oxathiazolin-2-oxide.

A series of isothiazol-1,1-dioxides was synthesised. Their olefinic double bond reacted diastereospecifically with nitrile oxides, a nitrile imine and an azide to give the corresponding bicycles, thus forming two new stereogenic centres. Two isothiazolin-1,1-dioxides lacking the olefinic double bond failed to react with DPP and 1,3-dipoles, thus confirming the lack of reactivity of the sulfonimine moiety observed with 1,2-thiazetin-1,1-dioxides.

Unsubstituted and *N*-acylated *β*- and *γ*-sultams were synthesised and assessed as taurine pro-drugs in laboratory Alzheimer and alcohol detoxification models.

Future work

First, the synthesis of 3-thioxo-*β*-sultams *via* the [2+2] cycloaddition of sulfenes with isothiocyanates can be further investigated, *e.g.* the generation of sulfene at lower temperatures. The [2+2] cycloaddition of thioketenes with *N*-sulfonylamines has not been explored and could

offer another route to access those molecules. Their subsequent alkylation would also need to be studied to attempt the synthesis of 3-alkylthio-1,2-thiazetin-1,1-dioxides.

Second, the 1,3-dipolar cycloaddition step requires further investigation such as the attempt to use other dipoles or other reaction conditions.

Finally, the access to other pyrrolizidines also requires further examination such as the use of other cyclopropenones and the functionalisation of the subsequent cycloadduct in order to target natural products. This latter aspect is currently being investigated in the laboratory.

CHAPTER 3

Experimental

General information

Unless otherwise stated or unnecessary, all reactions were conducted using oven-dried glassware under nitrogen dried through 4 Å molecular sieves and delivered through a gas manifold. Work-up procedures were carried out in air. All solvents were purchased from Fisher Chemicals and were of analytical grade.

Anhydrous grade solvents were freshly distilled using a continuous still under nitrogen. Acetone was dried overnight over 3 Å molecular sieves (10% w/v), and then distilled over freshly activated 3 Å molecular sieves over 3-4 h. Chloroform was dried over 4 Å molecular sieves or distilled over phosphorus pentoxide (3% w/v). Dichloromethane, ethyl acetate and toluene were distilled over calcium hydride (5% w/v) over 4-6 h. Diethyl ether and THF were pre-dried over sodium wires, and then distilled over sodium wires (1-2% w/v) with benzophenone (0.2-0.3% w/v) as an indicator. Absolute ethanol was dried over magnesium turning (5 g/L) and iodine (0.5 g/L) over 6 h. Any other anhydrous solvents were purchased from Acros or Sigma-Aldrich.

All reactions were monitored by TLC, which was carried out on 0.20 mm Macherey-Nagel Alugram® Sil G/UV_{254} silica gel-60 F_{254} precoated aluminium plates and visualisation was achieved using UV light and / or vanillin stain. Column chromatographies were performed on Merck silica gel (0.063-0.200 mm, 60 Å).

The NMR spectra were recorded on a Bruker DPX-400 instrument or on a Bruker Avance 500.

IR spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils, a drop for liquids or neat for solids.

Mass spectra were recorded on a Bruker Daltonics micrOTOF mass spectrometer operating at a positive ion mode under an electrospray ionisation (ESI +) method. High resolution mass spectra were recorded on a Finnegan MAT 900 XTL instrument operated by the EPSRC National Mass Spectrometry service at the University of Swansea.

Melting points were recorded on a Gallenkamp apparatus.

Crystallographic data were recorded on a Bruker Apex Duo instrument at the University of Huddersfield or at the EPSRC centre for crystallography at the University of Southampton.

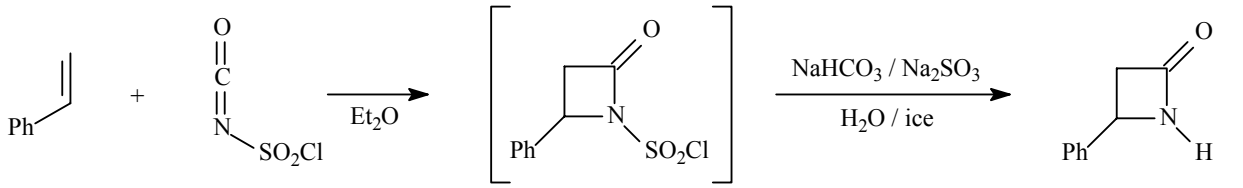
3 Experimental

3.1 Synthesis and reactivity of 1-azetines and 3,4-dihydro-2*H*-pyrrole

3.1.1 Synthesis of 1-azetines

3.1.1.1 Synthesis of 2-ethylthio-4-phenyl-1-azetine

3.1.1.1.1 Synthesis of 4-phenylazetidin-2-one



styrene — *N*-chlorosulfonyl isocyanate — (**178**) C_9H_9NO, MW = 147.17 g/mol

To styrene (3.7 mL, 3.32 g, 31.9 mmol) in dry ether (15 mL) was added, dropwise under an inert atmosphere, *N*-chlorosulfonyl isocyanate (CSI) (3.2 mL, 5.24 g, 37.0 mmol, 1.2 eq.) over 10 minutes. The mixture was stirred gently at room temperature for 1 h 40 min. The solvent was then removed *in vacuo* to give an oily residue, which was redissolved in ether (20 mL) and added over 10 minutes to a vigorously stirred solution of water (30 mL), sodium carbonate (9 g, 107.1 mmol, 3.3 eq.), sodium sulfite (6 g, 47.6 mmol, 1.5 eq.) and ice (20 g). The solution was stirred for 1 hour and filtered. The organic layer was separated, and the aqueous layer was washed with ether (5 x 20 mL). The combined organic extracts were dried over magnesium sulfate, the solution was filtered and the solvent evaporated under vacuum to yield the product as a white solid (**3.51g, 75%, m.p. = 102-103ºC**).

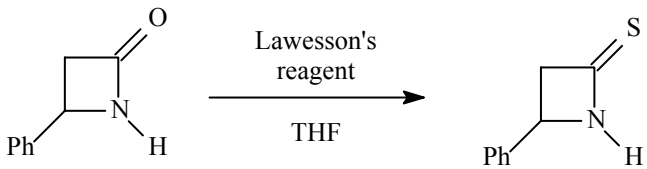
IR υ_{max} (cm^{-1}) 3207 (br, **NH**), 1737 (m), 1705 (s, **C=O**), 1491 (m), 1453 (m), 1404 (m) 1390 (w), 1368 (m), 1282 (w), 1214 (w), 1185 (m), 1171 (m), 1007 (w), 979 (m), 962 (m), 783 (w), 757 (s), 697 (s).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.34 (5H, m, **Ph**), 6.97 (1H, bs, **NH**), 4.67 (1H, dd, *J*=5.2 and 2.3 Hz, **CH**), 3.38 (1H, ddd, *J*=14.8, 5.2 and 2.3 Hz, **CH_2**), 2.80 (1H, dd, *J*=14.8 and 2.3 Hz, **CH_2**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 168.48 (**C=O**), 140.13 (**C** (Ph)), 128.44 (**CH** (Ph)), 127.93 (**CH** (Ph)), 125.47 (**CH** (Ph)), 50.15 (**CH**), 47.60 (**CH_2**)

MS (*m/z*): 170 $[M+Na]^+$, 317 $[2M + Na]^+$.

3.1.1.1.2 Synthesis of 4-phenylazetidin-2-thione



(**178**) (**179**)
C_9H_9NS
MW = 163.23 g/mol

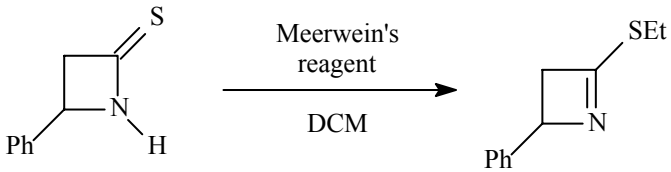
To 4-phenylazetidin-2-one (**178**) (1.07 g, 7.3 mmol) in dry THF (15 mL) was added Lawesson's reagent (1.54 g, 3.8 mmol, 0.5 eq.), and the whole was stirred under an inert atmosphere at room temperature for 1 h and at ~60ºC for 20 minutes. The solvent was removed by rotary evaporation to yield the crude product as an orange oil (3.30g). It was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 3/1, Rf = 0.24) to yield a slight brown / white solid (**0.73 g, 61%, m.p. = 117-118ºC**).

IR υ_{max} (cm^{-1}) 3136 (br, **NH**), 1486 (s, **C=S**), 1450 (s), 1403 (m), 1359 (m), 1263 (w), 1236 (s), 1176 (m), 1146 (m), 1068 (w), 980 (m), 963 (s), 756 (s), 694 (s).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 8.28 (1H, bs, **NH**), 7.38 (5H, m, **Ph**), 5.18 (1H, dd, *J*=4.6 and 1.8 Hz, **CH**), 3.51 (1H, ddd, *J*=15.5, 4.6 and 2.1 Hz, **CH_2**), 3.02 (1H, dd, *J*=15.5 and 1.8 Hz, **CH_2**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 204.42 (**C=S**), 138.03 (**C** (Ph)), 129.03 (**CH** (Ph)), 128.82 (**CH (**Ph)), 125.77 (**CH** (Ph)), 58.89 (**CH**), 51.26 (**CH_2**).

3.1.1.1.3 Synthesis of 2-ethylthio-4-phenyl-1-azetine



(**179**) (**180**)
$C_{11}H_{13}NS$
MW = 191.29 g/mol

To 4-phenylazetidin-2-thione (**179**) (580 mg, 3.56 mmol) was added Meerwein's reagent (1M solution in DCM, 5 mL, 5 mmol, 1.4 eq.) under an inert atmosphere. The whole was stirred at room temperature for 1 h, and then at reflux for 1 h. The solution was then added dropwise to a 50% solution of potassium carbonate (5 mL) at -10ºC. The solution was then filtered through Celite® and the organic layer was separated. The aqueous layer was washed with dichloromethane (2 x 10 mL), and the combined organic extracts were dried over magnesium sulphate. Filtration and concentration *in vacuo* gave the crude product as a dark orange oil. Purification by gravity silica chromatography (PE 40-60ºc / EtOAc : 5/1, Rf = 0.14) yielded the product as a yellow oil (**160 mg, 23%**).

IR υ_{max} (cm^{-1}) 3059 (w), 3030 (w), 2968 (w), 2926 (w), 1655 (m, **C=N**), 1554 (m), 1514 (m), 1493, (m), 1450 (m), 1374 (m), 1325 (m), 1264 (m), 1029 (m), 972 (m), 755 (m), 697 (s).

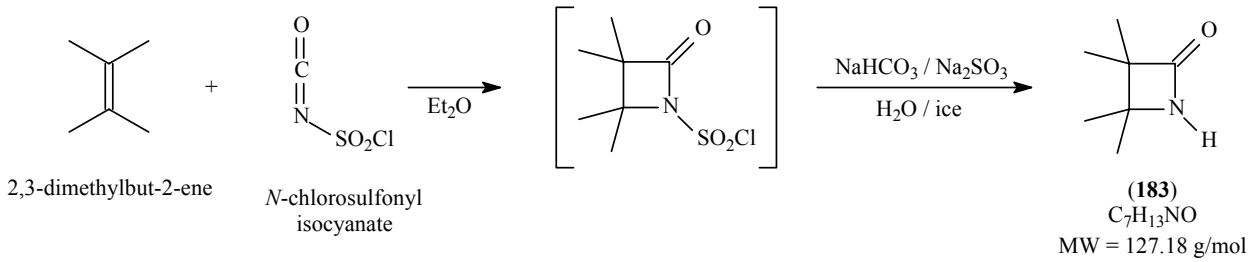
^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.30 (5H, m, **Ph**), 5.02 (1H, dd, *J*=4.3 and 2.0 Hz, **CH**), 3.56 (1H, dd, *J*=14.6 and 4.3 Hz, $\mathbf{CH_2}$), 3.06 (1H, q, *J*=7.4 Hz, S$\mathbf{CH_2}$$CH_3$), 3.06 (1H, q, *J*=7.4 Hz, S$\mathbf{CH_2}$$CH_3$), 2.96 (1H, dd, *J*=14.6 and 2.0 Hz, $\mathbf{CH_2}$), 1.40 (3H, t, *J*=7.4 Hz, $SCH_2\mathbf{CH_3}$).

^{13}C NMR δ (400 MHz, $CDCl_3$) 183.56 (EtS-**C**=N), 140.82 (**C** (Ph)), 128.37 (**CH** (Ph)), 127.34 (**CH** (Ph)), 125.96 (**CH** (Ph)), 65.10 (**CH**), 43.57 ($\mathbf{CH_2}$), 23.36 (S$\mathbf{CH_2}$$CH_3$), 14.65 ($SCH_2\mathbf{CH_3}$).

MS (*m/z*): 192.1 ($[M+H]^+$), 383.2 ($[M_2+H]^+$), 574.2 ($[M_3+H]^+$), 765.3 ($[M_4+H]^+$), 956.4 ($[M_5+H]^+$).

3.1.1.2 Synthesis of 2-thioethyl-3,3,4,4-tetramethyl-1-azetine

3.1.1.2.1 Synthesis of 3,3,4,4-tetramethylazetidin-2-one



2,3-dimethylbut-2-ene

N-chlorosulfonyl isocyanate

(**183**)
$C_7H_{13}NO$
MW = 127.18 g/mol

To 2,3-dimethylbut-2-ene (3.8 mL, 2.68 g, 31.9 mmol) in dry ether (15 mL) was added, dropwise over 10-15 minutes under an inert atmosphere, *N*-chlorosulfonyl isocyanate (CSI) (3.3 mL, 5.24 g, 37.0 mmol, 1.2 eq.). The mixture was stirred gently at room temperature for 2 h. The solvent was removed *in vacuo* to give a pale yellow solid. It was redissolved in diethyl ether (20 mL) and added, dropwise over 15 minutes, to a vigorously stirred solution of water (30 mL), sodium carbonate (9.0 g, 107.1 mmol, 3.3 eq.), sodium sulfite (6.0 g, 47.6 mmol, 1.5 eq.) and ice (20 g). The solution was stirred for 1 h and filtered. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (4 x 25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* yielded the product as a white solid (**3.04 g, 75%, m.p. = 102-104ºC**).

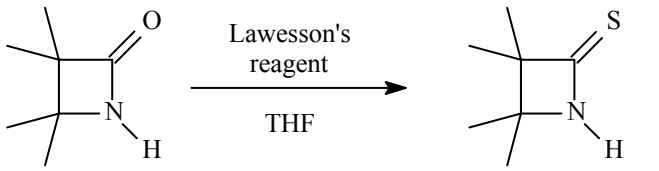
IR υ_{max} (cm^{-1}) 3187 (br, **NH**), 2982 (w), 1747 (m), 1704 (s, **C=O**), 1449 (w), 1396 (m), 1377 (m), 1311 (m), 1252 (w), 1200 (w), 1144 (s), 1126 (m), 957 (m), 783 (m), 745 (s), 718 (s), 674 (m), 586 (s).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 6.00 (1H, bs, **NH**), 1.32 (6H, s, 2 x **CH_3**), 1.21 (6H, s, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 174.91 (**C=O**), 58.18 (**C**), 54.54 (**C**), 24.40 (**CH_3**), 19.06 (**CH_3**).

MS (*m/z*) 150.1 $[M+Na]^+$, 255.2 $[M_2+H]^+$, 277.2 $[M_2+Na]^+$.

3.1.1.2.2 Synthesis of 3,3,4,4-tetramethylazetidin-2-thione



(**183**) (**184**)
$C_7H_{13}NS$
MW = 143.24 g/mol

To 3,3,4,4-tetramethylazetidin-2-one (**183**) (1.93 g, 15.2 mmol) in dry THF (31 mL) was added Lawesson's reagent (3.19 g, 7.9 mmol, 0.5 eq.) and the whole was stirred under an inert atmosphere at room temperature for 1 h, and then at ~60ºC for 20 minutes. The solvent was removed *in vacuo* and the crude product (6.20 g) was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 3/1, Rf = 0.34) to yield the product as a white solid (**2.06 g, 95%, m.p. = 122-124ºC**).

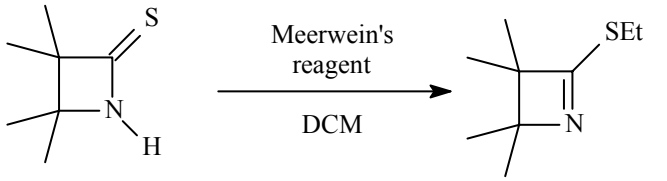
IR υ_{max} (cm^{-1}) 3116 (br, **NH**), 2988 (w), 1494 (s, **C=S**), 1455 (m), 1392 (w) 1369 (m), 1311 (w), 1261 (w), 1210 (w),1131 (s), 1066 (s), 976 (w), 949 (m), 838 (w), 716 (s).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 8.21 (1H, bs, **NH**), 1.39 (6H, s, 2 x **CH_3**), 1.23 (6H, s, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 212.29 (**C=S**), 68.57 (**C**), 56.84 (**C**), 23.54 (**CH_3**), 20.90 (**CH_3**).

MS (*m/z*) 144.1 $[M+H]^+$, 166.1 $[M+Na]^+$, 309.1 $[M_2+Na]^+$.

3.1.1.2.3 Synthesis of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine



(**184**) (**185**)
$C_9H_{17}NS$
MW = 171.30 g/mol

To 3,3,4,4-tetramethylazetidin-2-thione (**184**) (380 mg, 2.65 mmol) was added Meerwein's reagent (1M solution in DCM, 7.96 mL, 7.96 mmol, 3 eq.) under an inert atmosphere. The whole was stirred at room temperature for 2 h, and then at reflux for 2 h. The solution was then added dropwise to a 50% solution of potassium carbonate (4 mL) at -10ºC. The solution was filtered through Celite® and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 5mL) and the combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product as an orange oil (300 mg). It was purified by silica gravity chromatography (PE 40-60ºC / EtOAc : 5/1, Rf = 0.16) to yield the product as a pale yellow oil (**140 mg, 31%**).

IR υ_{max} (cm^{-1}) 2984 (m), 2958 (m), 2921 (m), 1532 (s, **C=N**), 1447 (m), 1369 (m), 1265 (w), 1224 (w), 1134 (s), 1050 (m), 1033 (s), 956 (s), 948 (s), 829 (w).

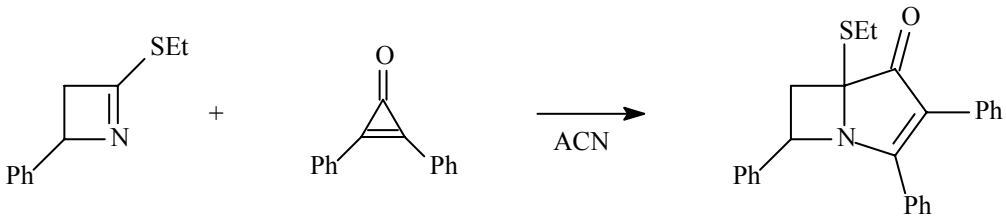
^{1}H NMR: δ (500 MHz, $CDCl_3$) 2.96 (2H, q, *J*=7.4 Hz, S**CH$_2$**CH_3), 1.33 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**), 1.25 (6H, s, 2 x **CH$_3$**), 1.12 (6H, s, 2 x **CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 186.98 (**C=N**), 69.88 (**C**), 51.28 (**C**), 23.83 (**CH$_3$**), 21.78 (S**CH$_2$**CH_3), 20.63 (**CH$_3$**), 14.52 (SCH_2**CH$_3$**).

MS (*m/z*) 172.1 $[M+H]^+$, 194.1 $[M+Na]^+$, 365.2 $[M_2+Na]^+$.

3.1.1.3 Reactivity of 2-ethylthio-4-phenyl-1-azetine

3.1.1.3.1 Reaction with diphenylcyclopropenone (DPP): synthesis of 5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one



(**180**) (**186**) (**187**)

$C_{26}H_{23}NOS$

MW = 397.53 g/mol

To 4-phenyl-2-ethylthio-1-azetine (**180**) (30 mg, 0.16 mmol) in dry acetonitrile (4 mL) was added diphenylcyclopropenone (DPP) (32 mg, 0.16 mmol, 1 eq.) in one portion. The solution was stirred at room temperature under an inert atmosphere overnight. The solvent was evaporated *in vacuo* and the crude product (310 mg) was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 4/1, Rf = 0.21) to yield the product as a mixture of diastereoisomers in a 1.6/1 ratio as a yellow oil (**40 mg, 64%**).

IR υ_{max} (cm^{-1}) 3068 (w), 3035 (w), 2964 (w), 2926 (w), 1675 (s, **C=O**), 1600 (m), 1581 (m), 1558 (m), 1507 (m), 1496 (m), 1448 (m), 1373 (m), 1311 (w), 1241 (m), 1180 (w), 1156 (m), 1106 (w), 1073 (m), 1026 (m), 971 (w), 912 (w), 755 (m), 693 (s), 669 (s), 647 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.61-6-81 (15H, m, 3x**Ph**), 5.57 (1H, t, *J*=8.2 Hz, Ph-**CH**-CH_2), 4.25 (1H, dd, *J*=5.5 and 9.6 Hz, Ph-**CH**-CH_2,), 3.16 (1H, dd, *J*=9.6 and 12.6 Hz, Ph-CH-**CH_2**), 3.00 (1H, dd, *J*=8.2 and 13.1 Hz Ph-CH-**CH_2**), 2.93 (1H, dd, *J*=8.2 and 13.1 Hz, Ph-CH-**CH_2**), 2.66 (2H, dq, *J*=7.4 and 12.2 Hz, S-**CH_2**-CH_3), 2.60 (1H, dq, *J*=7.4 and 12.2 Hz, S-**CH_2**-CH_3), 2.54 (1H, dq, *J*=7.4 and 12.2 Hz, S-**CH_2**-CH_3), 2.48 (1H, dd, *J*=5.5 and 12.6 Hz, Ph-CH-**CH_2**), 1.24 (3H, t, *J*=7.4 Hz, S-CH_2-**CH_3**), 1.23 (3H, t, *J*=7.4 Hz, S-CH_2-**CH_3**).

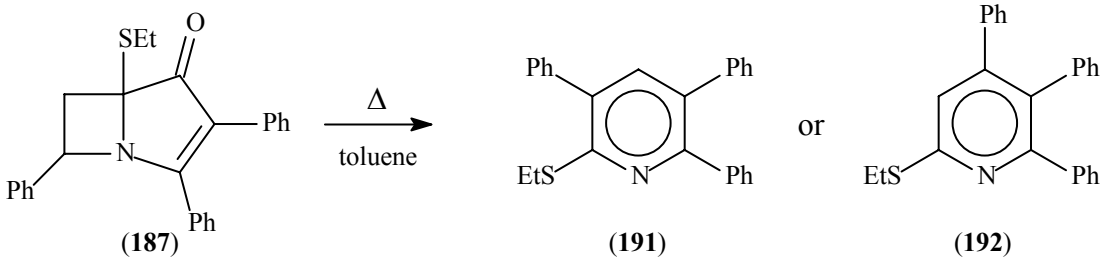
^{13}C NMR δ (500 MHz, $CDCl_3$) 202.69 (**C=O**), 202.29 (**C=O**), 176.83 (**C**=C-C=O), 174.66 (**C**=C-C=O), 141.20 (**C** (Ar)), 135.05 (**C** (Ar)), 131.88 (**C** (Ar)), 131.75 (**CH** (Ar)), 131.03 (**C** (Ar)), 130.95 (**C** (Ar)), 130.38 (**CH** (Ar)), 130.04 (**CH** (Ar)), 129.89 (**C** (Ar)), 129.36 (**CH** (Ar)), 128.77 (**CH** (Ar)), 128.72 (**CH** (Ar)), 128.47 (**CH** (Ar)), 128.45 (**CH** (Ar)), 128.37 (**CH** (Ar)), 128.33 (**CH** (Ar)), 128.15 (**CH** (Ar)), 127.79 (**CH** (Ar)), 127.71 (**CH** (Ar)), 127.57 (**CH**

(Ar)), 127.22 (**CH** (Ar)), 126.92 (**CH** (Ar)), 126.88 (**CH** (Ar)), 126.00 (C=**C**-C=O), 125.93 (**CH** (Ar)), 123.66 (C=**C**-C=O), 66.50 (**CH**), 65.85 (**CH**), 35.01 (**CH_2**), 31.74 (**CH_2**), 23.55 (S-**CH_2**-CH_3), 23.44 (S-**CH_2**-CH_3), 14.49 (S-CH_2-**CH_3**), 14.47 (S-CH_2-**CH_3**).

MS (*m/z*): 398.2 $[M+H]^+$, 420.1 $[M+Na]^+$, 817.3 $[M_2+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{26}H_{24}NOS$ calculated 398.1573 measured 398.1569.

3.1.1.3.2 Thermolysis of 5-ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one: synthesis of 2-ethylthio-3,5,6-triphenylpyridine or 2-ethylthio-4,5,6-triphenylpyridine



(**187**)

(**191**)
$C_{25}H_{21}NS$
MW = 367.50 g/mol

(**192**)
$C_{25}H_{21}NS$
MW = 367.50 g/mol

5-Ethylthio-2,3,7-triphenyl-1-azabicyclo[3.2.0]hept-2-en-4-one (**187**) (61 mg, 0.15 mmol) was heated at reflux in toluene under nitrogen until disappearance of the starting material on TLC. The solvent was evaporated under reduced pressure to give the crude product as a yellow oil (61 mg). It was purified by gravity silica chromatography (PE 40-60˚C/EtOAc: 20/1) to give the product as a yellow oil (**11 mg, 20%**).

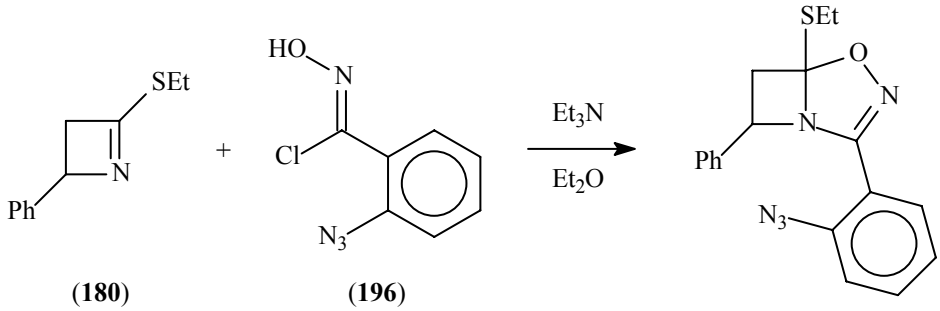
IR υ_{max} (cm^{-1}) 2956 (w), 2924 (m), 2854 (w) , 1716 (w), 1559 (w), 15221 (w), 1492 (w), 1445 (w), 1374 (w), 1260 (m), 1029 (m), 800 (m), 766 (m) , 699 (s), 669 (m).

^{1}H NMR: δ (500 MHz, $CDCl_3$) 7.30 (2H, m, **CH** (Ar)), 7.20-7.18 (7H, m, **CH** (Ar)), 7.07-7.03 (5H, m, **CH** (Ar)), 6.86 (2H, m, **CH** (Ar)), 3.29 (2H, q, *J*=7.3 Hz, **CH_2**), 1.46 (3H, t, *J*=7.3 Hz, **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 157.48 (**C**), 150.03 (**C**), 140.60 (**C**), 139.31 (**C**), 137.24 (**C**), 131.50 (**CH**), 130.26 (**C**), 130.06 (**CH**), 129.19 (**CH**), 127.81 (**CH**), 127.66 (**CH**), 127.41 (**CH**), 127.33 (**CH**), 127.30 (**CH**), 126.44 (**CH**), 121.56 (**CH**), 24.47 (**CH_2**), 14.91 (**CH_3**).

HRMS (*m/z*) $[M+H]^+$ for $C_{25}H_{21}NS$ calculated 367.1389 measured 367.1385.

3.1.1.3.3 Cycloaddition with 2-azidobenzohydroximoyl chloride: synthesis of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene



(**180**) (**196**)

(**197**)
$C_{18}H_{17}N_5OS$
MW = 351.42 g/mol

To 2-ethylthio-4-phenyl-1-azetine (**180**) (352 mg, 1.84 mmol) and 2-azidobenzohydroximoyl chloride (**196**) (181 mg, 0.92 mmol, 0.5 eq) was added triethylamine (0.15 mL, 112 mg, 1.10 mmol, 0.6 eq.) diluted in diethyl ether (5 mL) over 5 hours at room temperature. The mixture was stirred overnight under an inert atmosphere. The solution was filtered and the solvent was removed *in vacuo* to give the crude product as an orange oil (400 mg). It was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 9/1) to give the product as a single diastereoisomer as a yellow oil (**206 mg, 63%**).

IR υ_{max} (cm^{-1}) 2928 (w), 2114 (s, **N_3**), 1683 (m, **C=N**), 1592 (m), 1577 (m), 1559 (w), 1541 (w), 1498 (m), 1455 (m), 1418 (w), 1293 (m), 1164 (m), 1090 (m), 1054 (m), 989 (w), 829 (w), 749 (s), 698 (s).

^{1}H NMR: δ (400 MHz, $CDCl_3$) 7.57 (2H, d, *J*=7.1 Hz, **Ph**), 7.43-7.33 (5H, m, **Ph**), 7.24 (1H, d, *J*=7.4 Hz, **Ph**), 6.87 (1H, t, *J*=7.6 Hz, **Ph**), 4.81 (1H, dd, *J*=9.3 and 5.4 Hz, Ph**CH**N), 3.69 (1H, dd, *J*=13.1 and 9.3 Hz, PhCH**CH_2**), 2.86 (1H, dq, *J*=12.6 and 7.5 Hz, S**CH_2**CH_3), 2.75 (1H,

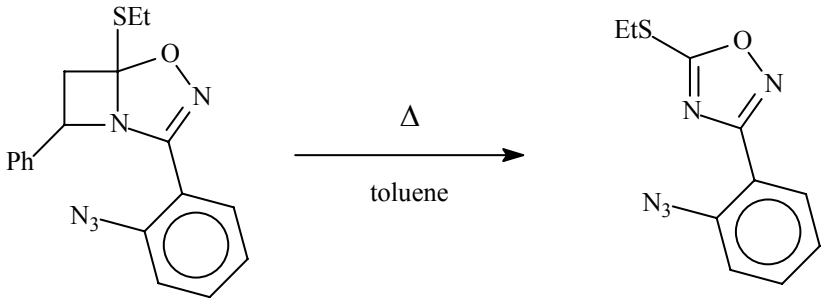
dq, *J*=12.6 and 7.5 Hz, S**CH$_2$**CH$_3$), 2.72 (1H, dd, *J*=13.1 and 5.4 Hz, PhCH**CH$_2$**), 1.36 (3H, t, *J*=7.5 Hz, SCH$_2$**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 158.55 (N-**C**=N), 140.45 (**C** (Ar)), 138.81 (**C** (Ar)), 131.65 (**CH** (Ph)), 130.82 (**CH** (Ph)), 128.56 (**CH** (Ph)), 128.02 (**CH** (Ph)), 126.12 (**CH** (Ph)), 124.58 (**CH** (Ph)), 119.40 (**CH** (Ph)), 110.92 (**C**-SEt), 66.79 (**CH**), 45.22 (S**CH$_2$**CH$_3$), 22.52 (**CH$_2$**), 14.58 (SCH$_2$**CH$_3$**).

MS (*m/z*) 352.1 $[M+H]^+$, 374.1 $[M+Na]^+$, 725.2 $[M_2 + Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{18}H_{17}N_5OS$ calculated 351.1148 measured 351.1145.

3.1.1.3.4 Thermolysis of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo-[3.2.0]hept-2-ene: formation of 3-(2-azidophenyl)-5-ethylthio-1,2,4-oxadiazole

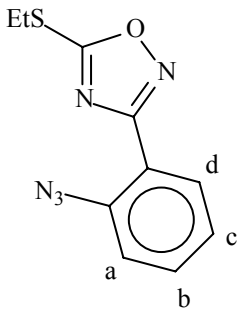


(**197**) (**199**)
$C_{10}H_9N_5OS$
MW = 247.27 g/mol

2-(2-Azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**197**) (120 mg, 0.34 mmol) was dissolved in toluene (5 mL) and heated at reflux for 47 h. The solvent was removed *in vacuo* and the crude product was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 7/1) to yield the product as an orange oil (**10 mg, 17%**).

IR υ_{max} (cm^{-1}) 2930 (w), 2130-2100 (s, **N$_3$**), 1601 (w), 1582 (m), 1520 (m), 1505 (m), 1470 (m), 1339 (s), 1304 (m), 1271 (m), 1187 (m), 750 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 7.99 (1H, dd, *J*=7.8 and 1.6 Hz, **CH**$_d$ (Ph))‡, 7.55 (1H, ddd, *J*=8.1 7.4 and 1.6 Hz,**CH**$_b$ (Ph))$^{\#}$, 7.27 (1H, dd, *J*=8.1 and 0.8 Hz, **CH**$_a$ (Ph))‡, 7.19 (1H, td, *J*=7.6 and 0.8 Hz, **CH**$_c$ (Ph))$^{\#}$, 3.34 (2H, q, *J*=7.4 Hz, S**CH$_2$**CH_3), 1.54 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**).

‡ Signals may be interchanged.

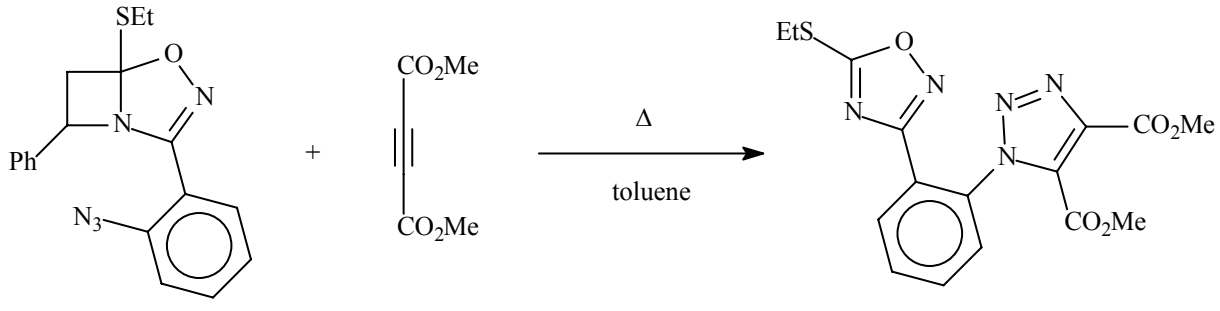
\# Signals may be interchanged.

^{13}C NMR δ (400 MHz, $CDCl_3$) 177.62 (EtS-**C**=N), 166.66 (N-**C**=N), 138.89 (**C** (Ar)), 132.09 (**CH**$_b$ (Ar)), 131.58 (**CH**$_d$ (Ar)), 124.87 (**CH**$_c$ (Ar)), 119.34 (**CH**$_a$ (Ar)), 118.23 (**C**-N_3 (Ar)), 27.27 (S**CH$_2$**CH_3), 14.77 (SCH_2**CH$_3$**).

MS (*m/z*) 248.1 $[M+H]^+$, 270.0 $[M+Na]^+$, 517.1 $[M_2+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{10}H_{10}N_5OS$ calculated 248.0601 measured 248.0603.

3.1.1.3.5 Reaction of 2-(2-azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]-hept-2-ene with DMAD



(**197**) (**200**) (**201**)
$C_{16}H_{15}N_5O_5S$
MW = 389.38 g/mol

2-(2-Azidophenyl)-5-ethylthio-7-phenyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**197**) (110 mg, 0.31 mmol) and dimethylacetylene dicarboxylate (DMAD) (**200**) (42µL, 49 mg, 0.34 mmol, 1 eq.) were dissolved in toluene (5 mL) and the whole was heated at reflux under nitrogen overnight. The solvent was removed *in vacuo* to give the crude product (130 mg) as an orange oil. It was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 10 / 1) to give the product as a yellow oil (**50 mg, 41%**).

IR υ_{max} (cm^{-1}) 2954 (w), 1735 (s, **C=O**), 1557 (w), 1507 (m), 1474 (m), 1448 (m), 1358 (s), 1290 (m), 1232 (m), 1181 (m), 1105 (m), 1078 (m), 1004 (w), 963 (w), 826 (w), 809 (w), 777 (w), 758 (m), 669 (w).

^{1}H NMR δ (500 MHz, $CDCl_3$) 8.25 (1H, dd, *J*=7.1 and 2.2 Hz, **CH** (Ar)), 7.71 (2H, m, **CH** (Ar)), 7.54 (1H, dd, *J*=7.4 and 1.6 Hz, **CH** (Ar)), 4.02 (3H, s, CO_2**Me**), 3.76 (3H, s, CO_2**Me**), 3.09 (2H, q, *J*=7.4 Hz, S**CH$_2$**CH_3), 1.36 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**).

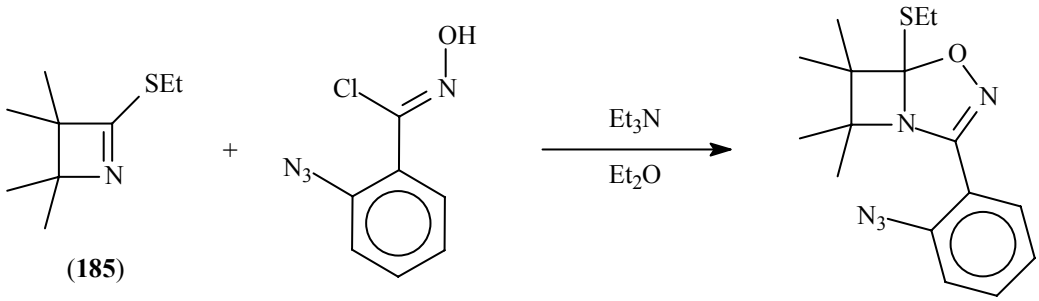
^{13}C NMR δ (500 MHz, $CDCl_3$) 178.85 (EtS-**C**=N), 165.49 (N-**C**=N), 160.40 (**C=O**), 158.10 (**C=O**), 139.06 (C (**Ar**)), 133.78 (**C**=C), 133.14 (C=**C**), 131.63 (**CH** (Ph)), 131.37 (**CH** (Ph)), 130.08 (**CH** (Ph)), 128.69 (**CH** (Ph)), 124.20 (**C**-triazole (**Ar**)), 53.31 (CO_2**CH$_3$**), 52.74 (CO_2**CH$_3$**), 27.42 (S**CH$_2$**CH_3), 14.53 (SCH_2**CH$_3$**).

MS (*m/z*) 390.1 $[M+H]^+$, 412.1 $[M+Na]^+$, 779.2 $[M_2+H]^+$, 801.1 $[M_2+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{16}H_{16}N_5O_5S$ calculated 390.0867 measured 390.0867.

3.1.1.4 Reactivity of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine

3.1.1.4.1 Cycloaddition of 2-ethylthio-3,3,4,4-tetramethyl-1-azetine with 2-azidobenzohydroximoyl chloride: synthesis of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene

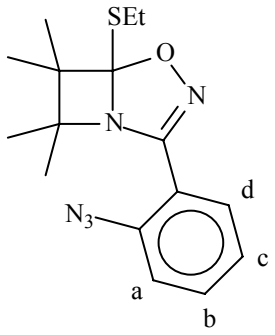


(**185**) (**196**) (**202**)
$C_{16}H_{21}N_5OS$
MW = 331.43 g/mol

To 2-ethylthio-3,3,4,4-tetramethyl-1-azetine (**185**) (190 mg, 1.11 mmol) and 2-azidobenzohydroximoyl chloride (**196**) (195 mg, 0.99 mmol, 0.9 eq.) in dry diethyl ether (4.5 mL) was added, dropwise over 6-7 hours at room temperature, triethylamine (170 µL, 120 mg, 1.19 mmol, 1.1 eq.) diluted in dry diethyl ether (34 mL). The solution was stirred overnight under nitrogen. The mixture was filtered, and the solvent was removed *in vacuo* to give the crude product as a pale yellow oil (0.330 g). It was purified by gravity silica chromatography (PE 40-60ºC / EtOAc : 19/1, Rf = 0.33) to yield the product as a yellow oily solid (**247 mg, 75%**).

IR υ_{max} (cm^{-1}) 2959 (m), 2925 (m), 2127 and 2093 (vs, **N_3**), 1581 (m, **C=N**), 1491 (s), 1447 (m), 1393 (w), 1372 (m), 1344 (m), 1300 (s), 1160 (m), 1090 (m), 1067 (m), 1051 (m), 909 (m), 860 (w). 825 (m), 758 (s), 708 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



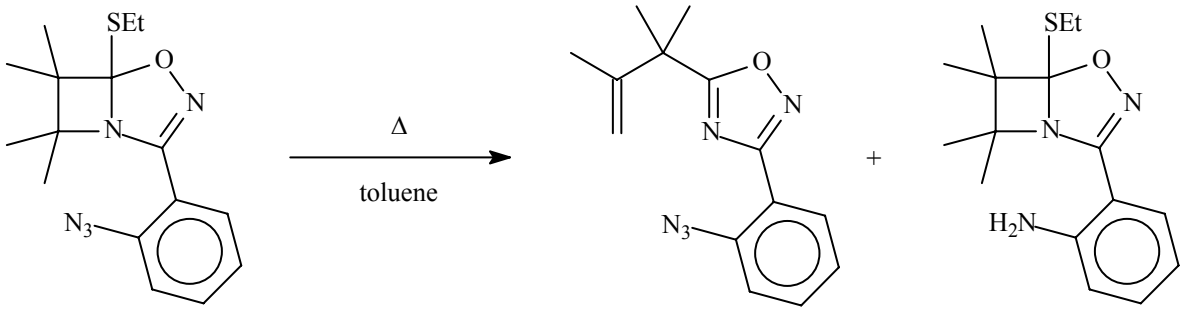
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.64 (1H, dd, *J*=7.6 and 1.6 Hz, **CH**$_d$ (Ar)), 7.46 (1H, ddd, *J*=8.0, 7.6 and 1.6 Hz, **CH**$_b$ (Ar)), 7.26 (1H, dd, *J*=8.0 and 1.0 Hz, **CH**$_a$ (Ar)), 7.18 (1H, td, *J*=7.6 and 1.0 Hz, **CH**$_c$ (Ar)), 2.72 (1H, dq, *J*=12.4 and 7.4 Hz, S**CH$_2$**CH_3), 2.66 (1H, dq, *J*=12.4 and 7.4 Hz, S**CH$_2$**CH_3), 1.51 (3H, s, **CH$_3$**), 1.31 (3H, s, **CH$_3$**), 1.29 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**), 1.26 (3H, s, **CH$_3$**), 0.96 (3H, s, **CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 156.69 (N-**C**=N), 137.84 (**C** (Ar)), 131.18 (**CH**$_b$ (Ar)), 130.31 (**CH**$_d$ (Ar)), 124.35 (**CH**$_c$ (Ar)), 119.21 (**CH**$_a$ (Ar)), 118.76 (**C**-N_3 (Ar)), 116.92 (**C**-SEt), 71.63 (**C**Me_2), 52.80 (**C**Me_2), 26.38 (C(**CH$_3$**)$_2$), 21.54 (S**CH$_2$**CH_3), 20.86 (C(**CH$_3$**)$_2$), 20.36 (C(**CH$_3$**)$_2$), 19.77 (C(**CH$_3$**)$_2$), 14.58 (SCH_2**CH$_3$**).

MS (*m/z*) 332.2 $[M+H]^+$, 354.1 $[M+Na]^+$, 685.3 $[M_2+Na]^+$, 1016.4 $[M_3+Na]^+$.

HRMS (*m/z*) $[M+H]^+$ for $C_{16}H_{21}N_5OS$ calculated 332.1540 measured 332.1540.

3.1.1.4.2 Thermolysis of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene



(**202**)

(**203**)
$C_{14}H_{15}N_5O$
MW = 269.30 g/mol

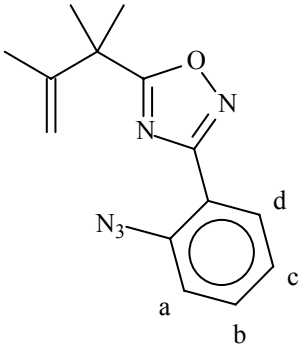
(**204**)
$C_{16}H_{23}N_3OS$
MW = 305.43 g/mol

2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**202**) (0.688 g, 2.07 mmol) was dissolved in toluene (5 mL) and heated at reflux under nitrogen. The reaction was monitored by TLC. After 47h, the solvent was evaporated *in vacuo* to give the crude product (602 mg) as a dark brown oily tar. It was purified by gravity silica chromatography (PE 40-60ºc / EtOAc : 20/1) to give compound (**203**) (**56 mg, 10 %**) and compound (**204**) (**138 mg, 22 %**).

3-(2-azidophenyl)-5-(2,3-dimethylbut-1-en-3-yl)-1,2,4-oxadiazole (**203**):

IR υ_{max} (cm^{-1}) 2955 (m), 2924 (s), 2854 (m), 2128 and 2096 (s, $\mathbf{N_3}$), 1586 (w), 1558 (m), 1484 (m), 1456 (m), 1346 (m), 1300 (m), 1161 (m), 1139 (m), 901 (m), 756 (s).

The assignment for NMR is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 8.00 (1H, dd, *J*=7.8 and 1.4 Hz, **CH**$_d$ (Ar)), 7.53 (1H, td, *J*=7.8 and 1.5 Hz, **CH**$_b$ (Ar)), 7.31 (1H, d, *J*=8.1 Hz, **CH**$_a$ (Ar)), 7.26 (1H, t, *J*=7.5 Hz, **CH**$_c$ (Ar)), 4.98 (1H, s, C=**CH$_2$**), 4.95 (1H, s, C=**CH$_2$**), 1.77 (3H, s, **CH$_3$**), 1.65 (6H, s, 2 x **CH$_3$**).

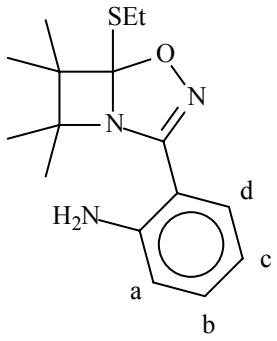
^{13}C NMR δ (500 MHz, $CDCl_3$) 183.82 (O-**C**=N), 166.14 (N-**C**=N), 147.09 (**C** (Ar)), 138.79 (**C**=CH_2), 131.87 (**CH** (Ar)), 131.67 (**CH** (Ar)), 124.84 (**CH** (Ar)), 119.30 (**CH** (Ar)), 118.74 (**C**-N_3 (Ar)), 111.81 (C=**CH$_2$**), 42.01 (**C**Me_2), 25.76 (C(**CH$_3$**)$_2$), 19.86 (**CH$_3$**-C=CH_2).

MS (*m/z*) 270.1 $[M+H]^+$, 292.1 $[M+Na]^+$, 561.2 $[M_2+Na]^+$.

2-(2-aminophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**204**):

IR υ_{max} (cm^{-1}) 3465 and 3349 (br, **NH$_2$**), 2965 (w), 2926 (w), 1617 (s, **C**=**N**), 1491 (m), 1447 (m), 1393 (m), 1372 (m), 1358 (m), 1317 (m), 1261 (m), 1159 (s), 1051 (m), 911 (m), 865 (m), 825 (m), 750 (s), 668 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 7.41 (1H, dd, *J*=7.7 and 1.4 Hz, **CH**$_d$ (Ar))‡, 7.19 (1H, td, *J*=7.7 and 1.4 Hz, **CH**$_b$ (Ar))$^{\#}$, 6.71 (1H, d, *J*=7.9 Hz, **CH**$_a$ (Ar))‡, 6.70 (1H, t, *J*=7.9 Hz, **CH**$_c$ (Ar))$^{\#}$, 5.41 (2H, bs, **NH$_2$**), 2.66 (2H, m, S**CH$_2$**CH_3), 1.56 (3H, s, **CH$_3$**), 1.33 (3H, s, **CH$_3$**), 1.27 (6H, s, 2 x **CH$_3$**), 1.26 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**), 0.99 (3H, s, **CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 159.77 (N-**C**=N), 146.32 (**C** (Ar)), 131.22 (**CH**$_b$ (Ar))‡, 129.70 (**CH**$_d$ (Ar))$^{\#}$, 116.39 (**CH**$_c$ (Ar))‡, 116.01 (**C**-SEt), 115.56 (**CH**$_a$ (Ar))$^{\#}$, 109.72 (**C**-NH_2 (Ar)),

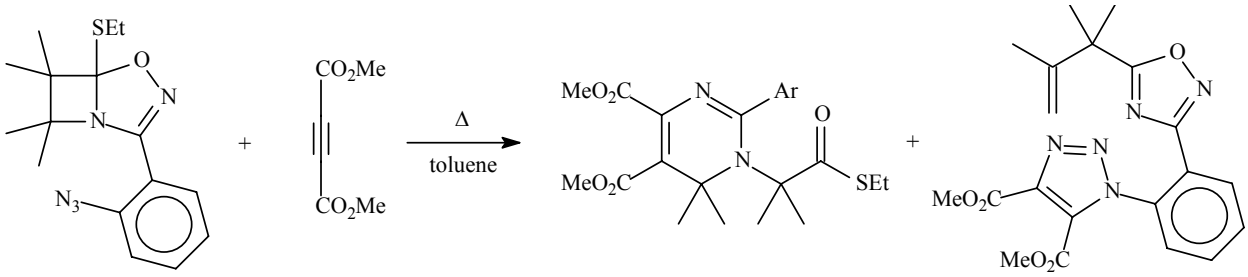
71.81 (**C**$(CH_3)_2$), 51.67 (**C**$(CH_3)_2$), 26.49 (C(**C**H_3)$_2$), 21.72 (S**C**$H_2$$CH_3$), 21.24 (C(**C**$H_3$)$_2$), 20.97 (C(**C**$H_3$)$_2$), 19.68 (C(**C**$H_3$)$_2$), 14.63 ($SCH_2$**C**$H_3$).

‡ The assignment may be interchanged.

The assignment may be interchanged.

MS (*m/z*) 306.2 $[M+H]^+$, 328.1 $[M+Na]^+$.

3.1.1.4.3 Reaction of 2-(2-azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiaza-bicyclo[3.2.0]hept-2-ene with DMAD



(**202**) (**200**)

(**209**)
Ar = 2-N_3Ph
$C_{22}H_{27}N_5O_5S$
MW = 473.54 g/mol

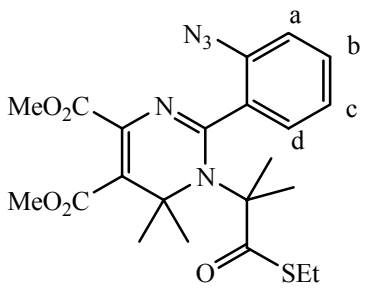
(**210**)
$C_{20}H_{21}N_5O_5$
MW = 411.41 g/mol

2-(2-Azidophenyl)-5-ethylthio-6,6,7,7-tetramethyl-4,1,3-oxadiazabicyclo[3.2.0]hept-2-ene (**202**) (97 mg, 0.29 mmol) and dimethylacetylene dicarboxylate (DMAD) (**200**) (40 µL, 46 mg, 0.32 mmol, 1 eq.) were dissolved in toluene (5 mL) and the reaction was heated at reflux under nitrogen for 21h. The solvent was removed *in vacuo* and the crude product (150 mg) was purified by flash column chromatography (hexane/EtOAc: 5/1) to give compounds (**209**) (**35 mg, 25%**) and (**210**) (**30 mg, 25%**) in a ~1:1 ratio.

2-(2-azidophenyl)-4,4-dimethyl-5,6-dimethoxycarbonyl-3-(1-ethylthio-2-methylpropan-1-on-2-yl)-4*H*-pyrimidine (**209**):

IR υ_{max} (cm^{-1}) 2953 (w), 2928 (w), 2126 (vs, **N_3**), 1734 (s, **C=O**), 1665 (m, **C=N**), 1599 (m), 1511 (m), 1445 (m), 1361 (m), 1289(m), 1232 (m), 1203 (m), 1172 (m), 1126 (m), 1079 (m), 1003 (m), 944(m), 824 (w), 807 (w), 762 (m).

The assignment for NMR was established from coupling constants, HSQC and HMBC data, and is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 7.51 (1H, dd, *J*=7.8 and 1.4 Hz, **CH**$_d$ (Ar)) ‡, 7.48 (1H, td, *J*=7.9 and 1.4 Hz, **CH**$_b$ (Ar))#, 7.35 (1H, dd, *J*=7.9 and 1.1 Hz, **CH**$_a$ (Ar)) ‡, 7.27 (1H, td, *J*=7.8 and 1.1 Hz, **CH**$_c$ (Ar))#, 4.01 (3H, s, CO_2**Me**), 3.88 (3H, s, CO_2**Me**), 2.83 (2H, q, *J*=7.4 Hz, S-**CH$_2$**-CH_3), 1.42 (6H, s, 2 x **Me**), 1.30 (6H, s, 2 x **Me**), 1.22 (3H, t, *J*=7.4 Hz, S-CH_2-**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 204.22 (O=**C**-SEt), 160.37 (**C=O**), 158.62 (**C=O**), 138.64 (N-**C**=N), 136.43 (**C** (Ar)), 133.04 (**C**=C), 131.89 (C=**C**), 131.41 (**CH**$_b$ (Ar)) ‡, 129.12, (**C** (Ar)), 127.23 (**CH**$_d$ (Ar))#, 124.90 (**CH**$_c$ (Ar)) ‡, 124.56 (**CH**$_a$ (Ar))#, 64.76 (**C**$(CH_3)_2$), 55.48 (**C**$(CH_3)_2$), 53.27 (CO_2**CH$_3$**), 52.68 (CO_2**CH$_3$**), 26.99 (C(**CH$_3$**)$_2$), 23.60 (S**CH$_2$**CH_3)), 21.72 (C(**CH$_3$**)$_2$), 14.27 (SCH_2**CH$_3$**).

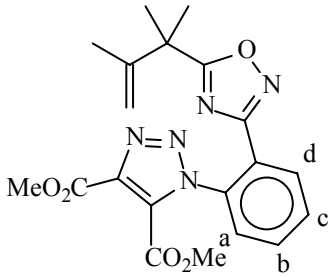
‡ The assignment may be interchanged.

The assignment may be interchanged.

HRMS (*m/z*) $[M+H]^+$ for $C_{22}H_{27}N_5O_5S$ calculated 474.1806 measured 474.1805.

3-(2-(1*H*-(4,5-dimethoxycarbonyl-1,2,3-triazolyl))phenyl)-5-(2,3-dimethylbut-1-en-3-yl)-1,2,4-oxadiazole (**210**):

The assignment for NMR was established by deduction from other analogues, and is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 8.25 (1H, dd, *J*=7.4 and 1.6 Hz, **CH**$_d$ (Ar)), 7.71 (2H, m, **CH** (Ar)), 7.56 (1H, dd, *J*=7.3 and 1.2 Hz, **CH**$_a$ (Ar)), 4.88 (1H, s, C=**CH$_2$**), 4.82 (1H, s, C=**CH$_2$**), 4.00 (3H, s, CO_2**CH$_3$**), 3.73 (3H, s, CO_2**CH$_3$**), 1.60 (3H, s, **CH$_3$**), 1.45 (6H, s, 2x**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 184.46 (O-**C**=N), 165.12 (N-**C**=N) ‡, 160.38 (**C=O**)‡, 158.16 (**C=O**) ‡, 146.67 (Me-**C**=CH_2), 139.01 (**C** (Ar))#, 133.89 (MeO_2C-**C**=C-CO_2Me)#, 133.36 (MeO_2C-C=**C**-CO_2Me)#, 131.46 (**CH** (Ar)), 131.28 (**CH** (Ar)), 130.06 (**CH** (Ar)), 128.60 (**CH** (Ar)), 124.64 (**C** (Ar)), 111.75 (Me-C=**CH$_2$**), 53.20 (CO_2**CH$_3$**), 52.65 (CO_2**CH$_3$**), 41.79 (**C**Me_2), 25.40 (C(**CH$_3$**)$_2$), 19.55 (**CH$_3$**-C=CH_2).

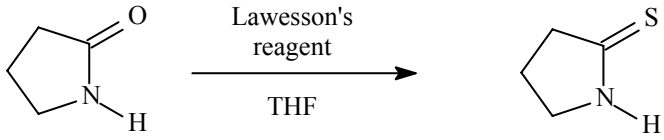
‡ The assignment may be interchanged.

The assignment may be interchanged.

HRMS (*m/z*) $[M+H]^+$ for $C_{20}H_{21}N_5O_5$ calculated 412.1615 measured 412.1613.

3.1.2 Synthesis and reactivity of a 3,4-dihydro-5-ethylthio-2*H*-pyrrole

3.1.2.1 Synthesis of pyrrolidin-2-thione



(**211**) (**212**)
C_4H_7NS
MW = 101.16 g/mol

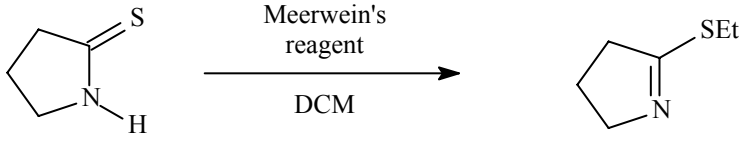
To pyrrolidin-2-one (**211**) (421 mg, 4.94 mmol) in dry THF (10 mL) was added Lawesson's reagent (1.040 g, 2.57 mmol, 0.5 eq.) and the reaction was stirred under nitrogen at RT for one hour, and then at ~60ºC for 20 minutes. The solvent was removed *in vacuo* and the yellow oily crude product (1.759 g) was purified by silica chromatography (hexane / EtOAc: 1/1) to yield the product as a pale yellow solid (**428 mg, 86%, m.p.=114-115ºC**).

IR υ_{max} (cm^{-1}) 3141 (br, **NH**), 2918 (w), 2884 (w), 1536 (m, **C=S**), 1469 (w), 1449 (m), 1292 (s), 1217 (m), 1111 (m), 1061 (m), 1035 (m), 972 (m), 787 (s).

^{1}H NMR δ (500 MHz, $CDCl_3$) 8.77 (1H, bs, **NH**), 3.65 (2H, t, *J*= 7.2 Hz, **CH_2**N), 2.90 (2H, t, *J*= 8.0 Hz, **CH_2**C=S), 2.20 (2H, m, CH_2**CH_2**CH_2).

^{13}C NMR δ (500 MHz, $CDCl_3$) 205.77 (**C=S**), 49.64 (**CH_2**), 43.23 (**CH_2**), 22.89 (**CH_2**).

3.1.2.2 Synthesis of 3,4-dihydro-5-ethylthio-2*H*-pyrrole



(**212**) (**213**)
$C_6H_{11}NS$
MW = 129.22 g/mol

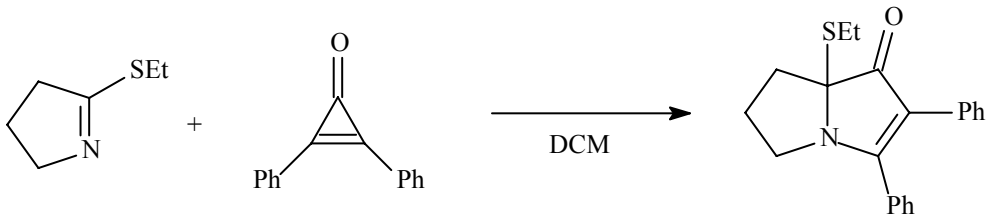
To pyrrolidin-2-thione (**212**) (268 mg, 2.65 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (4 mL of a 1M solution in DCM, 4.00 mmol, 1.5 eq.) under nitrogen. The reaction was stirred at RT for 1 hour, and then at reflux for 1 hour. The solution was then added dropwise to a 50% solution of potassium carbonate (4 mL) at -10ºC. The solution was filtered through Celite®, and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 4 mL) and the combined extracts were dried over anhydrous magnesium sulfate. Filtration and careful concentration (volatile compound) gave the crude product as a pale yellow oily solid (193 mg). It was carried through the next step without further purification.

^{1}H NMR δ (400 MHz, $CDCl_3$) 3.78 (2H, m, **CH_2**N), 2.98 (2H, q, *J*= 7.4 Hz, S**CH_2**CH_3), 2.53 (2H, m, **CH_2**C=N), 1.91 (2H, m, CH_2**CH_2**CH_2), 1.27 (3H, t, *J*= 7.4 Hz, SCH_2**CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 172.59 (EtS-**C**=N), 60.70 (**CH_2**N), 38.65 (**CH_2**), 24.97 (**CH_2**), 23.34 (**CH_2**), 14.38 (SCH_2**CH_3**).

3.1.2.3 Reaction with DPP: synthesis of 2,3-diphenyl-5-ethylthio-1-azabicyclo[3.3.0]oct-2-en-4-one

Method 1:

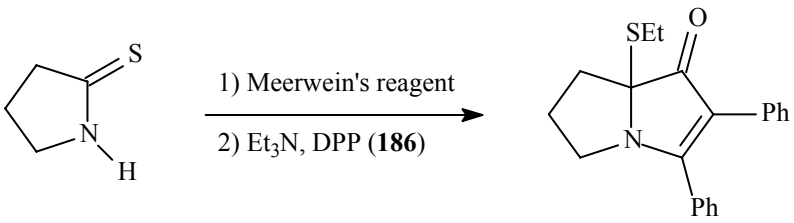


(**213**) (**186**) (**214**)
$C_{21}H_{21}NOS$
MW = 335.46 g/mol

To the crude 3,4-dihydro-5-ethylthio-2*H*-pyrrole (**213**) (96.5 mg, 0.75 mmol) in DCM (2.5 mL) was added diphenylcyclopropenone (**186**) (154 mg, 0.75 mmol, 1 eq.) in one portion. The whole was stirred at RT under nitrogen overnight. Concentration *in vacuo* gave the crude product as an dark yellow oil (269 mg). Purification by silica chromatography (PE 40-60ºC /

EtOAc: gradient elution 5/1-3/1-1/1) afforded the product as a strong yellow oil (**133 mg, ≥53%**).

Method 2:



(**212**) (**214**)
$C_{21}H_{21}NOS$
MW = 335.46 g/mol

To pyrrolidin-2-thione (**212**) (300 mg, 2.96 mmol) was added Meerwein's reagent (1M solution in DCM, 4.5 mL, 4.50 mmol, 1.5 eq.) under nitrogen. The mixture was stirred for 1 hour at RT, and for 1 hour at reflux temperature. Then, triethylamine (630 µL, 455 mg, 4.50 mmol, 1.5 eq.) was added to the mixture, and the whole was stirred at RT for 1 hour. Diphenylcyclopropenone (**186**) (610 mg, 2.96 mmol, 1 eq.) in DCM (10 mL) was added to the reaction, which was monitored by TLC. After 15 hours, the solvent was evaporated under reduced pressure and the crude product was purified by silica chromatography (PE 40-60ºC / EtOAc: 5 / 1) to give the product as a yellow oil (**284 mg, 29%**).

IR υ_{max} (cm^{-1}) 3059 (w), 2965 (w), 2925 (w), 1735 (w), 1674 (s, **C=O**), 1601 (m), 1581 (m), 1556 (m), 1498 (w), 1483 (w), 1448 (m), 1395 (m), 1300 (m), 1280 (m), 1183 (m), 1074 (w), 1026 (w), 976 (w), 927 (w), 779 (w), 723 (m), 696 (s).

^{1}H NMR δ (500 MHz, $CDCl_3$) 7.47-7.43 (3H, m, **CH** (Ph)), 7.39-7.36 (2H, m, **CH** (Ph)), 7.21 (4H, m, **CH** (Ph)), 7.14 (1H, m, **CH** (Ph)), 3.55 (1H, dt, *J*=11.1 and 6.6 Hz, N**CH$_2$**CH_2CH_2), 3.08 (1H, dt, *J*=11.1 and 6.7 Hz, N**CH$_2$**CH_2CH_2), 2.65 (1H, dq, *J*=12.0 and 7.4 Hz, S**CH$_2$**CH_3), 2.56 (1H, dq, *J*=12.0 and 7.4 Hz, S**CH$_2$**CH_3), 2.23 (2H, m, **CH$_2$**), 2.07 (1H, m, **CH$_2$**), 1.94 (1H, m, **CH$_2$**), 1.20 (3H, t, *J*=7.4 Hz, SCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 200.09 (**C=O**), 174.95 (PhC_α=**C**$_\beta$Ph), 131.31 (**C** (Ph)), 131.05 (**CH** (Ph)), 131.00 (**C** (Ph)), 129.54 (**CH** (Ph)), 128.72 (**CH** (Ph)), 128.63 (**CH** (Ph)), 127.98

(**CH** (Ph)), 126.08 (**CH** (Ph)), 116.21 (Ph**C**$_{\alpha}$=C$_{\beta}$Ph), 80.40 (**C** ring junction), 48.42 (N**CH$_2$**), 32.87 (**CH$_2$**), 26.46 (**CH$_2$**), 23.11 (S**CH$_2$**CH$_3$), 14.25 (SCH$_2$**CH$_3$**).

MS (*m/z*) 358.1 $[M+Na]^+$, 693.3 $[2M+Na]^+$.

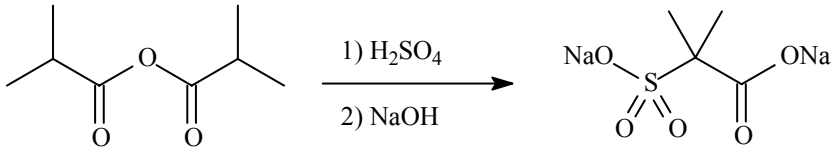
HRMS (*m/z*) $[M+Na]^+$ for $C_{21}H_{21}NNaOS$ calculated 358.1236 measured 358.1232.

3.2 Synthesis and reactivity of 1,2-thiazetin-1,1-dioxides

3.2.1 Synthesis of 4,4-dialkyl-3-oxo-*β*-sultams

3.2.1.1 Synthesis of 4,4-dimethyl-1,2-thiazetidin-3-one-1,1-dioxide (4,4-dimethyl-3-oxo-*β*-sultam)

3.2.1.1.1 Synthesis of disodium 2-methyl-2-sulfonato propanoate



(**219**) (**220**)
$C_4H_6Na_2O_5S$
MW = 212.12 g/mol

Concentrated sulfuric acid (5.3 mL, 9.70 g, 98.9 mmol, 0.78 eq.) was added dropwise to isobutyric anhydride (**219**) (21 mL, 20.03 g, 126.6 mmol) and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was then stirred at 90˚C for 22 hours at which time the reaction had reached completion*. The hot mixture was poured into ice-cold water (50 mL), and extracted with ether (3 x 40 mL). To the aqueous layer, a solution of sodium hydroxide (12.32 g, 308 mmol, 2.4 eq.) in water (40 mL) was added in small portions to adjust the pH to around 10. The aqueous solution was evaporated to dryness under reduced pressure at 40˚C. The residue was dissolved in hot water (30 to 40 mL) and precipitated by addition of ethanol (~300 mL), and the resulting precipitate was isolated by vacuum filtration. Several crops were isolated by adding ethanol to the mother liquor. The product was isolated as a white solid (**18.70 g, 89 %**) and was carried through to the next step without any further purification.

*The completion of the reaction was checked with barium chloride: a solution of $BaCl_2$ (1 mL) was added to a sample of the reaction mixture, if no precipitation occurred the reaction was judged to be complete.

IR υ_{max} (cm^{-1}) (neat) 3564 (br), 3424 (br), 2981 (w), 1590-1577 (s, **C=O**), 1459 (w), 1405 (m)*, 1371 (m, **SO_2**)*, 1262 (m), 1204 (s, **SO_2**)#, 1156 (s)#, 1033(s), 943 (w), 855 (m), 795 (w), 713 (m), 640 (s).

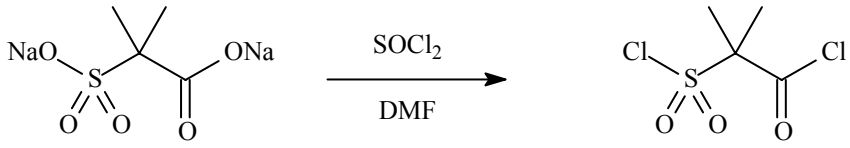
* Assignments may be interchanged.

Assignments may be interchanged.

^{1}H NMR δ (500 MHz, D_2O) 1.49 (6H, s, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, D_2O) 177.67 (**C=O**), 66.02 (**C**$(CH_3)_2$), 22.56 (**CH_3**).

3.2.1.1.2 Synthesis of 2-(chlorosulfonyl)-2-methylpropanoyl chloride



(**220**) (**221**)
$C_4H_6Cl_2O_3S$
MW = 205.05 g/mol

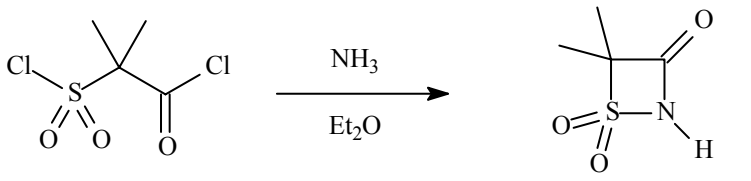
Disodium 2-methylsulfonatopropanoate (**220**) (4.88 g, 23 mmol) was added to thionyl chloride (18.3 mL, 251 mmol, 10.9 eq.) in small portions over 10 minutes at 0˚C with stirring. DMF (0.37 mL, 0.349 g, 4.78 mmol, 0.2 eq.) was added dropwise over 2 minutes and the mixture was heated to 70˚C. After gas evolution was complete, the mixture was heated for a further 4 hours at 70˚C. Excess thionyl chloride was evaporated under reduced pressure, yielding a pale yellow slurry which was dissolved in ether. The resultant white solid (NaCl) was filtered off, and concentration *in vacuo* gave the product as an orange oil **(3.65 g, 77%)**. It was carried through the next step with no further purification.

IR υ_{max} (cm^{-1}) 3014 (w), 2950 (w), 1824 (w), 1763 (m, **C=O**), 1463 (w), 1364 (s, **SO_2**), 1172 (m, **SO_2**), 1124 (m), 1036 (w), 1014 (w), 947 (m), 883 (m), 858 (m), 720 (w), 668 (m), 633 (m), 594 (s), 556 (s), 534 (m), 510 (s), 463 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 2.01 (6H, s, 2 x **CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 169.36 (**C=O**), 85.37 (**C**$(CH_3)_2$), 22.20 (**CH_3**).

3.2.1.1.3 Synthesis of 4,4-dimethyl-3-oxo-*β*-sultam



(**221**) (**215a**)
$C_4H_7NO_3S$
MW = 149.16 g/mol

2-Chlorosulfonyl-2-methylpropionyl chloride (**221**) (1.00 g, 4.90 mmol) was dissolved in ether (2.4 mL) and added dropwise over 45 minutes to liquid ammonia (~6 mL, 3.54 g, 208 mmol, large excess) in diethyl ether (2.4 mL) at -78˚C. The mixture was allowed to warm to RT and stirred until all solvent had evaporated (overnight). The residue was dissolved in chloroform (2.5 mL) and water (2.5 mL). The solution was cooled to 0˚C and the pH adjusted to 1 with a 2M HCl solution. The aqueous layer was extracted with chloroform (3 x 5 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to yield a white solid (**0.246 g, 34%, m.p.=145-146ºC,** lit.: 149-151ºC[61]).

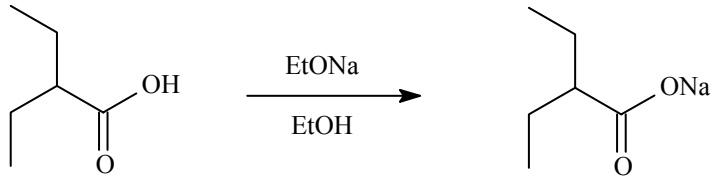
IR υ_{max} (cm^{-1}) 3115 (br, **NH**), 2999 (w), 2922 (w), 1748 (m, **C=O**), 1458 (w), 1328 (s, **SO_2**), 1262 (m), 1213 (m), 1157 (m, **SO_2**), 1112 (m), 957 (w), 843 (w), 741 (m), 729 (w), 659 (m), 614 (s), 568 (s).

^{1}H NMR δ (400 MHz, $CDCl_3$) 8.27 (1H, bs, **NH**), 1.76 (6H, s, 2 x **CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 163.87 (**C=O**), 82.36 (**C**$(CH_3)_2$), 18.55 (**CH_3**).

3.2.1.2 Synthesis of 4,4-diethyl-1,2-thiazetidin-3-one-1,1-dioxide (4,4-diethyl-3-oxo-*β*-sultam)

3.2.1.2.1 Synthesis of sodium 2-ethylbutyrate (sodium 2-ethylbutanoate)



(**222**) (**223**)
$C_6H_{11}NaO_2$
MW = 138.14 g/mol

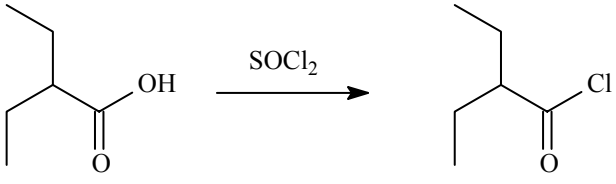
2-Ethylbutyric acid (**222**) (10 mL, 9.24 g, 79.5 mmol) was added dropwise to a solution of sodium ethoxide in ethanol (1.98 g, 86.1 mmol, 1.1 eq. of sodium in 32 mL of ethanol) at RT. The reaction mixture was stirred for 1 hour, and the solvent was removed under reduced pressure at 50˚C. The residue was washed with toluene (2x20 mL) to yield the product as a white solid (**10.99g, 100%**).

IR υ_{max} (cm^{-1}) 2960 (m), 2932 (w), 2874 (w), 1548 (s, **C=O**), 1460 (m), 1412 (s), 1378 (w), 1318 (m), 1294 (w), 1245 (w), 1105 (w), 809 (m), 773 (w), 637 (w), 517 (m).

^{1}H NMR: δ (500 MHz, D_2O) 2.04 (1H, tt, *J*=8.3 and 6.5 Hz, **CH**), 1.44 (4H, m, 2 x **CH_2**), 0.86 (6H, t, *J*=7.4 Hz, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, D_2O) 186.44 (**C=O**), 53.02 (**CH**), 25.79 (**CH_2**), 11.71 (**CH_3**).

3.2.1.2.2 Synthesis of 2-ethylbutyryl chloride (2-ethylbutanoyl chloride)



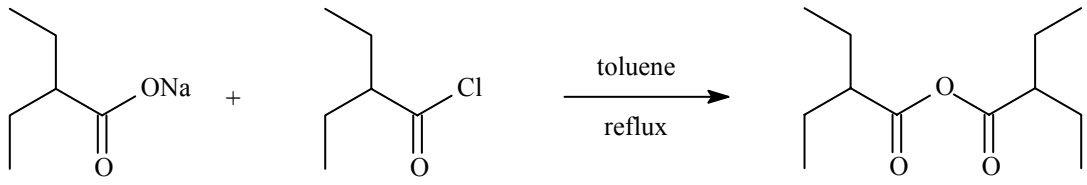
(**222**) (**224**)
$C_6H_{11}ClO$
MW = 134.60 g/mol

Thionyl chloride (6.6 mL, 10.76 g, 90.5 mmol, 1.14 eq.) was added dropwise to 2-ethylbutyric acid (**222**) (10 mL, 9.24 g, 79.5 mmol) at 30˚C over 25 minutes. The reaction mixture was then heated at reflux for 30 minutes. The product was isolated by distillation as a colourless liquid (**6.99 g, 65%, b.p.= 138-140˚C at 760 mm Hg**).

^{1}H NMR δ (400 MHz, $CDCl_3$) 2.68 (1H, tt, *J*=8.2 and 5.5 Hz, **CH**), 1.80 (1H, q , *J*=7.5 Hz, **CH_2**), 1.78 (1H, q , *J*=7.5 Hz, **CH_2**),1.69 (1H, dq, *J*=7.5 and 5.5 Hz, **CH_2**), 1.65 (1H, dq, *J*=5.5 and 7.5 Hz, **CH_2**), 0.99 (6H, t, *J*=7.5 Hz, 2 x **CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 177.23 (**C=O**), 60.22 (**CH**), 24.65 (**CH_2**), 11.27 (**CH_3**).

3.2.1.2.3 Synthesis of 2-ethylbutyric anhydride (2-ethylbutanoic anhydride)



(**223**) (**224**) (**225**)
$C_{12}H_{22}O_3$
MW = 214.30 g/mol

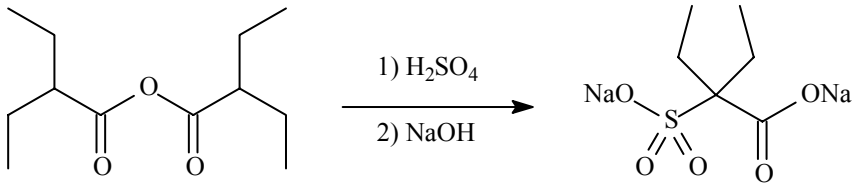
2-Ethylbutyryl chloride (**224**) (6.87 g, 51.03 mmol, 1 eq.) was added dropwise over 15 minutes to a solution of sodium 2-ethylbutyrate (**223**) (7.05 g, 51.03 mmol) in toluene (35 mL). An exotherm was observed during the addition. The mixture was heated at reflux for 1 hour 15 minutes, and then allowed to cool to RT. Ice (28 g) was added to the reaction mixture which was stirred until the ice was melted. The two layers were separated and the organic layer was dried over anhydrous sodium sulfate. Concentration under vacuum gave the crude product as a clear yellow oil (10.65 g). Vacuum distillation afforded the product as a colourless liquid (**7.96 g, 73%, b.p.= 82-84˚C at ~1 mm Hg**, lit.: 115.5˚C at 10 mm Hg[61]).

IR υ_{max} (cm^{-1}) 2968 (s), 2938 (s), 2879 (s), 1811 (s, **C=O**), 1744 (s, **C=O**), 1461 (s), 1385 (m), 1263 (m), 1225 (m), 1163 (m), 1081 (m), 1010 (s), 910 (m).

^{1}H NMR δ (500 MHz, $CDCl_3$) 2.31 (2H, tt, *J*=8.2 and 5.5 Hz, **CH**), 1.68 (4H, m, 4 x 1H from the four **CH_2**), 1.58 (4H, m, 4 x 1H from the four **CH_2**), 0.96 (12H, t, *J*=7.5 Hz, 4 x **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 171.79 (**C=O**), 49.68 (**CH**), 24.34 (**CH_2**), 11.53 (**CH_3**).

3.2.1.2.4 Synthesis of disodium 2-ethyl-2-sulfonatobutyrate (disodium 2-ethyl-2-sulfonatobutanoate)



(**225**) (**226**)
$C_6H_{10}Na_2O_5S$
MW = 240.18 g/mol

Concentrated sulfuric acid (2 mL, 3.66 g, 37.3 mmol, 1 eq.) was added dropwise to 2-ethylbutyric anhydride (**225**) (7.84 g, 36.6 mmol) and the solution was stirred for 30 minutes at 20-35˚C. The reaction mixture was heated at 90˚C and stirred overnight until shown to be complete*. The hot viscous reaction mixture was poured into ice-cold water (15 mL) and then extracted with diethyl ether (3 x 15 mL). To the aqueous layer, a solution of sodium hydroxide (3.50 g, 87.5 mmol, 2.4 eq.) in water (12 mL) was added dropwise to adjust the pH to around 8. The aqueous solution was then evaporated to dryness under reduced pressure at 40˚C. The pale brown solid residue was dissolved in hot water (8 mL)** and precipitated by adding ethanol (30 mL). Vacuum filtration afforded the product as a pale brown solid (**5.51 g, 63%**), which was carried through the next step without any further purification.

*The completion of the reaction was checked with barium chloride: a solution of $BaCl_2$ (1 mL) was added to a sample of the reaction mixture, if no precipitation occurred the reaction was judged to be complete.

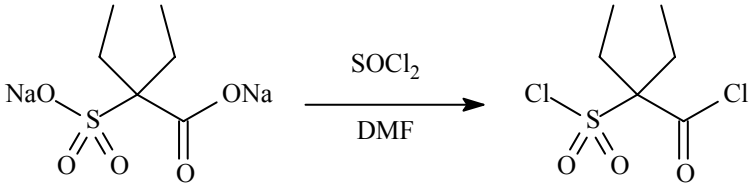
** In some cases, the solution was dark brown/orange, and so charcoal was added to it before the addition of ethanol.

IR υ_{max} (cm^{-1}) 2980 (w), 2914 (w), 2858 (w), 1578 (s, **C=O**), 1439 (w), 1385 (m, **SO_2**), 1291 (w), 1238 (m), 1160 (s, **SO_2**), 1143 (s), 1125 (s), 1034 (s), 997 (w), 946 (w), 893 (w), 809 (m), 746 (w), 710 (m), 650 (s), 616 (m), 565 (m), 531 (m), 499 (m).

^{1}H NMR δ (500 MHz, D_2O) 1.97 (2 x 1H, q, *J*=7.5 Hz, **CH_2**), 1.97 (2 x 1H, q, *J*=7.5 Hz, **CH_2**), 0.96 (6H, t, *J*=7.5 Hz, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, D_2O) 176.27 (**C=O**), 73.81 (**C**), 25.35 (**CH_2**), 9.01 (**CH_3**).

3.2.1.2.5 Synthesis of 2-chlorosulfonyl-2-ethylbutyroyl chloride (2-chlorosulfonyl-2-ethylbutanoyl chloride)



(**226**) (**227**)
$C_6H_{10}Cl_2O_3S$
MW = 233.11 g/mol

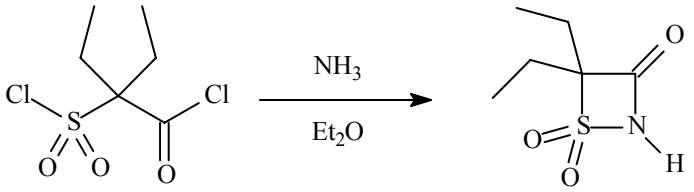
Disodium 2-ethylsulfonatobutanoate (**226**) (5.47 g, 22.8 mmol) was added to thionyl chloride (20 mL, 33.21 g, 279 mmol, 12.2 eq.) in small portions over 10 minutes at 0˚C with stirring. DMF (0.37 mL, 0.35 g, 4.8 mmol, 0.2 eq.) was added dropwise over 2 minutes and the mixture was heated to 70˚C. After gas production was complete, the mixture was heated for a further 5 hours at 70˚C. Excess thionyl chloride was evaporated off under reduced pressure at 40˚C, yielding a pale yellow sticky residue which was dissolved in ether. The resultant white solid (NaCl) was filtered off, and concentration *in vacuo* gave the product as a yellow oil (**2.80 g, 53%)**. It was carried through the next step with no further purification.

IR υ_{max} (cm^{-1}) 2984 (w), 2949 (w), 2877 (w) 1791 (m, **C=O**), 1765 (m, **C=O**), 1449 (m), 1371 (s, **SO_2**), 1171 (s, **SO_2**), 1113 (w), 1070 (w), 1039 (w), 1012 (w), 966 (m), 857 (w), 809 (s), 779 (m), 721 (m), 644 (m), 592 (s), 550 (s), 505 (s).

^{1}H NMR δ (500 MHz, $CDCl_3$) 2.48 (4H, q, *J*=7.4 Hz, 2 x **CH_2**), 1.22 (6H, t, *J*=7.4 Hz, 2 x **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 169.10 (**C=O**), 94.09 (**C**), 26.98 (**CH_2**), 8.82 (**CH_3**).

3.2.1.2.6 Synthesis of 4,4-diethyl-3-oxo-*β*-sultam



(**227**) (**215b**)
$C_6H_{11}NO_3S$
MW = 177.21 g/mol

A solution of 2-chlorosulfonyl-2-ethylbutyryl chloride (**227**) (2.041 g, 8.75 mmol) in dry diethyl ether (30 mL) was added dropwise at -78˚C to liquid ammonia (~11 mL, 6.49 g, 378 mmol, large excess) in dry diethyl ether (30 mL). The mixture was allowed to warm to RT and stirred until all the solvent had evaporated. The residue was dissolved in chloroform (15 mL) and water (15 mL) at 0˚C. The pH of the solution was adjusted to 1 with a 2M HCl solution. The aqueous layer was extracted with chloroform (3 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. Filtration and concentration under vacuum gave the product as an orange oil (**0.517 g, 33%**).

IR υ_{max} (cm^{-1}) 3237 (br, **NH**), 2979 (w), 2947 (w), 1772 (s, **C=O**), 1457 (w), 1339 (s, **SO_2**), 1238 (m), 1182 (w), 1145 (m, **SO_2**), 1110 (m), 796 (w), 720 (w), 669 (m), 617 (m), 590 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 9.00 (1H, bs, **NH**), 2.18 (4H, q, *J*=7.5 Hz, 2 x **CH_2**), 1.14 (6H, t, *J*=7.5 Hz, 2 x **CH_3**).

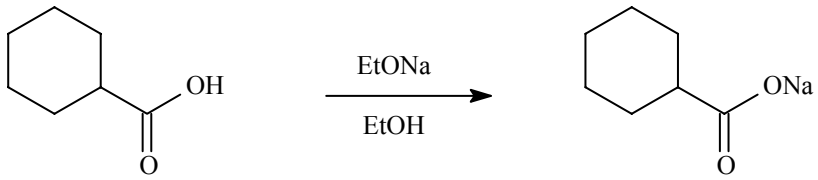
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.83 (**C=O**), 89.67 (**C**), 22.50 (**CH_2**), 8.20 (**CH_3**).

^{1}H NMR δ (400 MHz, DMSO-D_6) 3.80 (1H, bs, **NH**), 2.05 (2H, q, *J*=7.5 Hz, **CH_2**), 2.05 (2H, q, *J*=7.5 Hz, **CH_2**), 1.02 (6H, t, *J*=7.5 Hz, 2 x **CH_3**).

^{13}C NMR δ (400 MHz, DMSO-D_6) 163.65 (**C=O**), 88.73 (**C**), 22.09 (**CH_2**), 8.14 (**CH_3**).

3.2.1.3 Synthesis of 4-*spiro*-cyclohexyl-1,2-thiazetidin-3-on-1,1-dioxide (4-*spiro*-cyclohexyl-3-oxo-*β*-sultam)

3.2.1.3.1 Synthesis of sodium cyclohexanecarboxylate

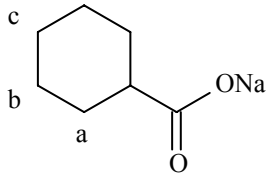


(**228**) (**229**)
$C_7H_{11}NaO_2$
MW = 150.15 g/mol

Cyclohexane carboxylic acid (**228**) (10 g, 78.02 mmol) was added in small portions over 5 to 10 minutes to a solution of sodium ethoxide in ethanol (1.80 g, 78.29 mmol, 1 eq. of sodium in 29 mL of ethanol) at RT. The reaction mixture was stirred for 1 hour, and the solvent was removed under reduced pressure. The residue was washed with toluene (2 x 20 mL) to yield the product as a white solid (**11.71 g, 100%**).

IR υ_{max} (cm^{-1}) 2923 (m), 2849 (m), 1567 and 1549 (s, **C=O**), 1412 (s, **C=O**), 1328 (w), 1280 (w), 1253 (w), 1224 (w), 1204 (w), 1180 (w), 1136 (w), 1037 (w), 934 (w), 893 (m), 803 (w), 779 (m), 734 (w), 644 (w), 504 (w).

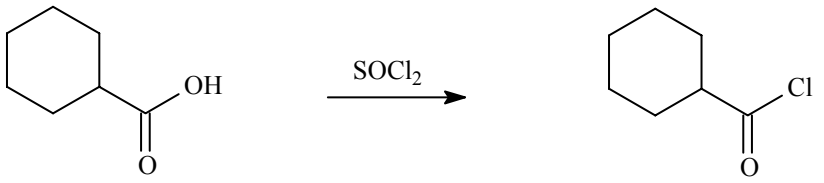
The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



^{1}H NMR δ (500 MHz, D_2O) 2.14 (1H, tt, *J*=11.3 and 3.4 Hz, **CH**), 1.81 (2H, m, cyclohexyl **CH_2**), 1.72 (2H, m, cyclohexyl **CH_2**), 1.64 (1H, m, cyclohexyl **CH_2**), 1.26 (5H, m, cyclohexyl **CH_2**).

^{13}C NMR δ (500 MHz, D_2O) 186.60 (**C=O**), 46.86 (**CH**), 29.78 (**CH_{2a}**), 25.59 (**CH_{2c}**), 25.44 (**CH_{2b}**).

3.2.1.3.2 Synthesis of cyclohexanecarbonyl chloride

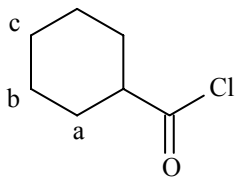


(**228**) (**230**)
$C_7H_{11}ClO$
MW = 146.61 g/mol

Thionyl chloride (6.4 mL, 10.44 g, 87.7 mmol, 1.1 eq.) was added dropwise to cyclohexane carboxylic acid (**228**) (10 mL, 9.24 g, 79.5 mmol) at 30˚C over 25 minutes. The reaction mixture was then heated at reflux for 30 minutes. The product was isolated by vacuum distillation as a colorless liquid (**8.97 g, 78%, b.p.= 42-43˚C at ~1 mm Hg**).

IR υ_{max} (cm^{-1}) 2938 (s), 2859 (s), 1794 (s, **C=O**), 1704 (m), 1452 (s), 1359 (w), 1327 (w), 1292 (m), 1265 (w), 1235 (w), 1184 (w), 1138 (m), 1091 (m), 1045 (m), 953 (s), 924 (m), 895 (m), 867 (w), 841 (m), 794 (s), 737 (s).

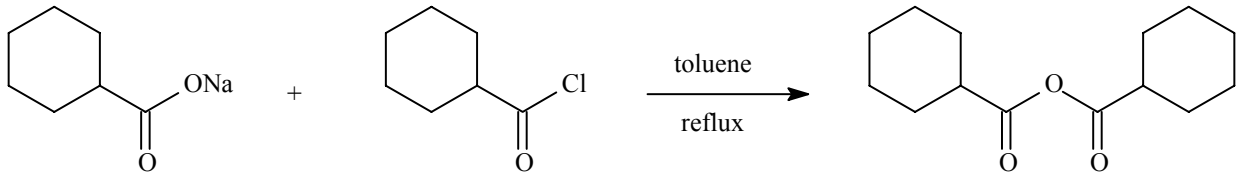
The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 2.66 (1H, tt, *J*=11.0 and 3.6 Hz, **CH**), 2.02 (2H, m, cyclohexyl **CH_2**), 1.73 (2H, m, cyclohexyl **CH_2**), 1.59 (1H, m, cyclohexyl **CH_2**), 1.46 (2H, m, cyclohexyl **CH_2**), 1.21 (3H, m, cyclohexyl **CH_2**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 176.86 (**C=O**), 54.91 (**CH**), 28.96 (**CH_{2a}**), 25.35 (**CH_{2c}**), 24.93 (**CH_{2b}**).

3.2.1.3.3 Synthesis of cyclohexanecarboxylic anhydride

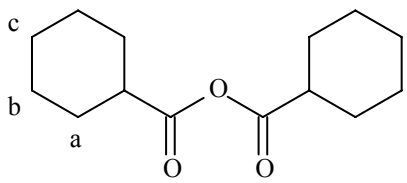


(**229**) (**230**) (**231**)
$C_{14}H_{22}O_3$
MW = 238.32 g/mol

Cyclohexanecarbonyl chloride (**230**) (8.83 g, 60.2 mmol) was added dropwise over 10 minutes to a solution of sodium cyclohexane carboxylate (**229**) (9.04 g, 60.2 mmol, 1 eq.) in toluene (72 mL). An exotherm was observed during the addition. The mixture was heated at reflux for 1 hour 15 minutes, and then allowed to cool to RT. Ice (27 g) was added to the reaction mixture which was stirred until the ice was melted. The two layers were separated and the organic layer was dried over anhydrous Na_2SO_4. Concentration under vacuum gave the crude product as a clear pale yellow oil (15.75 g). Vacuum distillation afforded the product as a colorless liquid (**10.96 g, 76%, b.p.= 138-140˚C at ~1 mm Hg**, lit.: b.p. = 155-156˚C at 0.7 mm Hg[255]).

IR υ_{max} (cm^{-1}) 2934 (s), 2857 (s), 1810 and 1742 (s, **C=O**), 1704 (s), 1452 (s), 1418 (w), 1372 (w), 1309 (m), 1260 (w), 1239 (m), 1213 (w) 1184 (w), 1140 (m), 1122 (m), 1083 (s), 1067 (s), 992 (s), 922 (m), 895 (m), 839 (w).

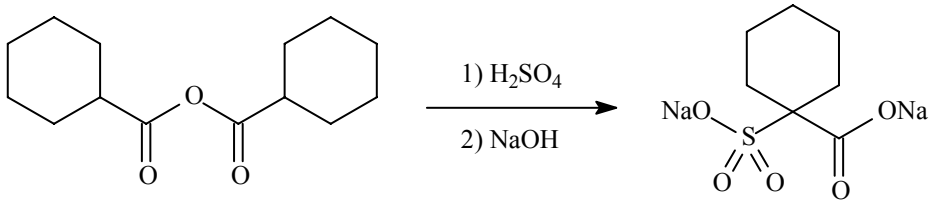
The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 2.40 (1H, tt, *J*=11.1 and 3.6 Hz, **CH**), 1.95 (2H, m, **CH_2**), 1.78 (2H, m, **CH_2**), 1.64 (1H, m, **CH_2**), 1.48 (2H, m, **CH_2**), 1.28 (3H, m, **CH_2**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 171.84 (**C=O**), 43.91 (**CH**), 28.35 (**CH_{2a}**), 25.53 (**CH_{2c}**), 25.12 (**CH_{2b}**).

3.2.1.3.4 Synthesis of disodium 1-sulfonylcyclohexanecarboxylate



(**231**) (**232**)
$C_7H_{10}Na_2O_5S$
MW = 252.19 g/mol

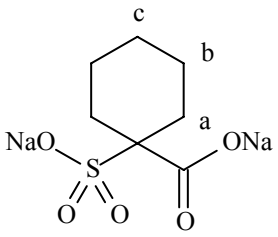
Concentrated sulfuric acid (2.5 mL, 4.57 g, 46.6 mmol, 1 eq.) was added dropwise to cyclohexanecarboxylic anhydride (**231**) (10.80 g, 45.3 mmol) and the solution was stirred for 30 minutes at 20-35˚C. The reaction mixture was heated at 90˚C and stirred overnight until shown to be complete*. The hot viscous reaction mixture was poured into ice-cold water (18 mL) and then extracted with diethyl ether (3 x 20 mL). To the aqueous layer, a solution of sodium hydroxide (4.70 g, 117.5 mmol, 2.6 eq.) in water (16 mL) was added dropwise to adjust the pH to around 10. The aqueous solution was then evaporated to dryness under reduced pressure at 40˚C. The pale brown solid residue was dissolved in hot water (27 mL)** and precipitated by adding ethanol (80 mL). Several crops could be obtained by adding ethanol to the mother liquor. Vacuum filtration afforded the product as a pale brown solid (**6.93 g, 61%**), which was carried through the next step without any further purification.

*The completion of the reaction was checked with barium chloride: a solution of $BaCl_2$ (1 mL) was added to a sample of the reaction mixture, if no precipitation occurred the reaction was judged to be complete.

** In some cases, the solution was dark brown/orange, and thus charcoal was added to it before the addition of ethanol.

IR υ_{max} (cm^{-1}) 2989 (w), 2934 (w), 2855 (w), 1581(s, **C=O**), 1444 (w), 1431 (w), 1386 (m, **SO_2**), 1343 (w), 1286 (w), 1235 (m), 1169 (s, **SO_2**), 1110 (s), 1068 (s), 1035 (w), 1014 (m), 945 (w), 903 (w), 846 (w), 836 (w), 781 (w), 729 (w), 636 (s), 614 (m), 574 (m), 563 (w), 529 (m), 499 (w).

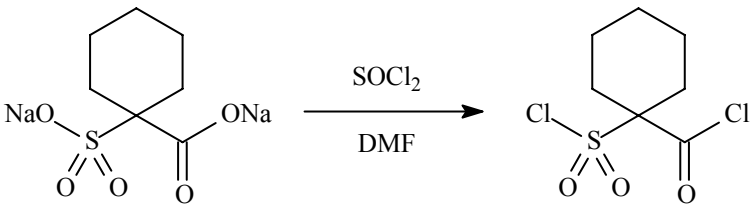
The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



^{1}H NMR δ (500 MHz, D_2O) 2.39 (2H, m, **CH_2**), 1.72 (2H, m, **CH_2**), 1.61 (3H, m, **CH_2**), 1.21 (3H, m, **CH_2**).

^{13}C NMR δ (500 MHz, D_2O) 175.24 (**C=O**), 70.83 (**C**), 30.51 (**CH_{2a}**), 25.28 (**CH_{2c}**), 23.83 (**CH_{2b}**).

3.2.1.3.5 Synthesis of 1-chlorosulfonylcyclohexanecarbonyl chloride

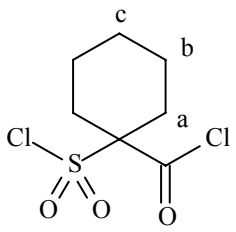


(**232**) (**233**)
$C_7H_{10}Cl_2O_3S$
MW = 245.12 g/mol

Disodium 1-sulfonylcyclohexanecarboxylate (**232**) (7.42 g, 29.4 mmol) was added in small portions to thionyl chloride (23.5 mL, 38.47 g, 323 mmol, 11 eq.) over 10 minutes at 0˚C with stirring. DMF (0.55 mL, 0.52 g, 7.2 mmol, 0.2 eq.) was added dropwise over 2 minutes and the mixture was heated to 70˚C. After gas production was complete, the mixture was heated for a further 5 hours at 70˚C. Excess thionyl chloride was evaporated under reduced pressure yielding a pale yellow residue which was dissolved in ether. The resultant white solid (NaCl) was filtered off, and concentration *in vacuo* gave the product as a clear brown oil (**3.82 g, 53%)**. It was carried through the next step with no further purification.

IR υ_{max} (cm^{-1}) 2946 (w), 2866 (w), 1767 (s, **C=O**), 1454 (m), 1376 (s, **SO_2**), 1346 (m), 1291 (w), 1200 (m), 1169 (s, **SO_2**), 1155 (m), 1072 (w), 1028(w), 1014 (w), 973 (s), 933 (w), 907 (w), 872 (w), 850 (s), 829 (w), 771 (m), 650 (w), 588 (s), 558 (s), 540 (s).

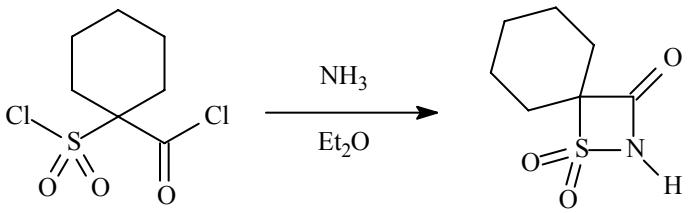
The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 2.87 (2H, m, **CH_2**), 2.15 (2H, m, **CH_2**), 2.01 (2H, m, **CH_2**), 1.80 (1H, m, **CH_2**), 1.39 (3H, m, **CH_2**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 169.64 (**C=O**), 90.30 (**C**), 30.73 (**CH_{2a}**), 23.89 (**CH_{2c}**), 22.95 (**CH_{2b}**).

3.2.1.3.6 Synthesis of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam



(**233**) (**215c**)

$C_7H_{11}NO_3S$

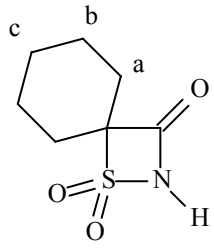
MW = 189.22 g/mol

A solution of 1-chlorosulfonylcyclohexane carbonyl chloride (**233**) (3.82 g, 15.6 mmol) in dry diethyl ether (26 mL) was added dropwise at -78˚C to liquid ammonia (~19 mL, 11.21 g, 658 mmol, 42.2 eq.) in dry diethyl ether (36 mL). The mixture was allowed to warm to RT and stirred until all the solvent had evaporated. The residue was dissolved in chloroform (18 mL) and water (18 mL) at 0˚C. The pH of the solution was adjusted to 1 with a 2M HCl solution. The aqueous layer was extracted with chloroform (3 x 18 mL) and the combined organic layers were

dried over anhydrous sodium sulfate. Filtration and concentration under vacuum gave the product as a white solid (**1.31 g, 44%**).

IR υ_{max} (cm^{-1}) 3099 (br, **NH**), 2956 (m), 2858 (m), 1759 (s, **C=O**), 1450 (m), 1443 (m), 1331 (s, **SO_2**), 1299 (m), 1239 (m), 1161 (s, **SO_2**), 1133 (s), 1086 (m), 957 (w), 771 (m), 729 (m), 684 (m), 669 (m), 649 (m), 623 (m), 603 (s).

The assignment for the cyclohexyl moiety used for NMR analysis is as follows:



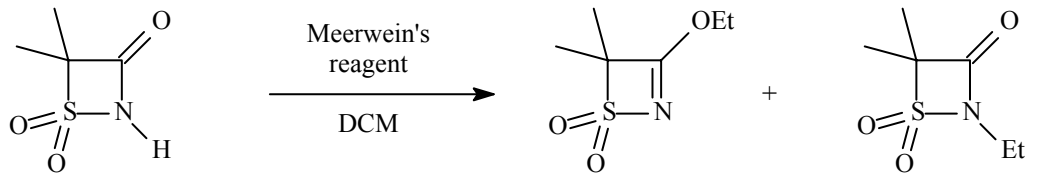
^{1}H NMR δ (400 MHz, $CDCl_3$) 8.42 (1H, bs, **NH**), 2.32 (2H, m, **CH_2**), 1.91 (2H, m, **CH_2**), 1.82 (2H, m, **CH_2**), 1.64 (1H, m, **CH_2**), 1.51 (2H, m, **CH_2**), 1.35 (1H, m, **CH_2**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 163.50 (**C=O**), 86.79 (**C**), 28.05 (**CH_{2a}**), 24.01 (**CH_{2c}**), 22.60 (**CH_{2b}**).

3.2.2 Synthesis of 1,2-thiazetin-1,1-dioxides

3.2.2.1 Alkylation of 3-oxo-*β*-sultams: synthesis of 1,2-thiazetin-1,1-dioxides

3.2.2.1.1 Alkylation of 4,4-dimethyl-3-oxo-*β*-sultam



(**215a**)

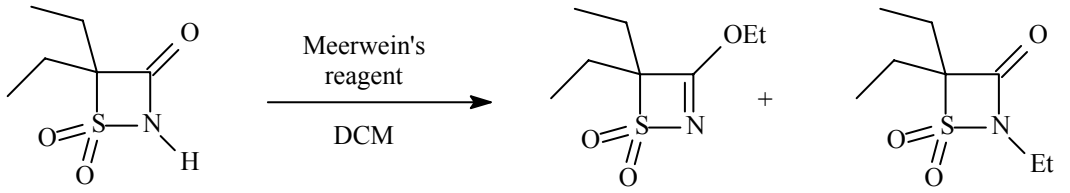
(**161a**)
$C_6H_{11}NO_3S$
MW = 177.21 g/mol

(**234a**)
$C_6H_{11}NO_3S$
MW = 177.21 g/mol

To 4,4-dimethyl-1,2-thiazetidin-3-one (**215a**) (179 mg, 1.20 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (1.8 mL of a 1M solution in DCM, 1.80 mmol, 1.5 eq.) under nitrogen. The whole was stirred at RT for 1 hour and then at reflux for 1 hour. The reaction mixture was then added dropwise to a 50% solution of potassium carbonate (1.8 mL) at -10˚C. The solution was then filtered through Celite®. The cake of Celite® was washed with water and DCM. The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product (56 mg) as yellow needles.

IR υ_{max} (cm^{-1}) 2925 (w), 1774 (s, **C=O**), 1584 (m, **C=N**), 1462 (w), 1390 (w), 1331 (s, **SO_2**), 1191 (m), 1180 (m), 1120 (s, **SO_2**), 1006 (w), 966 (w), 922 (w), 846 (w), 749 (w), 669 (w), 651 (w), 633 (m), 615 (w), 582 (m).

3.2.2.1.2 Alkylation of 4,4-diethyl-3-oxo-*β*-sultam



(**215b**) (**161b**) $C_8H_{15}NO_3S$ MW = 205.27 g/mol (**234b**) $C_8H_{15}NO_3S$ MW = 205.27 g/mol

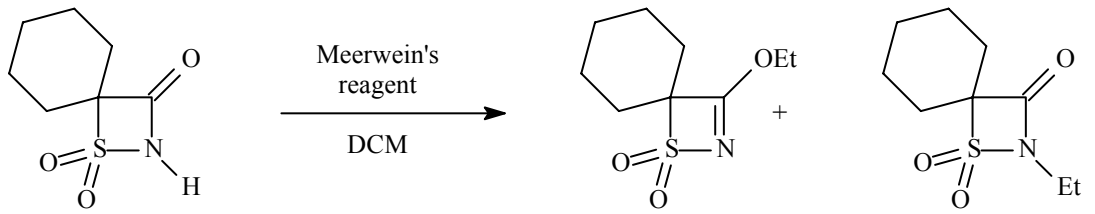
To 4,4-diethyl-1,2-thiazetidin-3-one (**215b**) (517 mg, 2.92 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (4.40 mL of a 1M solution in DCM, 4.40 mmol, 1.5 eq.) under nitrogen. The whole was stirred at RT for 1 hour and then at reflux for 1 hour. The reaction mixture was then added dropwise to a 50% solution of potassium carbonate (5 mL) at -10˚C. The solution was then filtered through Celite®. The cake of Celite® was washed with water and DCM. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product (383 mg) as a yellow oil. It was purified by silica chromatography (PE 40-60˚C / EtOAc: 1/1) to yield a mixture of *O*- and *N*-alkylated product as an oil (**99 mg, 16%, ratio *O*-/*N*- alkylation: ~1/2**).

IR υ_{max} (cm^{-1}) 2979 (w), 1766 (s, **C=O**), 1579 (s, **C=N**), 1459 (m), 1384 (w), 1321 (s, **SO_2**), 1172 (s, **SO_2**), 1156 (s, **SO_2**), 1110 (m), 1005 (w), 925 (w), 630 (m), 598 (s).

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.50 (2H, q, *J*=7.1 Hz, O**CH_2**CH_3), 3.54 (2H, q, *J*=7.4 Hz, N**CH_2**CH_3), 2.18 (2H, q, *J*=7.5 Hz, **CH_2**CH_3), 2.17 (2H, q, *J*=7.5 Hz, **CH_2**CH_3), 2.14 (4H, m, **CH_2**CH_3), 1.47 (3H, t, *J*=7.1 Hz, OCH_2**CH_3**), 1.40 (3H, t, *J*=7.4 Hz, NCH_2**CH_3**), 1.16 (6H, t, *J*=7.5 Hz, CH_2**CH_3**), 1.12 (6H, t, *J*=7.5 Hz, CH_2**CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 180.98 (**C=O**), 163.63 (**C=N**), 93.85 (**C**), 90.55 (**C**), 68.38 (O**CH_2**CH_3), 35.72 (N**CH_2**CH_3), 23.08 (**CH_2**CH_3), 22.53 (**CH_2**CH_3), 13.90 (OCH_2**CH_3**), 13.39 (NCH_2**CH_3**), 8.44 (CH_2**CH_3**), 8.43 (CH_2**CH_3**).

3.2.2.1.3 Alkylation of 4-*spiro*-cyclohexyl-3-oxo-*β*-sultam



(**215c**) (**161c**) $C_9H_{15}NO_3S$ MW = 217.28 g/mol (**234c**) $C_9H_{15}NO_3S$ MW = 217.28 g/mol

To 4-*spiro*-cyclohexyl-1,2-thiazetidin-3-one (**215c**) (504 mg, 2.66 mmol) was added triethyloxonium tetrafluoroborate (Meerwein's reagent) (4 mL of a 1M solution in DCM, 4.00 mmol, 1.5 eq.) under nitrogen. The whole was stirred at RT for 1 hour and then at reflux for 1 hour. The reaction mixture was then added dropwise to a 50% solution of potassium carbonate (4 mL) at -10°C. The solution was then filtered through Celite®. The cake of Celite® was washed with water and DCM. The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 4 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product as an oily orange solid mixture of *O*- and *N*-alkylated product (**137 mg, 24%, ratio O-/N- alkylation: 1/2.75**).

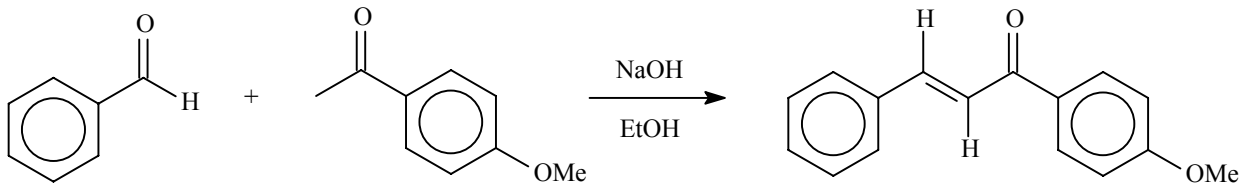
IR υ_{max} (cm^{-1}) 2939 (w), 2862 (w), 1768 (s, **C=O**), 1581 (s, **C=N**), 1450 (m), 1381 (w), 1326 (s, **SO_2**), 1165 (s, **SO_2**), 1090 (w), 1002 (w), 958 (w), 924 (m), 872 (w), 844 (m), 802 (w), 740 (w), 710 (w), 662 (m), 629 (s), 604 (s).

^{1}H NMR δ (400 MHz, $CDCl_3$) 4.43 (2H, q, *J*=7.1 Hz, O**CH_2**CH_3), 3.49 (2H, q, *J*=7.4 Hz, N**CH_2**CH_3), 2.60-1.53 (20H, m, 10 x **CH_2**), 1.42 (3H, t, *J*=7.1 Hz, OCH_2**CH_3**), 1.35 (3H, t, *J*=7.4 Hz, NCH_2**CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 180.91 (**C=O**), 163.71 (**C=N**), 91.60 (**C**), 87.53 (**C**), 68.25 (O**CH_2**CH_3), 35.73 (N**CH_2**CH_3), 28.54 (**CH_2**), 27.83 (**CH_2**), 24.12 (**CH_2**), 24.01 (**CH_2**), 22.79 (**CH_2**), 22.65 (**CH_2**), 13.76 (OCH_2**CH_3**), 13.22 (NCH_2**CH_3**).

3.2.2.2 Synthesis of 4-cyano-3-diethylamino-4-(4-methoxyphenyl)-1,2-thiazetin-1,1-dioxide

3.2.2.2.1 Synthesis of 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one

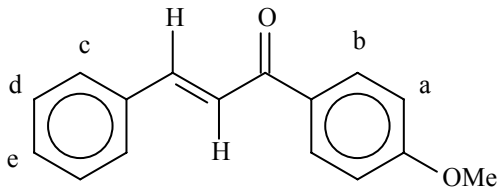


(**238**) (**239**) (**240**)
$C_{16}H_{14}O_2$
MW = 238.28 g/mol

Benzaldehyde (**238**) (6 mL, 6.300 g, 59.4 mmol) and 4'-methoxyacetophenone (**239**) (8.92 g, 59.4 mmol) were dissolved in dry ethanol (25 mL). Sodium hydroxide (0.70 g, 17.5 mmol, 0.3 eq.) in water (2 mL) was added to the mixture. The whole was stirred for 5-10 minutes. The resulting yellow solution was allowed to stand for 10 minutes and cooled in an ice bath to form a yellow solid. Recrystallisation from ethanol gave the product as pale yellow needles (**12.07 g, 85%, m.p.=107-108˚C**).

IR υ_{max} (cm^{-1}): 3058 (w), 2972 (w), 2936 (w), 1655 (s, **C=O**), 1599 (s), 1572 (m), 1447 (m), 1339 (m), 1261 (m), 1228 (m), 1186 (m), 1036 (m), 973 (m), 829 (m), 762 (s).

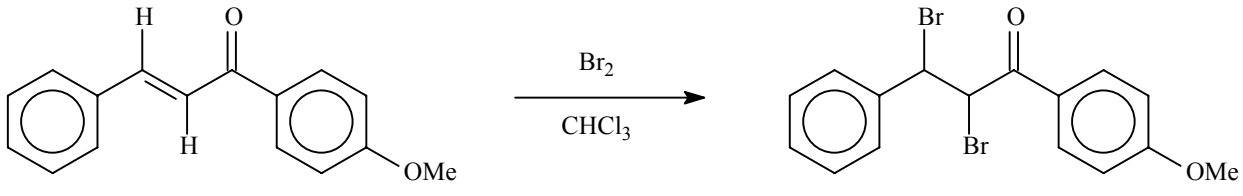
The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 8.07 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 7.83 (1H, d, *J*=15.6 Hz, Ph**CH**=CH), 7.66 (2H, m, **CH**$_c$ (Ph)), 7.58 (1H, d, *J*=15.6 Hz, PhCH=**CH**), 7.43 (3H, m, **CH**$_{d,e}$ (Ph)), 7.01 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 3.92 (3H, s, ArO**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 188.70 (**C=O**), 163.40 (**C**-OMe (Ar)), 143.96 (Ph**CH**=CH)), 135.05 (**C** (Ph)), 131.06 (**C**-CO (Ar)), 130.81 (**CH**$_b$ (ArOMe)), 130.32 (**CH**$_e$ (Ph)), 128.91 (**CH**$_d$ (Ph)), 128.35 (**CH**$_c$ (Ph)), 121.83 (PhCH=**CH**)), 113.82 (**CH**$_a$ (ArOMe)), 55.49 (**CH$_3$**)).

3.2.2.2.2 Synthesis of 2,3-dibromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one

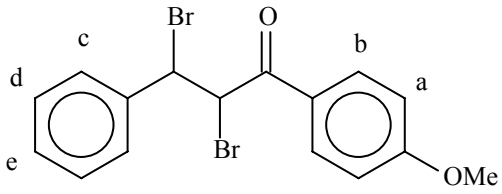


(**240**) (**241**)
$C_{16}H_{14}Br_2O_2$
MW = 398.09 g/mol

1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (**240**) (12.07 g, 50.6 mmol) was dissolved in dry chloroform (30 mL). A solution of bromine (59 mL of a 1M solution in chloroform, 59.0 mmol, 1.2 eq.) was added dropwise over 15 minutes at room temperature to the mixture which turned from pale yellow to dark orange. Petroleum ether 60-80˚C (90 mL) was added to the solution, which was corked and left to stand at room temperature for 30 minutes. The resulting white solid was collected by vacuum filtration and washed with cold petroleum ether. Recrystallisation from chloroform and petroleum ether 60-80˚c gave the product as a white solid (**14.33 g, 71%, m.p.=156-158˚C**).

IR υ_{max} (cm^{-1}) 3006 (w), 2837 (w), 1667 (s, **C=O**), 1599 (s), 1513 (m), 1455 (m), 1418 (w), 1378 (m), 1327 (m), 1309 (m), 1270 (s), 1229 (m), 1171 (m), 1157 (s), 1124 (m), 1023 (m), 982 (m), 840 (s), 809 (w), 751 (s), 693 (s), 611 (m), 578 (s), 563 (s).

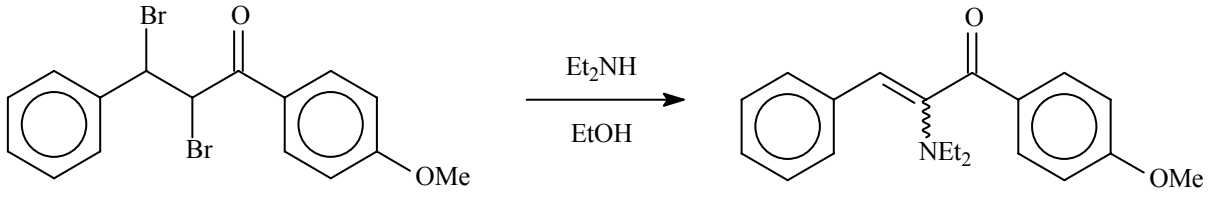
The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 8.12 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 7.56 (2H, m, **CH**$_c$ (Ph)), 7.46 (2H, m, **CH**$_d$ (Ph)), 7.42 (1H, m, **CH**$_e$ (Ph)), 7.05 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 5.84 (1H, d, *J*=11.3 Hz, **CH**), 5.68 (1H, d, *J*=11.3 Hz, **CH**), 3.94 (3H, s, ArO**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 189.63 (**C=O**), 164.43 (**C** (Ar)), 138.41 (**C** (Ar)), 131.36 (**CH**$_b$ (Ar)), 129.23 (**CH**$_e$ (Ar)), 128.83 (**CH**$_d$ (Ar)), 128.35 (**CH**$_c$ (Ar)), 127.17 (**C** (Ar)), 114.26 (**CH**$_a$ (Ar)), 55.63 (**CH$_3$**), 49.99 (**CH**$_α$), 46.72 (**CH**$_β$).

3.2.2.2.3 Synthesis of 2-diethylamino-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one



(**241**) (**242**)
$C_{20}H_{23}NO_2$
MW = 309.40 g/mol

Dry ethanol (6.5 mL) was added to 2,3-dibromo-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**241**) (6.508 g, 20.52 mmol) to form a damp solid mixture. Diethylamine (4.2 mL, 2.982 g, 40.78 mmol, 2 eq.) was rapidly added to the mixture at room temperature, which, after 10 minutes, turned to a dark red solution. The whole was stirred under nitrogen for 26 hours (monitored by TLC). After 26 hours, a solution of sodium ethoxide (0.472 g; 20.52 mmol; 1 eq. of sodium in 10 mL of dry ethanol) was added to the mixture. The reaction mixture was stirred

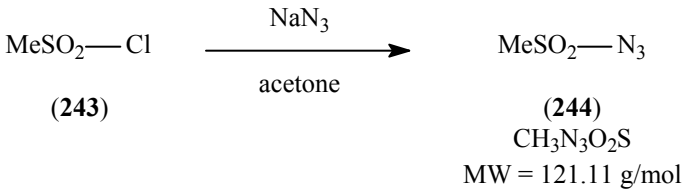
for a further 18 hours (monitored by TLC). The solvent was removed *in vacuo* to give the crude product as a dark red oil (m=8.56 g). It was purified by gravity silica chromatography (PE 40-60ºC / ethyl acetate: 10/1) to give the product as an orange oil (**5.119 g, 81%**).

IR υ_{max} (cm^{-1}) 2976 (w), 2839 (w), 1708 (w, **C=O**), 1657 (m, **C=C**-NEt_2), 1594 (s, **Ar**), 1509 (m), 1454 (m), 1378 (m), 1307 (m), 1250 (s), 1167 (s), 1025 (m), 838 (m).

^{1}H NMR δ (500 MHz, $CDCl_3$) 8.06 (2H, d, *J*=8.8 Hz, **CH** (Ar)), 7.05 (4H, m, **CH** (Ph)), 6.93 (1H, m, **CH** (Ph)), 6.89 (2H, d, *J*=8.8 Hz, **CH** (Ar)), 5.60 (1H, s, **CH**), 3.85 (3H, s, ArO**CH_3**), 3.15 (4H, q, *J*=7.0 Hz, N**CH_2**CH_3), 1.16 (6H, t, *J*=7.0 Hz, NCH_2**CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 195.70 (**C=O**), 163.86 (**C**), 145.57 (**C**), 137.35 (**C**), 131.96 (**CH** (Ar)), 129.70 (**C**), 127.98 (**CH** (Ar)), 127.09 (**CH** (Ar)), 124.28 (**CH** (Ar)), 113.74 (**CH** (Ar)), 102.16 (**CH**=C-NEt_2)), 55.48 (ArO**CH_3**), 43.51 (N**CH_2**CH_3), 12.39 (NCH_2**CH_3**).

3.2.2.2.4 Synthesis of methanesulfonyl azide



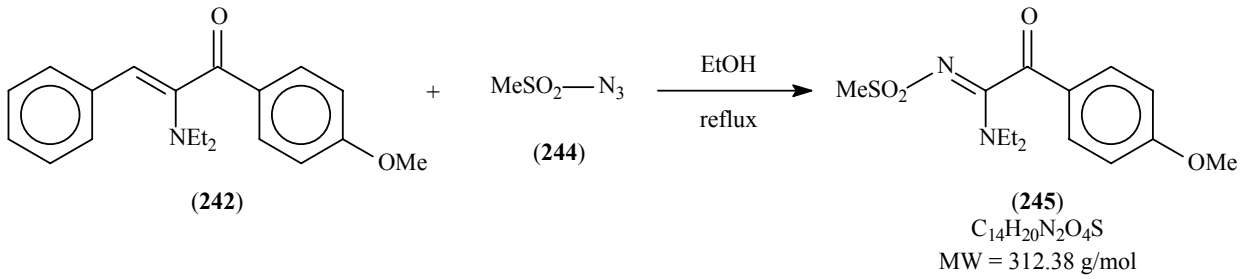
To a solution of methanesulfonyl chloride (**243**) (3 mL, 4.444 g, 38.8 mmol) in dry acetone (20 mL) was added sodium azide (3.770 g, 58 mmol, 1.5 eq.) under nitrogen over 40 minutes in small portions using a powder addition funnel. The mixture was stirred for 2 to 3 days at room temperature. The reaction mixture was filtered, and the salt was washed with dry acetone (3 x 5 mL). The solvent was removed *in vacuo* at 25˚C to give the product as a pale yellow oil (**4.144 g, 88%**).

IR υ_{max} (cm^{-1}) 3034 (w), 2937 (w), 2132 (s, **N_3**), 1349 (s, **SO_2**), 1327 (s), 1193 (s), 1148 (s, **SO_2**), 963 (s), 773 (s), 727 (s).

^{1}H NMR δ (500 MHz, $CDCl_3$) 3.29 (3H, s, **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 42.75 (**CH_3**).

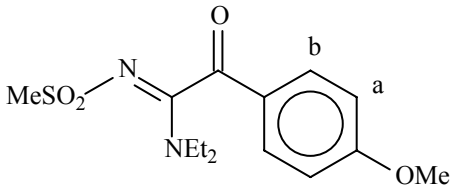
3.2.2.2.5 Synthesis of *N*-methanesulfonylamidine



A solution of methanesulfonyl azide (**243**) (0.825 g, 6.81 mmol) in dry ethanol (7 mL) was added to a solution of 2-diethylamino-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**242**) (2.108 g, 6.81 mmol, 1 eq.) in dry ethanol (14 mL) under nitrogen. The whole was heated at reflux for 22 hours. The solvent was evaporated under reduced pressure to give the crude product as a dark orange oil. It was crystallised from dry diethyl ether (20 mL) to give the product as a yellow solid (**1.754 g, 82%, m.p.=123-125˚C**, lit.: m.p. = 116˚C[178]).

IR υ_{max} (cm^{-1}) 2979 (w), 2938 (w), 1674 (m, **C=O**), 1596 (s, **C=N**), 1544 (s, **Ar**), 1512 (m), 1457 (m),1423 (w), 1383 (w), 1360 (w), 1288 (s, **SO_2**), 1264 (s), , 1243 (s), 1214 (m), 1170 (s), 1154 ((m), 1129 (s, **SO_2**), 1082 (w), 1020 (m), 981 (m), 961 (w), 881 (m), 855 (w), 831 (s), 786 (m), 728 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



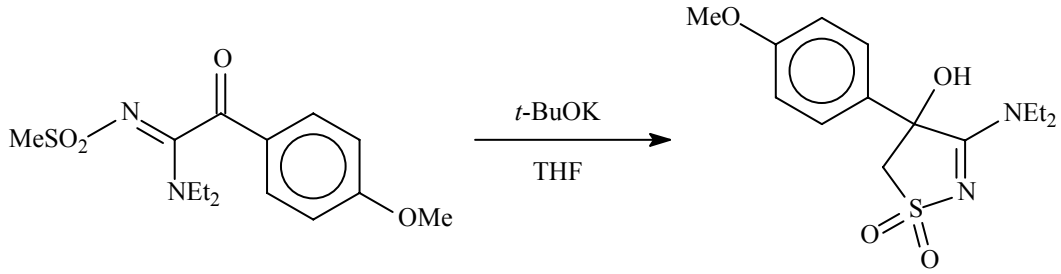
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.87 (2H, bd, *J*=7.2 Hz, **CH_b** (Ar)), 7.00 (2H, d, *J*=9.1 Hz, **CH_a** (Ar)), 3.89 (3H, s, ArO**CH_3**), 3.73 (1H, dq, *J*=13.5 and 7.1 Hz, N**CH_2**CH_3), 3.53 (1H, dq, *J*=13.5 and 7.1 Hz, N**CH_2**CH_3), 3.20 (1H, dq, *J*=14.2 and 7.1 Hz, N**CH_2**CH_3), 3.17 (1H, dq, *J*=14.2 and 7.1 Hz, N**CH_2**CH_3), 2.98 (3H, s, **CH_3**SO_2), 1.33 (3H, t, *J*=7.1 Hz, NCH_2**CH_3**), 1.10 (3H, t, *J*=7.1 Hz, NCH_2**CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 190.58 (**C=O**), 164.88 (**C**-OMe (Ar)), 162.24 (**C=N**), 131.40 (**CH**$_b$ (Ar)), 127.68 (**C** (Ar)), 114.54 (**CH**$_a$ (Ar)), 55.63 (ArO**CH$_3$**), 44.12 (N**CH$_2$**CH_3), 42.57 (**CH$_3$**SO_2), 42.46 (N**CH$_2$**CH_3), 13.71 (NCH_2**CH$_3$**), 11.90 (NCH_2**CH$_3$**).

MS (*m/z*): 313.1 ($[M+H]^+$), 335.1 ($[M+Na]^+$), 647.2 ($[2M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{14}H_{20}N_2NaO_4S$ calculated 335.1036 measured 335.1033.

3.2.2.2.6 Synthesis of 3-diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide

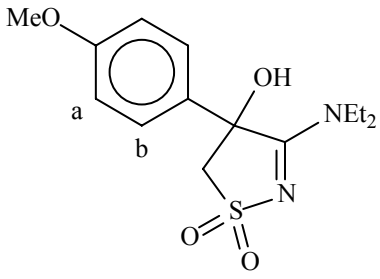


(**245**) (**246**)
$C_{14}H_{20}N_2O_4S$
MW = 312.38 g/mol

N-Methanesulfonyl amidine (**245**) (1.674 g, 5.36 mmol) was dissolved in dry THF (10 mL) under nitrogen. Potassium *tert*-butoxide (3 mL of a 20% solution in THF, 0.601 g, 5.36 mmol, 1 eq.) was added to the mixture which turned very milky. The whole was stirred for 2 hours. The reaction mixture was neutralised with 1M HCl. The aqueous layer was extracted with DCM (2 x 5 mL). The combined organic layers were washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* to yield the product as a yellow solid (**1.486g, 89%, m.p.=169-170˚C**, lit.: m.p. = 177˚C[178]).

IR υ_{max} (cm^{-1}) 3384 (br, **OH**), 2976 (w), 1582 (s, **C=N**), 1513 (s), 1442 (m), 1383 (w), 1361 (w), 1297(s, **SO$_2$**), 1252 (s), 1228 (s), 1179 (m), 1148 (s), 1125 (s, **SO$_2$**), 1080 (m), 1031 (m), 969 (m), 949 (m), 914 (m), 854 (m), 834 (m), 800 (w), 783 (m), 768 (w), 732 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



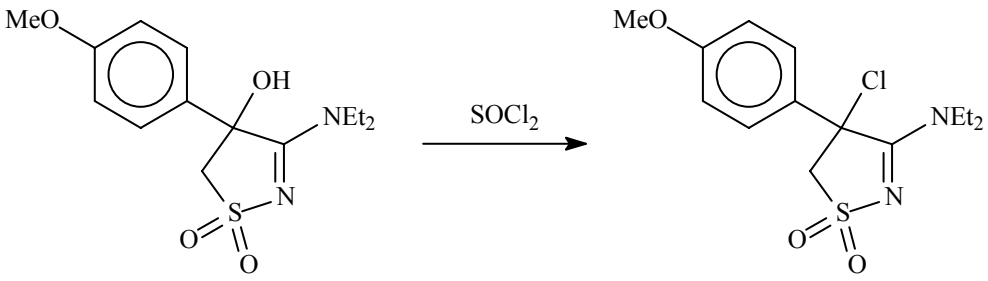
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.45 (2H, d, *J*=8.8 Hz, **CH**$_b$ (Ar)), 6.94 (2H, d, *J*=8.8 Hz, **CH**$_a$ (Ar)), 5.54 (1H, bs, **OH**), 3.93 (1H, d, *J*=14.0 Hz, **CH$_2$**SO_2), 3.83 (3H, s, ArO**CH$_3$**), 3.65 (1H, d, *J*=14.0 Hz, **CH$_2$**SO_2), 3.54 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.45 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.32 (1H, q, *J*=7.0 Hz, N**CH$_2$**CH_3), 3.31 (1H, q, *J*=7.0 Hz, N**CH$_2$**CH_3), 1.25 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 0.81 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 168.84 (Et_2N-**C**=N), 159.47 (**C**-OMe (Ar)), 133.03 (**C** (Ar)), 125.27 (**CH**$_b$ (Ar)), 114.31 (**CH**$_a$ (Ar)), 83.47 (**C**), 64.68 (**CH$_2$**SO_2), 55.31 (ArO**CH$_3$**), 44.88 (N**CH$_2$**CH_3), 43.36 (N**CH$_2$**CH_3), 12.73 (NCH_2**CH$_3$**), 11.33 (NCH_2**CH$_3$**).

MS (*m/z*): 335.1 ($[M+Na]^+$), 647.2 ($[2M+Na]^+$), 959.3 ($[3M+Na]^+$), 1271.4 ($[4M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{14}H_{20}N_2NaO_4S$ calculated 335.1036 measured 335.1028.

3.2.2.2.7 Synthesis of 4-chloro-3-diethylamino-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide



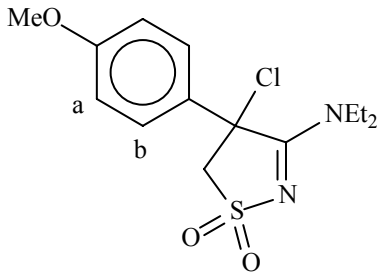
(**246**)

(**247**)
$C_{14}H_{19}ClN_2O_3S$
MW = 330.82 g/mol

3-Diethylamino-4-hydroxy-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**246**) (1.222 g, 3.91 mmol) was heated in thionyl chloride (2 mL, 3.262, 27.42 mmol) at reflux temperature for 2 hours. Excess thionyl chloride was evaporated under reduced pressure. The residue was dissolved in DCM (10 mL) and neutralised with a 10% solution of $NaHCO_3$. The aqueous layer was extracted with DCM (2 x 10 mL), and the combined organic layers were washed with water (2 x 10 mL). The organic layer was separated, dried over anhydrous $NaSO_4$, filtered, and concentrated to give the crude product as an oily yellow solid. Purification by gravity silica chromatography (petroleum ether/ethyl acetate: 2/1) gave the desired product as a yellow solid (**1.230 g, 95%, m.p.= 103-105˚C**, lit.: m.p. = 102˚C[178]). Upon repeat reactions, also isolated on occasion were compounds (**248**) (**431 mg, 10%**) and (**261**) (**225 mg, 4%**).

IR υ_{max} (cm^{-1}) 2974 (w), 1578 (s, **C=N**), 1509 (s), 1439 (m),1416 (w), 1383 (w), 1360 (w), 1310 (s, **SO_2**), 1237 (s), 1207 (m), 1183 (m), 1137 (s, **SO_2**), 1082 (w), 1053 (m), 1028 (m), 971 (m), 938 (w), 906 (s), 826 (s), 783 (m), 751 (w), 735 (w).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



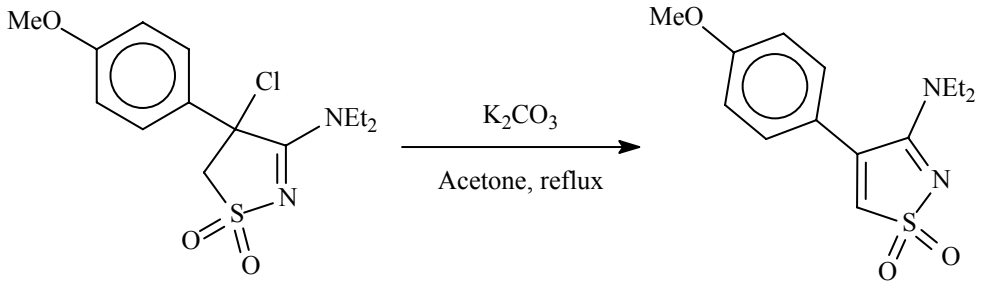
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.42 (2H, d, *J*=8.9 Hz, **CH_b** (Ar)), 6.93 (2H, d, *J*=8.9 Hz, **CH_a** (Ar)), 4.17 (1H, d, *J*=14.5 Hz, **CH_2SO_2**), 3.85 (3H, s, ArO**CH_3**), 3.82, (1H, d, *J*=14.5 Hz, **CH_2SO_2**), 3.67 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH_2CH_3**), 3.51 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH_2CH_3**), 3.21 (1H, dq, *J*=14.4 and 7.1 Hz, N**CH_2CH_3**), 3.08 (1H, dq, *J*=14.4 and 7.1 Hz, N**CH_2CH_3**), 1.30 (3H, t, *J*=7.1 Hz, NCH_2**CH_3**), 0.90 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 164.59 (**C=N**), 160.09 (**C**-OMe (Ar)), 130.35 (**C** (Ar)), 126.08 (**CH_b** (Ar)), 114.74 (**CH_a** (Ar)), 71.03 (**C**), 67.81 (**CH_2SO_2**), 55.43 (ArO**CH_3**), 44.97 (N**CH_2CH_3**), 43.98 (N**CH_2CH_3**), 12.30 (NCH_2**CH_3**), 11.06 (NCH_2**CH_3**).

MS (*m/z*) (^{35}Cl): 353.1 ($[M+Na]^+$), 683.2 ($[2M+Na]^+$).

HRMS (*m/z*)(^{35}Cl): $[M+Na]^+$ for $C_{14}H_{19}ClN_2NaO_3S$ calculated 353.0697 measured 353.0690.

3.2.2.2.8 Synthesis of 3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

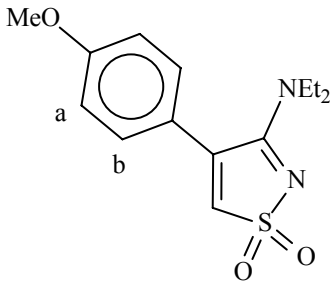


(**247**) (**248**)
$C_{14}H_{18}N_2O_3S$
MW = 294.36 g/mol

4-Chloro-3-diethylamino-4-(4-methoxyphenyl)-4,5*H*-isothiazolin-1,1-dioxide (**247**) (0.999 g, 3.02 mmol) was dissolved in dry acetone (6 mL) and potassium carbonate (0.417 g, 3.02 mmol, 1 eq.) was added to the solution in one portion. The whole was heated at reflux under nitrogen for 4 days and 20 hours. The solvent was evaporated under reduced pressure, and the residue was redissolved in DCM (10 mL), and neutralised with a 10% solution of hydrochloric acid (2.5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 2.5 mL). The combined organic layers were washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield the product as a yellow solid (**0.761 g, 86%, m.p. = 133-135°C**, lit.: m.p. = 134°C[178]). The product was used at the next step with no further purification.

IR υ_{max} (cm^{-1}) 3075 (w), 2975 (w), 2839 (w), 1603 (m, **C=N**), 1556 (s), 1506 (s), 1443 (m), 1408 (m), 1383 (w), 1358 (m), 1288 (s, **SO_2**), 1245 (s), 1189 (s, **SO_2**), 1159 (m), 1122 (s), 1083 (m), 1028 (m), 970 (m), 945 (m), 914 (m), 826 (m), 790 (m), 776 (m), 743 (m), 683 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



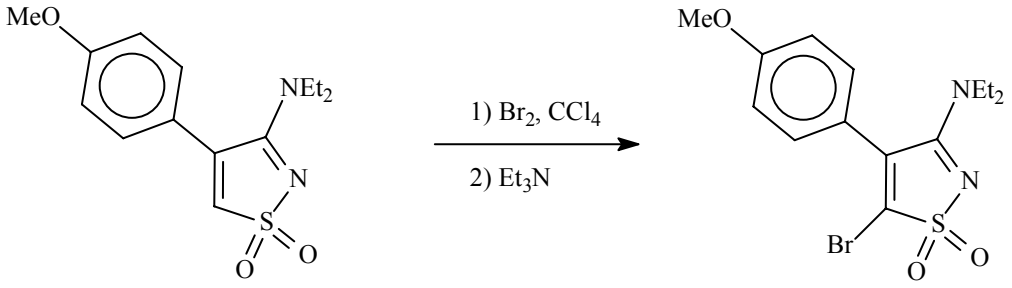
^{1}H NMR δ (400 MHz,$CDCl_3$) 7.24 (2H, d, *J*=8.8 Hz, **CH**$_b$ (Ar)), 7.17 (1H, s, **CH**), 6.97 (2H, d, *J*=8.8 Hz, **CH**$_a$ (Ar)), 3.86 (3H, s, ArO**Me**), 3.64 (2H, bd, *J*=6.3 Hz, N**CH$_2$**CH_3), 3.14 (2H, bd, *J*=6.3 Hz, N**CH$_2$**CH_3), 1.31 (3H, bs, NCH_2**CH$_3$**), 0.93 (3H, bs, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz,$CDCl_3$) 161.09 (Et_2N-**C**=N), 160.61 (**C**-OMe (Ar)), 142.94 (C=**CH**), 139.67 (**C**=CH), 128.71 (**CH**$_b$ (Ar)), 123.82 (**C** (Ar)), 114.56 (**CH**$_a$ (Ar)), 55.45 (ArO**CH$_3$**), 46.67 (N**CH$_2$**CH_3), 43.90 (N**CH$_2$**CH_3), 14.12 (NCH_2**CH$_3$**), 11.93 (NCH_2**CH$_3$**).

MS (*m/z*): 295.1 ($[M+H]^+$), 317.1 ($[M+Na]^+$), 611.2 ($[2M+Na]^+$), 905.3 ($[3M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{14}H_{18}N_2NaO_3S$ calculated 317.0930 measured 317.0931.

3.2.2.2.9 Synthesis of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide



(**248**) (**249**)
$C_{14}H_{17}BrN_2O_3S$
MW = 373.26 g/mol

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (0.942 g, 3.20 mmol) was dissolved in carbon tetrachloride (9.4 mL) and dichloromethane (4.7 mL), and a solution of

bromine (164 μL, 0.511 g, 3.20 mmol, 1 eq.) in carbon tetrachloride (1.9 mL) was added dropwise to the mixture at room temperature under nitrogen. After 2 hours, the starting material had disappeared on TLC, and triethylamine (446 μL, 0.324 g, 3.20 mmol, 1 eq.) was added to the reaction mixture, which was stirred for a further 5 hours. The reaction mixture was washed with an aqueous solution of sodium metabisulfite ($Na_2S_2O_5$) (28 mL), the organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to yield the product as a yellow solid (**1.114 g, 93%, m.p. = 144-145°C**, lit.: m.p. = 163-164°C[183]).

IR υ_{max} (cm^{-1}) 2939 (w), 1619 (w, **C=N**), 1603 (m, **C=C**), 1562 (s), 1506 (s), 1470 (w), 1439 (m), 1400 (w), 1361 (w), 1306 (s, **SO_2**)*, 1291 (s)*, 1251 (s), 1179 (w), 1150 (s, **SO_2**), 1110 (m), 1096 (m), 1017 (m), 1004 (m), 1004 (m), 972 (m), 868 (s), 827 (s), 797 (m), 774 (s), 748 (m), 705 (s).

* Assignments may be interchanged.

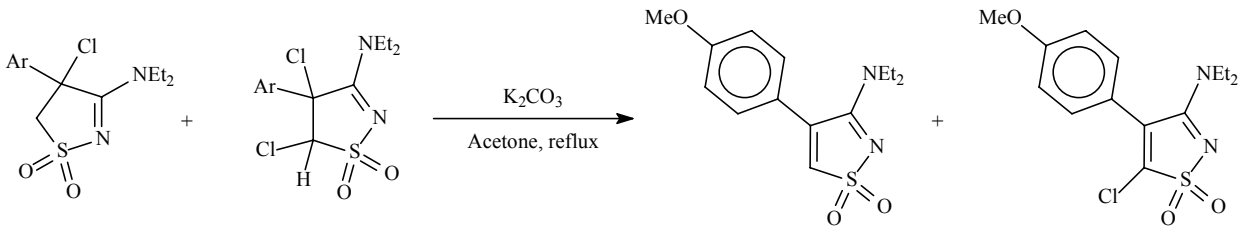
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.14 (2H, d, *J*=8.8 Hz, CH (**Ar**)), 6.98 (2H, d, *J*=8.8 Hz, CH (**Ar**)), 3.81 (3H, s, ArO**Me**), 3.58 (2H, q, *J*=7.1 Hz, N**CH_2**CH_3), 3.09 (2H, q, *J*=7.0 Hz, N**CH_2**CH_3), 1.24 (3H, t, *J*=7.1 Hz, NCH_2**CH_3**), 0.86 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 160.92 (Et_2N-**C**=N), 160.36 (**C**-OMe (Ar)), 137.90 (C=**C**-Br), 135.87 (**C**=CBr), 128.77 (**CH_b** (Ar)), 122.62 (**C** (Ar)), 114.67 (**CH_a** (Ar)), 55.17 (ArO**CH_3**), 46.31 (N**CH_2**CH_3), 43.77 (N**CH_2**CH_3), 13.84 (NCH_2**CH_3**), 11.62 (NCH_2**CH_3**).

MS (*m/z*): 395.0 (^{79}Br) ($[M+Na]^+$), 397.0 (^{81}Br) ($[M+Na]^+$), 769.0 ($[2M+Na]^+$), 1143.0 ($[3M+Na]^+$).

HRMS (^{79}Br) (*m/z*): $[M+Na]^+$ for $C_{14}H_{17}BrN_2NaO_3S$ calculated 395.0035 measured 395.0038.

3.2.2.2.10 Isolation of 5-chloro-3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide



(**247**)
Ar = 4-MeOPh

(**261**)
Ar = 4-MeOPh
$C_{14}H_{17}ClN_2O_3S$
MW = 328.81 g/mol

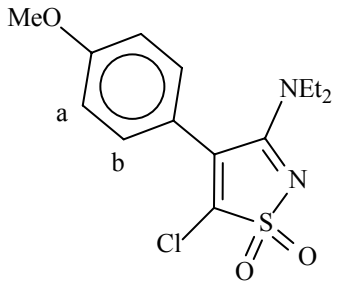
(**248**)
$C_{14}H_{18}N_2O_3S$
MW = 294.36 g/mol

(**264**)
$C_{14}H_{17}ClN_2O_3S$
MW = 328.81 g/mol

A mixture 4-chloroisothiazol-1,1-dioxide (**247**) and 4,5-dichloroisothiazolin-1,1-dioxide (**261**) (3.231 g, ~10/1 mixture approximately from NMR) was dissolved in dry acetone (10 mL) and potassium carbonate (1.350 g, 9.77 mmol, 1 eq.) was added in one portion. The mixture was heated at reflux temperature under nitrogen for 7 days and 19 hours. The solvent was removed *in vacuo* and the residue was dissolved in DCM (~12 mL). It was neutralised with a 10% solution of hydrochloric acid. The aqueous layer was extracted with DCM (2 x 10 mL) and the organic layer was washed with water (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give the crude product as a sticky orange solid (2.207 g). Purification by gravity silica chromatography (PE/EtOAc: 2/1) afforded the isothiazol-1,1-dioxide (**248**) (**1.243 g**) and the 5-chloroisothiazol-1,1-dioxide (**264**) as a yellow solid (**224 mg, m.p. = 123-125°C**).

IR υ_{max} (cm^{-1}) 2976 (w), 2840 (w), 1624 (m, **C=N**), 1604 (m), 1564 (m), 1508 (s), 1443 (w), 1399 (w), 1384 (w), 1357 (w), 1306 (s, **SO_2**), 1248 (s), 1206 (w), 1153 (s, **SO_2**), 1111 (w), 1097 (w), 1082 (w), 1050 (w), 1024 (m), 972 (w), 884 (s), 830 (m), 802 (m), 770 (m), 755 (w), 736 (w), 713 (w).

The assignment for NMR data is as follows:



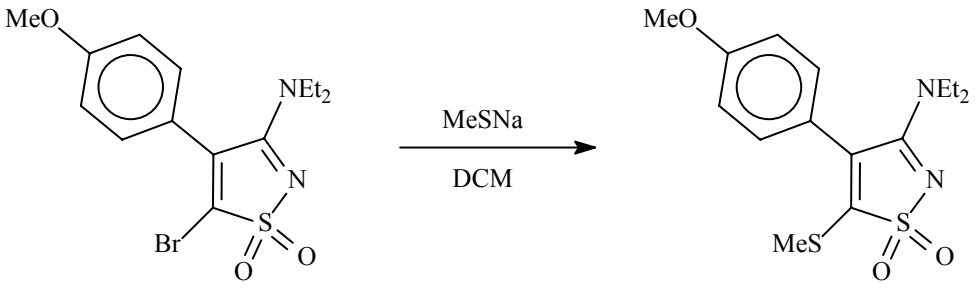
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.20 (2H, d, *J*=8.5 Hz, **CH**$_b$ (Ar)), 7.03 (2H, d, *J*=8.5 Hz, **CH**$_a$ (Ar)), 3.87 (3H, s, O**CH$_3$**), 3.65 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 3.15 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 1.30 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.91 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 160.69 (Et_2N-**C**=N), 160.42 (**C**-OMe (Ar)), 147.75 (C=**C**-Cl), 132.28 (**C**=C-Cl), 129.19 (**CH**$_b$ (Ar)), 121.89 (**C** (Ar)), 114.94 (**CH**$_a$ (Ar)), 55.38 (O**CH$_3$**), 46.46 (N**CH$_2$**CH_3), 43.72 (N**CH$_2$**CH_3), 14.10 (NCH_2**CH$_3$**), 11.92 (NCH_2**CH$_3$**).

MS (*m/z*) (^{35}Cl): 329.1 ($[M+H]^+$).

HRMS (*m/z*) (^{35}Cl): $[M+H]^+$ for $C_{14}H_{18}ClN_2O_3S$ calculated 329.0721 measured 329.0719.

3.2.2.2.11 Synthesis of 3-diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide



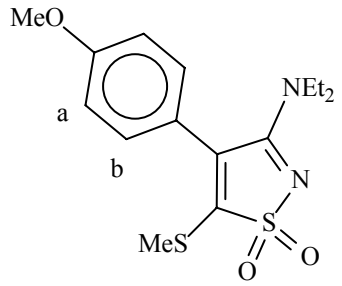
(**249**)

(**250**)
$C_{15}H_{20}N_2O_3S_2$
MW = 340.45 g/mol

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**249**) (0.706 g, 1.89 mmol) was dissolved in dichloromethane (15 mL). Sodium thiomethoxide (0.132 g, 1.89 mmol, 1 eq.), and triethylamine (270 μ0.196 g, 1.93 mmol, 1 eq.) were added to the mixture at room temperature under stirring. The reaction was stirred under nitrogen for 5 hours. The mixture was neutralised with a 10% solution of hydrochloric acid, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated *in vacuo* to yield the product as a yellow solid (**0.627g, 97%, m.p.=170-171˚C**, lit.: m.p. = 174˚C[184]).

IR υ_{max} (cm^{-1}) 2935 (w), 1608 (w), 1583 (s, **C=N**), 1550 (m), 1505 (m), 1440 (w), 1393 (m), 1286 (s, **SO_2**), 1245 (s), 1145 (s, **SO_2**), 1109 (m), 1096 (m) ,1081 (m), 1025 (m), 968 (w), 886 (m), 828(m), 801 (m), 777 (m), 731 (s), 694 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



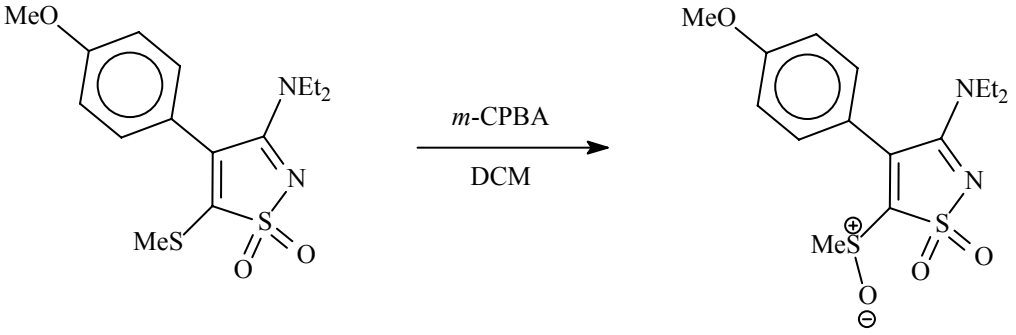
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.19 (2H, d, *J*=8.7 Hz, CH (**Ar**)), 7.01 (2H, d, *J*=8.7 Hz, CH (**Ar**)), 3.87 (3H, s, ArO**CH_3**), 3.61 (2H, q, *J*=7.0 Hz, N**CH_2**CH_3), 3.11 (2H, q, *J*=7.0 Hz, N**CH_2**CH_3), 2.79 (3H, s, S**Me**), 1.30 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**), 0.89 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 160.97 (N=**C**-NEt_2), 160.26 (**C**-OMe (Ar)), 157.02 (**C**-SMe), 129.55 (**CH_b** (Ar)), 125.73 (C (Ar-**C**=C-SMe)), 124.17 (**C** (Ar)), 114.95 (**CH_a** (Ar)), 55.32 (O**CH_3**), 46.39 (N**CH_2**CH_3), 43.30 (N**CH_2**CH_3), 14.09 (NCH_2**CH_3**), 12.92 (S**CH_3**), 12.15 (NCH_2**CH_3**).

MS (*m/z*) 341.1 ($[M+H]^+$), 703.2 ($[2M+Na]^+$).

HRMS (*m/z*): $[M+H]^+$ for $C_{15}H_{21}N_2O_3S_2$ calculated 341.0988 measured 341.0992.

3.2.2.2.12 Synthesis of 3-diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

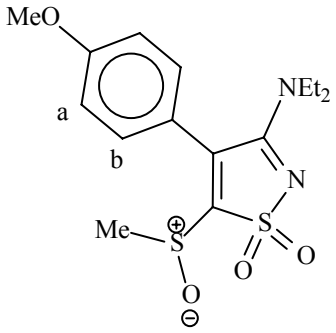


(**250**) (**265**)
$C_{15}H_{20}N_2O_4S_2$
MW = 356.45 g/mol

3-Diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**250**) (500 mg, 1.47 mmol), was dissolved in dry DCM (10 mL) and *m*-CPBA (253 mg, 1.47 mmol, 1 eq.) was added in one portion. The reaction was stirred at RT under nitrogen. The reaction was monitored by thin layer chromatography and other portions of *m*-CPBA were added to the mixture to complete the reaction (after 6 hours: 51 mg, 0.30 mmol, 0.2 eq.; after 27 hours: 25 mg, 0.14 mmol, 0.1 eq.; after 50 hours: 25 mg, 0.14 mmol, 0.1 eq.). After 54 hours, the metachlorobenzoic acid precipitate was filtered off, and the filtrate was washed with a 20% $NaHCO_3$ solution (5 mL) and water (2 x 5 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give the crude product as a yellow solid. It was purified by gravity silica chromatography (PE 40-60ºC / ethyl acetate: gradient elution 2/1, 3/2, 1/1) to yield the product as a yellow solid (**350 mg, 67%, m.p.=167-169˚C**).

IR υ_{max} (cm^{-1}) 2977 (w), 1601 (s, **C=N**), 1561 (s), 1507 (s), 1443 (m), 1406 (m), 1384 (w),1358 (m), 1290 (s, **SO_2**), 1247(s), 1205 (m), 1146 (s, **SO_2**), 1066 (s), 1021 (s), 964 (s), 921 (w), 873 (w), 829 (s), 799 (w), 777 (m), 733 (m), 708 (m).

The assignment for NMR in $CDCl_3$ was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 7.41 (1H, bs, **CH**$_b$ (Ar)), 7.15 (1H, bs, **CH**$_b$ (Ar)), 7.02 (2H, bs, **CH**$_a$ (Ar)), 3.87 (3H, s, O**CH$_3$**), 3.66 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.60 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.16 (3H, s, **CH$_3$**SO), 3.11 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 1.31 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.92 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 161.02 (**C**-OMe (Ar)), 158.54 (Et_2N-**C**=N), 155.81 (ArC=**C**SOCH_3), 141.21 (Ar**C**=CSOCH_3), 129.72 (**CH**$_b$ (Ar)), 128.66 (**CH**$_b$ (Ar)), 120.84 (**C** (Ar)), 114.91 (**CH**$_a$ (Ar)), 114.56 (**CH**$_a$ (Ar)), 55.40 (O**CH$_3$**), 47.26 (N**CH$_2$**CH_3), 43.75 (N**CH$_2$**CH_3), 38.34 (**CH$_3$**SO), 14.16 (NCH_2**CH$_3$**), 11.72 (NCH_2**CH$_3$**).

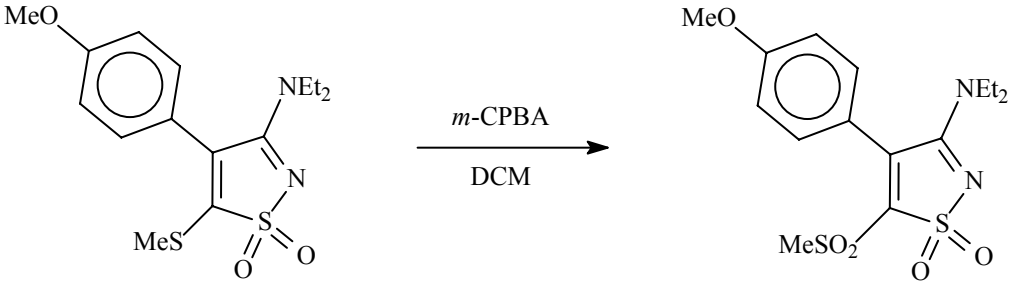
^{1}H NMR δ (500 MHz, DMSO-D_6) 7.54 (1H, bd, *J*=8.2 Hz, **CH**$_b$ (Ar)), 7.47 (1H, bd, *J*=8.2 Hz, **CH**$_b$ (Ar)), 7.09 (1H, bd, *J*=8.2 Hz, **CH**$_a$ (Ar)), 7.06 (1H, bd, *J*=8.2 Hz, **CH**$_a$ (Ar)), 3.81 (3H, s, O**CH$_3$**), 3.53 (2H, bq, *J*=7.0 Hz, N**CH$_2$**CH_3), 3.08 (2H, bq, *J*=7.0 Hz, N**CH$_2$**CH_3), 3.04 (3H, s, **CH$_3$**SO), 1.20 (3H. t, *J*=7.0 Hz, NCH_2**CH$_3$**), 0.83 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, DMSO-D_6) 160.29 (**C**), 157.68 (**C**), 154.79 (**C**), 139.89 (**C**), 129.98 (**CH** (Ar)), 129.21 (**CH** (Ar)), 121.33 (**C**), 114.47 (**CH** (Ar)), 114.28 (**CH** (Ar)), 55.30 (O**CH$_3$**), 46.54 (N**CH$_2$**CH_3), 43.40 (N**CH$_2$**CH_3), 38.90 (CH_3SO), 13.60 (NCH_2**CH$_3$**), 11.47 (NCH_2**CH$_3$**).

MS (*m/z*) 357.1 ($[M+H]^+$), 713.2 ($[2M+H]^+$), 735.2 ($[2M+Na]^+$).

HRMS (*m/z*): $[M+NH_4]^+$ for $C_{15}H_{24}N_3O_4S_2$ calculated 374.1203 measured 374.1198.

3.2.2.2.13 Synthesis of 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)isothiazol-1,1-dioxide

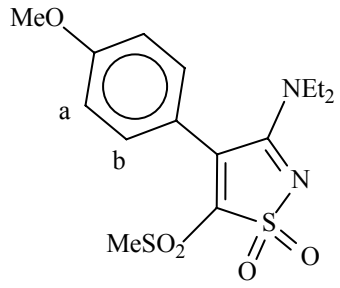


(**250**) (**251**)
$C_{15}H_{20}N_2O_5S_2$
MW = 372.45 g/mol

3-Diethylamino-5-methanesulfanyl-4-(4-methoxyphenyl)-isothiazole-1,1-dioxide (**250**) (2.65 g, 7.78 mmol) was dissolved in dry DCM (60 mL), and *m*-CPBA (2.69 g, 15.59 mmol, 2 eq.) was added in one portion. The solution was stirred under nitrogen at room temperature, and the reaction was monitored by thin layer chromatography (TLC). More *m*-CPBA was added to the mixture until disappearance of the starting material on TLC (1.35 g (1 eq.) after 5 hours, 0.68 g (0.5 eq.) after 24 hours, 0.27 g (0.2 eq.) after 29 hours). The whole was stirred for 31 hours overall. Then, the metachlorobenzoic acid precipitate was filtered off and the filtrate was washed with a 20% sodium bicarbonate solution (18 mL), and then with water (2 x 18 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness affording the crude product as a yellow solid (3.23 g). It was crystallised from DCM (10 mL) / diethyl ether (5 mL) to give the product as a yellow solid (**1.469g, 51%, m.p.=172˚C**, lit.: m.p.=159-161˚C[174])

IR υ_{max} (cm^{-1}) 2980 (w), 1605 (m, **C=N**), 1568 (m), 1509 (m), 1464 (w), 1443 (w), 1405 (m), 1360 (w), 1332 (s), 1316 (m), 1292 **(s, SO_2)**, 1249 (m), 1204 (m)1162 (s), 1153 (s), 1141 (s, **SO_2**), 1099 (m), 1073 (m), 1047 (m), 1021 (m), 968 (s), 921 (m), 880 (m), 841 (m), 810 (m), 779 (m), 766 (m), 743 (m), 714(m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



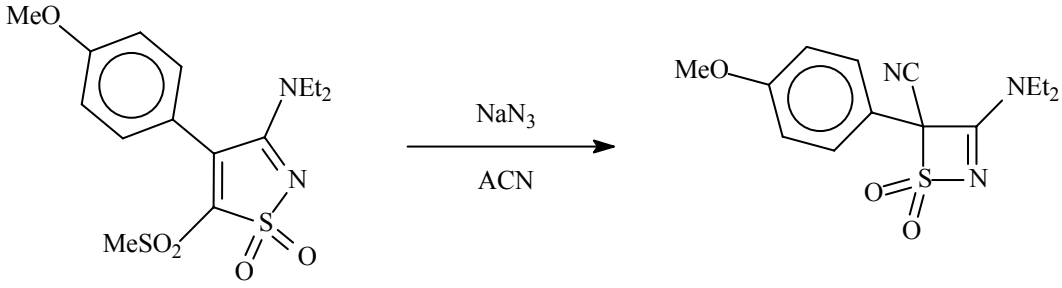
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.33 (2H, d, *J*=8.8 Hz, **CH**$_b$ (Ar)), 7.03 (2H, d, *J*=8.8 Hz, **CH**$_a$ (Ar)), 3.87 (3H, s, O**CH$_3$**), 3.64 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH$_3$), 3.17 (3H, s, **CH$_3$**SO$_2$), 3.08 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH$_3$), 1.32 (3H, t, *J*=7.1 Hz, NCH$_2$**CH$_3$**), 0.91 (3H, t, *J*=7.1 Hz, NCH$_2$**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 161.23 (**C**-OCH$_3$ (Ar)), 158.24 (Et$_2$N-**C**=N), 152.63 (ArC=**C**SO$_2$Me), 142.15 (Ar**C**=CSO$_2$Me), 129.08 (**CH**$_b$ (Ar)), 119.84 (C (Ar)), 114.57 (**CH**$_a$ (Ar)), 55.37 (O**CH$_3$**), 47.86 (N**CH$_2$**CH$_3$), 44.05 (N**CH$_2$**CH$_3$), 43.93 (SO$_2$**CH$_3$**), 14.19 (NCH$_2$**CH$_3$**), 11.65 (NCH$_2$**CH$_3$**).

MS (*m/z*) 395.1 ([M+Na]$^+$), 767.2 ([2M+Na]$^+$).

HRMS (*m/z*): [M+Na]$^+$ for $C_{15}H_{20}N_2NaO_5S_2$ calculated 395.0706 measured 395.0710.

3.2.2.2.14 Ring contraction of 3-diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide: synthesis of 4-cyano-3-diethylamino-4-(4-methoxy-phenyl)-1,2-thiazetin-1,1-dioxide



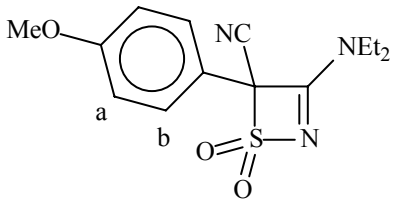
(**251**)

(**252**)
$C_{14}H_{17}N_3O_3S$
MW = 307.36 g/mol

3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**251**) (360 mg, 0.97 mmol) was dissolved in dry acetonitrile (18 mL). Sodium azide (63 mg, 0.97 mmol, 1 eq.) was added to the mixture, and the reaction was stirred under nitrogen at room temperature until disappearance of the starting material on TLC (after 5 hours). The solvent was evaporated *in vacuo*, and the residue was taken up with DCM (70 mL), and washed with water (2 x 35 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the crude product as an orange oil (330 mg). It was purified by flash silica chromatography (petroleum ether / ethyl acetate: gradient elution 5/2→1/1) to give the product as a white solid (**170 mg, 57%, m.p.=104-105°C**, lit.: m.p. = 121°C[174]).

IR υ_{max} (KBr, cm^{-1}) 2981 (w), 2246 (w, **CN**), 1641 (s, **C=N**), 1608 (m), 1513 (s), 1464 (w), 1386 (w), 1336 (s, **SO_2**), 1308 (m), 1262 (s), 1173 (s), 1158 (s, **SO_2**), 1030 (m), 966 (w), 942 (w), 907 (w), 814 (m), 788 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 7.40 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 7.00 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 3.81 (3H, s, O**CH$_3$**), 3.61 (1H, dq, *J*=13.9 and 7.2 Hz, N**CH$_2$**CH_3), 3.43 (1H, dq, *J*=13.9 and 7.2 Hz, N**CH$_2$**CH_3), 3.12 (1H, dq, *J*=14.4 and 7.2 Hz, N**CH$_2$**CH_3), 3.09 (1H, dq, *J*=14.4 and 7.2 Hz, N**CH$_2$**CH_3). 1.28 (3H, t, *J*=7.2 Hz, NCH_2**CH$_3$**), 1.06 (3H, t, *J*=7.2 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 161.68 (**C**-OMe (Ar)), 160.58 (Et_2N-**C**=N), 128.37 (**CH**$_b$ (Ar)), 116.45 (**C** (Ar)), 115.08 (**CH**$_a$ (Ar)), 111.14 (**CN**), 86.23 (**C**), 55.38 (O**CH$_3$**), 45.31 (N**CH$_2$**CH_3), 42.19 (N**CH$_2$**CH_3), 12.63 (NCH_2**CH$_3$**), 11.32 (NCH_2**CH$_3$**).

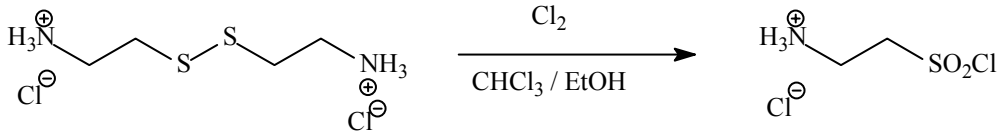
MS (*m/z*): 330.1 ($[M+Na]^+$), 637.2 ($[2M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{14}H_{17}N_3NaO_3S$ calculated 330.0883 measured 330.0888.

3.3 Synthesis of *β*-sultams and *γ*-sultams

3.3.1 Synthesis of *β*-sultams (ethanesultams)

3.3.1.1 Synthesis of taurine sulfonyl chloride

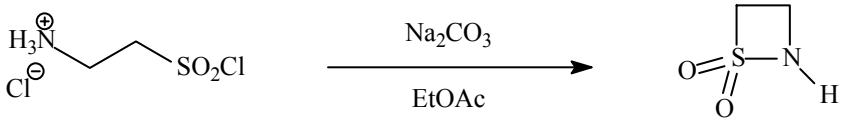


(**286**) (**287**)
$C_2H_7Cl_2NO_2S$
MW = 166.06 g/mol

A suspension of cystamine dihydrochloride (**286**) (10.0 g, 44.4 mmol) was mixed in dry chloroform (250 mL) and dry ethanol (125 mL). Chlorine was passed into the solution at -10˚C under an atmosphere of nitrogen until complete saturation, noted by a permanent pale green colouration (1 hour). The system was purged with nitrogen, and dry diethyl ether (60 mL) was added to the mixture, which was stirred for a further 1 hour at room temperature. The reaction mixture was stored at 4˚C overnight. The white precipitate was filtered off under vacuum and washed with dry diethyl ether to give the product as a white solid (**13.82 g, 94%**).

IR υ_{max} (cm^{-1}) 2995 (w), 2912 (w), 2910 (bs, **NH_3**), 1599 (w), 1558 (w), 1515 (w), 1399 (w) 1371 (s, **SO_2**), 1279 (w), 1173 (m), 1159 (s, **SO_2**), 1107 (w), 1085 (m), 1040 (w), 1029 (w), 943 (w), 837 (w), 773 (m), 701 (s), 600 (w).

3.3.1.2 Synthesis of 1,2-thiazetidin-1,1-dioxide (*β*-sultam)



(**287**) (**284**)
$C_2H_5NO_2S$
MW = 107.12 g/mol

Taurine sulfonyl chloride (**287**) (13.54 g, 81.5 mmol) was added to finely ground anhydrous sodium carbonate (17.28 g, 163.0 mmol, 2 eq.) in dry ethyl acetate (370 mL) and stirred at RT for 46 hours. The reaction mixtutre was filtered through Celite®. The solvent was removed *in*

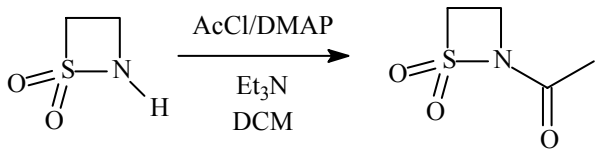
vacuo to give the product as a white solid (**2.62-5.29 g, 14-60 %, m.p.= 50-52˚C**, lit: m.p.= 53˚C[29]).

IR υ_{max} (cm^{-1}) 3581 (br), 3297 (br, **NH**), 3048 (w), 2987 (w), 2919 (w), 1629 (w), 1485 (w), 1415 (w), 1300 (s, **SO_2**), 1252 (s), 1150 (s, **SO_2**), 1114 (m), 992 (w), 963 (m), 917 (w), 763 (m), 654 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 5.32 (1H, bs, **NH**), 4.25 (2H, dt, *J*=7.0 and 1.7 Hz, **CH_2SO_2**), 3.33 (2H, dt, *J*=7.0 and 3.9 Hz, **CH_2**NH).

^{13}C NMR δ (400 MHz, $CDCl_3$) 60.93 (**CH_2SO_2**), 28.14 (**CH_2**NH).

3.3.1.3 *N*-Acylation of *β*-sultam



(**284**) (**285**)
$C_4H_7NO_3S$
MW = 149.16 g/mol

Freshly distilled acetyl chloride (380 µL, 419 mg, 5.34 mmol, 1 eq.) was added dropwise to a solution of *β*-sultam (**284**) (566 mg, 5.28 mmol) and *N,N*-dimethylaminopyridine (49 mg, 0.40 mmol, 0.2 eq.) in dry dichloromethane (15 mL) at -78˚C. The reaction mixture was stirred for 30 minutes before the addition of triethylamine (750 µL, 542 mg, 5.36 mmol, 1 eq.) at -78˚C over 5 minutes. The mixture was then allowed to warm to RT and stirred for 27 hours. Filtration and concentration under reduced pressure gave the crude product as a yellow oily solid (1.414 g). It was purified by silica chromatography (PE 40-60˚C/EtOAc : 1/2) to give the product as a white solid (**439 mg, 56%, m.p.=74-75˚C**, lit.: m.p.=74˚C[256]).

IR υ_{max} (cm^{-1}) 2982 (w), 1695 (s, **C=O**), 1557 (w), 1373 (m), 1316 (s, **SO_2**), 1286 (m), 1199 (s, **SO_2**)*, 1158 (s)*, 1037 (w), 959 (w), 907 (s), 779 (m), 724 (s), 688 (m), 648 (m), 623 (w), 588 (w), 547 (s).

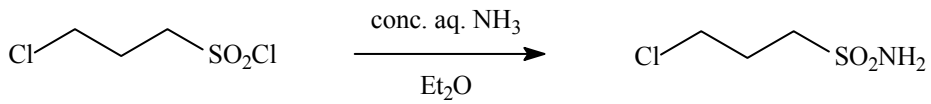
*Assignments may be interchanged

^{1}H NMR δ (500 MHz, $CDCl_3$) 4.17 (2H, t, *J*=7.2 Hz, **CH_2SO_2**), 3.65 (2H, t, *J*=7.2 Hz, **CH_2N**), 2.25 (3H, s, **CH_3**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 167.34 (**C=O**), 57.37 (**CH_2SO_2**), 31.02 (**CH_2N**), 23.33 (**CH_3**).

3.3.2 Synthesis of γ-sultams (propanesultams)

3.3.2.1 Synthesis of 3-chloropropanesulfonamide



(**302**) (**303**)
$C_3H_8ClNO_2S$
MW = 157.61 g/mol

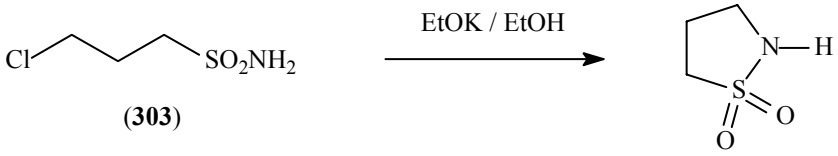
A solution of concentrated aqueous ammonia (2.157 g, 7 mL of a 35% sol., 126.6 mmol, 2.2 eq.) in dry ether (57 mL) was cooled in an ice bath. A solution of 3-chloropropanesulfonyl chloride (**302**) (10.192 g, 7 mL, 57.6 mmol), in dry ether (29 mL) was added to the stirred mixture at such a rate as to maintain the temperature at 5˚C (over 1 hour). After further stirring at ice temperature for 30 minutes, the ether layer was separated and dried over anhydrous sodium sulfate. The ether solution was filtered, treated with petroleum ether 40-60˚C to faint turbidity and cooled in a freezer overnight. The deposited white solid was filtered under vacuum (3.0 g, m.p. = 63-64˚C). The filtrate was evaporated to dryness under reduced pressure, giving a sticky white solid residue, which was combined with the solid obtained by evaporation of the aqueous layer of the reaction mixture and extracted with toluene (3 x 30 mL). A residual oil left at the bottom of toluene was carefully separated and toluene was evaporated under reduced pressure to a quarter of its initial volume, and the mixture was left in the freezer overnight. Vacuum filtration gave an additional crop (0.5 g) of the product as a white solid (**3.5 g, 38% overall yield, m.p.=63-64˚C**, lit. m.p.=64-65˚C[241]).

IR υ_{max} (cm^{-1}) 3351 and 3244 (br, **NH_2**), 1535 (w), 1439 (w), 1302 (s, **SO_2**), 1265 (s), 1192 (m), 1157 (s), 1120 (s, **SO_2**), 1057 (m), 1028 (m), 908 (s), 862 (m), 798 (m), 781 (m), 745 (s), 645 (s), 572 (s).

^{1}H NMR: δ (400 MHz, $CDCl_3$) 4.90 (2H, bs, **NH_2**), 3.71 (2H, t, *J*=6.2 Hz, **CH_2**Cl), 3.33 (2H, m, **CH_2**SO_2), 2.35 (2H, m, **CH_2**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 52.52 (**CH_2**), 42.63 (**CH_2**), 27.04 (**CH_2**).

3.3.2.2 Synthesis of γ-sultam



(**303**) (**304**)
$C_3H_7NO_2S$
MW = 121.15 g/mol

To a solution of 3-chloropropanesulfonamide (**303**) (1.500 g, 9.51 mmol), in dry ethanol (13 mL) freshly distilled over magnesium and iodine, was added a solution of potassium hydroxide (0.533 g, 9.51 mmol, 1 eq.) in dry ethanol (4 mL) The solution became turbid almost at once. The mixture was heated at reflux under nitrogen for 75 minutes. The pH of the reaction mixture was acidic (pH~4). An additional portion of potassium hydroxide (0.127 g, 2.26 mmol, 0.2 eq.) was added to the mixture, which was heated at reflux for a further 45 minutes (2 hours overall). The reaction mixture was slightly basic (pH~8-9). The solvent was removed *in vacuo* to yield the crude product as a yellow oil (1.128g). It was purified by flash silica chromatography (PE 40-60˚C / ethyl acetate: 1/2) to yield the product as a colourless oil (**0.865 g, 75%**).

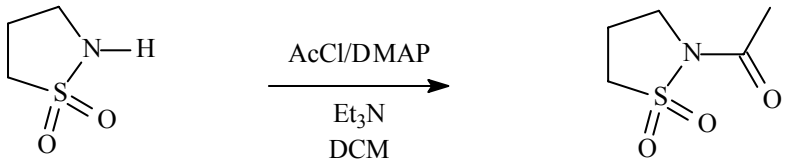
IR υ_{max} (cm^{-1}) 3269 (br, **NH**), 2962 (w), 1731 (w), 1453 (w), 1387 (m), 1289 (s, **SO_2**), 1175 (m), 1130 (s, **SO_2**), 1042 (m), 997 (m), 923 (m), 729 (s), 700 (m), 597 (m).

^{1}H NMR: δ (400 MHz, $CDCl_3$) 4.39 (1H, bs, **NH**), 3.43 (2H, q, *J*=6.5 Hz, **CH_2**NH), 3.09 (2H, t, *J*=7.5 Hz, **CH_2**SO_2), 2.48 (2H, m, CH_2**CH_2**CH_2).

^{13}C NMR δ (400 MHz, $CDCl_3$) 46.53 (**CH_2**), 42.20 (**CH_2**), 23.87 (**CH_2**).

MS (*m/z*): 144.0 ($[M+Na]^+$).

3.3.2.3 *N*-Acylation of γ-sultam



(**304**) (**305**)
$C_5H_9NO_3S$
MW = 163.19 g/mol

To a solution of propanesultam (**304**) (0.865 g, 7.14 mmol) and DMAP (0.058 g, 0.47 mmol) in dry DCM (20 mL) was added freshly distilled acetyl chloride (0.507 mL, 0.560 g, 7.14 mmol, 1 eq.) at 0˚C. The reaction mixture was stirred under nitrogen for 30 minutes before triethylamine (1 mL, 0.729 g, 7.21 mmol, 1 eq.) was added dropwise over 5 minutes at 0˚C. The mixture was then allowed to warm at RT and was stirred overnight. The mixture was filtered and the solvent was removed *in vacuo* to yield the crude product (2.052 g) as yellow sticky needles. It was purified by gravity silica chromatography (PE 40-60ºC/ethyl acetate: 1/2) to yield the product as a white solid (**0.721 g, 62%, m.p. = 73-74˚C**).

IR υ_{max} (cm^{-1}) 2959 (w), 1687 (s, **C=O**), 1416 (w), 1376 (m), 1303 (s, **SO_2**), 1270 (m), 1144 (s, **SO_2**), 1099 (w), 1036 (w), 1000 (m), 966 (w), 870 (w), 730 (m).

^{1}H NMR: δ (400 MHz, $CDCl_3$) 3.86 (2H, t, *J*=6.8 Hz, **CH_2**NAc), 3.42 (2H, t, *J*=7.2 Hz, **CH_2**SO_2), 2.43 (3H, s, **CH_3**), 2.41 (2H, m, CH_2**CH_2**CH_2).

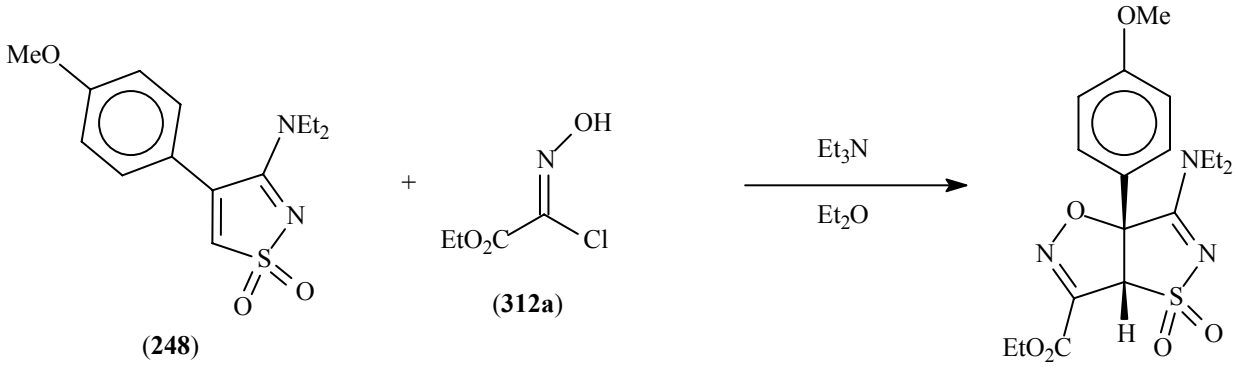
^{13}C NMR δ (400 MHz, $CDCl_3$) 167.77 (**C=O**), 49.81 (**CH_2**), 44.53 (**CH_2**), 22.82 (**CH_3**), 18.05 (**CH_2**).

HR-CIMS (*m/z*): $[M+NH_4]^+$ for $C_5H_{13}N_3O_3S$ calculated 181.0641 measured 181.0642.

3.4 1,3-Dipolar cycloadditions

3.4.1 Reaction of 3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide with nitrile oxides

3.4.1.1 Synthesis of (+/-)-3-diethylamino-6-ethoxycarbonyl-3a-(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide

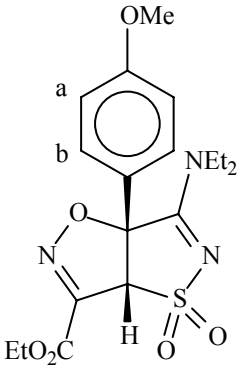


(**315a**)
$C_{18}H_{23}N_3O_6S$
MW = 409.45 g/mol

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg; 0.34 mmol) and ethyl chlorooximidoacetate (**312a**) (51 mg; 0.34 mmol; 1 eq.) were dissolved in dry diethyl ether (5 mL) under nitrogen. Triethylamine (47 µL; 34 mg; 0.34 mmol; 1 eq) in dry diethyl ether (10 mL) was added dropwise to the mixture over 20 hours, and the mixture was stirred overnight. Filtration and evaporation under reduced pressure gave the crude product as a yellow oil (214 mg). Purification by flash silica chromatography (PE 40-60˚C/EtOAc: 2/1) afforded the product as a colorless oil (**120 mg; 86 %**).

IR υ_{max} (cm^{-1}) 2980 (w), 1742 (m, **C=O**), 1597 (s, **C=N**), 1514 (m), 1443 (m), 1328 (m, **SO_2**), 1254 (m), 1211 (m), 1179 (s, **SO_2**), 1135 (m), 1092 (m), 1030 (w), 971 (w), 948 (m), 907 (w), 835 (m).

The assignment for NMR was established from HSQC, HMBC, NOE, selective 1D NOE and INADEQUATE data and is as follows:



^{1}H NMR δ (500 MHz, $CDCl_3$) 7.28 (2H, d, *J*=8.8 Hz, **CH**$_b$ (Ar)), 6.98 (2H, d, *J*=8.8 Hz, **CH**$_a$ (Ar)), 4.97 (1H, s, **CH** (ring junction)), 4.42 (2H, q, *J*=7.1 Hz, O**CH$_2$**CH_3) 3.84 (3H, s, O**CH$_3$**), 3.66 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.42 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.28 (1H, dq, *J*=14.4 and 7.0 Hz, N**CH$_2$**CH_3), 3.19 (1H, dq, *J*=14.4 and 7.0 Hz, N**CH$_2$**CH_3), 1.38 (3H, t, *J*=7.1 Hz, OCH_2**CH$_3$**), 1.26 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 0.88 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

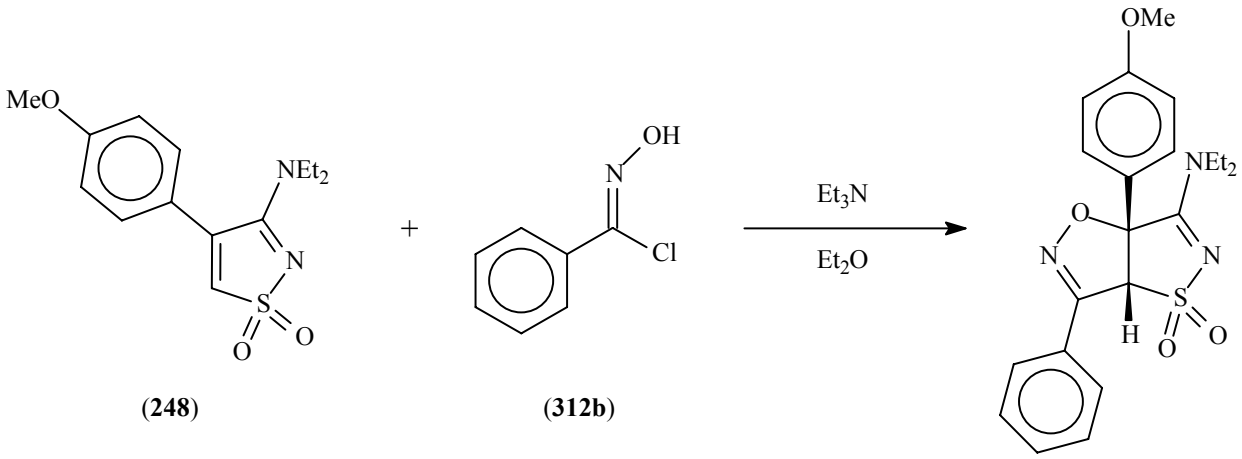
^{13}C NMR δ (500 MHz, $CDCl_3$) 162.50 (N=**C**-NEt_2), 160.55 (**C**-OMe), 157.97 (**C**=O), 147.65 (N=**C**-CO_2Et), 127.19 (**C** (PhOMe)), 124.96 (**CH**$_b$ (Ar)), 115.09 (**CH**$_a$ (Ar)), 100.40 (**C** (ring junction)), 77.26 (**CH** (ring junction)), 62.92 (O**CH$_2$**CH_3), 55.38 (O**CH$_3$**), 45.09 (N**CH$_2$**CH_3), 44.10 (N**CH$_2$**CH_3), 13.85 (OCH_2**CH$_3$**), 12.64 (NCH_2**CH$_3$**), 11.19 (NCH_2**CH$_3$**).

MS (*m/z*): 432.1 ($[M+Na]^+$), 841.3 ($[2M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{18}H_{23}N_3NaO_6S$ calculated 432.1200 measured 432.1209.

Crystallograpic data: appendix XVI

3.4.1.2 Synthesis of (+/-)-3-diethylamino-3a-(4-methoxyphenyl)-6-phenylisothiazolino-[4,5-*d*]isoxazolin-1,1-dioxide



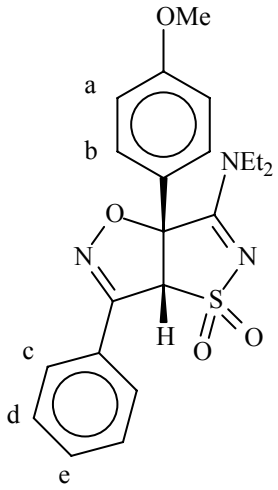
(**248**) (**312b**)

(**315b**)
$C_{21}H_{23}N_3O_4S$
MW = 413.49 g/mol

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg; 0.34 mmol) and benzohydroximoyl chloride (**312b**) (53 mg; 0.34 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (47 µL; 34 mg; 0.34 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture over 4-5 hours. The mixture was stirred overnight (20 hours) under nitrogen. It was filtered, and the solvent was evaporated under reduced pressure to give the crude product as a pale yellow solid (170 mg). It was purified by gravity silica chromatography (PE 40-60˚C / AcOEt: 2/1) to give the product as a white fluffy solid (**99 mg; 71%; m.p.=78-80°C**).

IR υ_{max} (cm^{-1}) 2975 (w), 1593 (s, **C=N**), 1512 (m), 1445 (m), 1352 (m), 1320 (s, **SO_2**), 1252 (s), 1210 (w), 1177 (s, **SO_2**), 1136 (s), 1096 (m), 1031 (m), 968 (m), 947 (m), 920 (m), 890 (m), 832 (m), 773 (m), 732 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



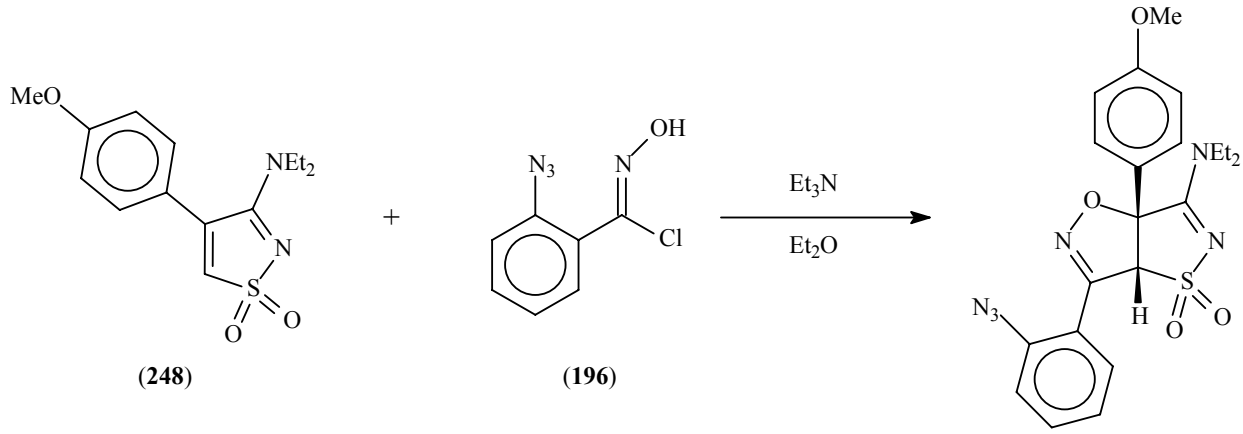
^{1}H NMR δ (400 MHz, $CDCl_3$) 7.79 (2H, dd, *J*=7.5 and 1.6 Hz, **CH**$_c$ (Ph)), 7.44 (3H, m, **CH**$_{d,e}$ (Ph)), 7.36 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 6.98 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 5.12 (1H, s, **CH** (ring junction)), 3.84 (3H, s, O**CH$_3$**), 3.70 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.43 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.27 (2H, m, N**CH$_2$**CH_3), 1.29 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.87 (3H, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 163.54 (Et_2N-**C**=N), 160.40 (**C**-OMe (Ar)), 152.52 (Ph-**C**=N-O), 131.13 (**CH**$_e$ (Ph)), 128.90 (**CH**$_d$ (Ph)), 128.86 (**C** (Ar)), 127.55 (**CH**$_c$ (Ph)), 126.82 (**C** (Ph)), 125.10 (**CH**$_b$ (ArOMe)), 115.05 (**CH**$_a$ (ArOMe)), 99.16 (**C** (ring junction)), 79.27 (**CH** (ring junction)), 55.44 (O**CH$_3$**), 45.04 (N**CH$_2$**CH_3), 44.21 (N**CH$_2$**CH_3), 12.76 (NCH_2**CH$_3$**), 11.38 (NCH_2**CH$_3$**).

MS (*m/z*): 436.1 ($[M+Na]^+$), 849.3 ($[2M+Na]^+$), 1262.4 ($[3M+Na]^+$), 1675.6 ($[4M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{21}H_{23}N_3NaO_4S$ calculated 436.1301 measured 436.1303.

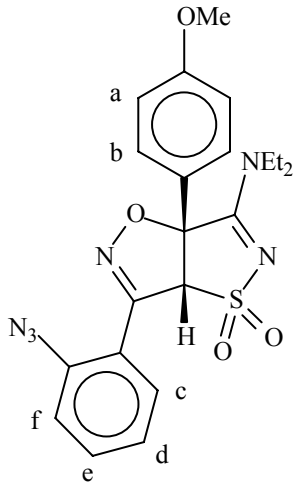
3.4.1.3 Synthesis of (+/-)-6-(2-azidophenyl)-3-diethylamino-3a-(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg; 0.34 mmol) and 2-azidobenzohydroximoyl chloride (**196**) (67 mg; 0.34 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (47 µL; 34 mg; 0.34 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture over 10 hours. The mixture was stirred overnight (24 hours) under nitrogen. It was filtered, and the solvent was evaporated under reduced pressure to give the crude product as a pale brown solid (189 mg). It was purified by gravity silica chromatography (PE 40-60˚C / EtOAc: gradient elution 4/1 to 1/1) to give the product as a pale brown solid (**43 mg; 28%; m.p.=159-160°C**).

IR υ_{max} (cm^{-1}) 2980 (w), 2132 (m, **N_3**), 1595 (s, **C=N**), 1513 (m), 1487 (w),1447 (m), 1346 (m), 1323 (s, **SO_2**), 1253 (m), 1176 (s, **SO_2**), 1134 (m), 1091 (w), 1033 (w), 969 (w), 946 (w), 907 (w), 893 (w), 833 (m), 783 (w), 756 (w).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J*=7.9 and 1.4 Hz, **CH**$_c$ (PhN_3)), 7.47 (1H, m, **CH**$_d$ (PhN_3)), 7.37 (2H, d, *J*=8.9 Hz, **CH**$_b$ (PhOMe)), 7.20 (1H, m, **CH**$_f$ (PhN_3)), 7.18 (1H, m, **CH**$_e$ (PhN_3)), 7.00 (2H, d, *J*=8.9 Hz, **CH**$_a$ (PhOMe)), 5.70 (1H, s, **CH** (ring junction)), 3.84 (3H, s, O**CH$_3$**), 3.69 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3). 3.39 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.29 (1H, dq, *J*=14.4 and 7.1 Hz, N**CH$_2$**CH_3), 3.21 (1H, dq, *J*=14.4 and 7.1 Hz, N**CH$_2$**CH_3), 1.26 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.90 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

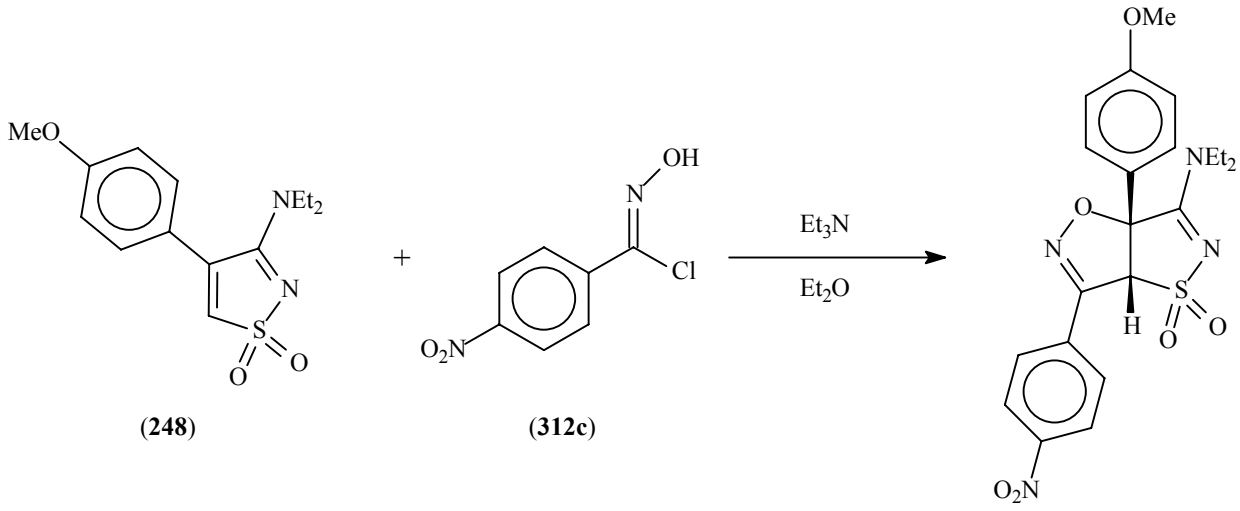
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.58 (Et_2N-**C**=N), 160.32 (**C**-OMe (PhOMe)), 151.00 (N=**C**-PhN_3), 138.01 (**C** (PhN_3)), 132.00 (**CH**$_d$ (PhN_3)), 129.94 (**CH**$_c$ (PhN_3)), 128.61 (**C** (PhOMe)), 125.21 (**CH**$_b$ (PhOMe)), 124.99 (**CH**$_e$ (PhN_3)), 118.94 (**CH**$_f$ (PhN_3)), 118.67 (**C**-N_3 (PhN_3)), 114.96 (**CH**$_a$ (PhOMe)), 98.47 (**C** (ring junction)), 79.35 (**CH** (ring junction)), 55.37 (**CH$_3$** (OMe)), 44.73 (N**CH$_2$**CH_3), 43.91 (N**CH$_2$**CH_3), 12.78 (NCH_2**CH$_3$**), 11.28 (NCH_2**CH$_3$**).

MS (*m/z*): 477.1 ($[M+Na]^+$), 931.3 ($[2M+Na]^+$), 1385.4 ($[3M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{21}H_{22}N_6NaO_4S$ calculated 477.1315 measured 477.1316.

HRMS (*m/z*): $[M+H]^+$ for $C_{21}H_{23}N_6O_4S$ calculated 454.1418 measured 454.1418.

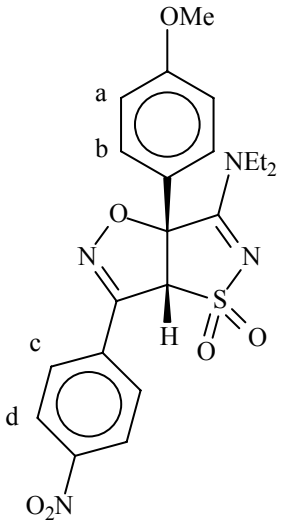
3.4.1.4 Synthesis of (+/-)-3-diethylamino-3a-(4-methoxyphenyl)-6-(4-nitrophenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg; 0.34 mmol) and 4-nitrobenzohydroximoyl chloride (**312c**) (68 mg; 0.34 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (47 µL; 34 mg; 0.34 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture over 4-5 hours. The mixture was stirred for 5 days and 19 hours under nitrogen. It was filtered, and the solvent was evaporated under reduced pressure to give the crude product as an orange solid (95 mg). It was purified by gravity silica chromatography (PE 40-60˚C / EtOAc: gradient elution 3/1 to 2/1) to give the product as a yellow oil (**43 mg; 28%**).

IR υ_{max} (cm^{-1}) 2980 (w), 1597 (s, **C=N**), 1514 (s), 1443 (m), 1342 (s), 1321 (s, **SO_2**), 1253 (s), 1209 (w), 1178 (s, **SO_2**), 1137 (m), 1095 (w), 1030 (w), 969 (m), 947 (w), 933 (w), 908 (w), 852 (m), 833 (m), 783 (w), 746 (w).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



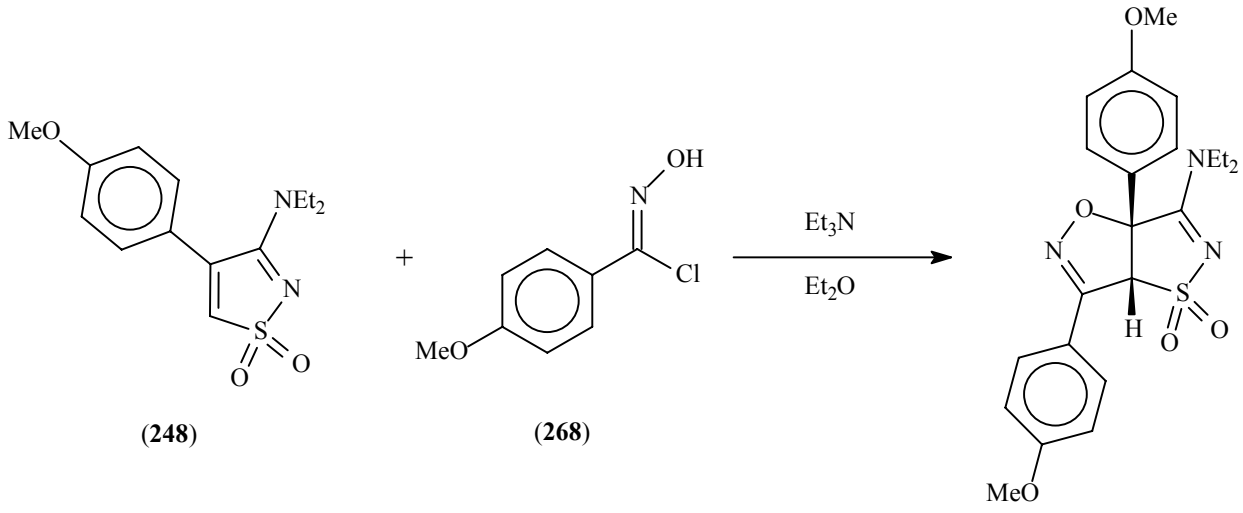
^{1}H NMR δ (400 MHz, $CDCl_3$) 8.28 (2H, d, *J*=8.9 Hz, **CH**$_d$ ($PhNO_2$)), 7.96 (2H, d, *J*=8.9 Hz, **CH**$_c$ ($PhNO_2$)), 7.35 (2H, d, *J*=8.9 Hz, **CH**$_b$ (PhOMe)), 7.00 (2H, d, *J*=8.9 Hz, **CH**$_a$ (PhOMe)), 5.12 (1H, s, **CH** (ring junction)), 3.84 (3H, s, **CH$_3$** (OMe)), 3.70 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.43 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.32 (1H, dq, *J*=14.3 and 7.3 Hz, N**CH$_2$**CH_3), 3.25 (1H, dq, *J*=14.3 and 7.3 Hz, N**CH$_2$**CH_3), 1.29 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.90 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 163.26 (Et_2N-**C**=N), 160.59 (**C** (PhOMe)), 151.28 (O_2NPh-**C**=N-O)), 148.89 (**C**-NO_2 ($PhNO_2$)), 132.95 (**C** ($PhNO_2$)), 128.43 (**CH**$_c$ ($PhNO_2$)), 128.03 (**C** (PhOMe)), 125.04 (**CH**$_b$ (PhOMe)), 124.04 (**CH**$_d$ ($PhNO_2$)), 115.18 (**CH**$_a$ (PhOMe)), 100.16 (**C** (ring junction)), 78.25 (**CH** (ring junction)), 55.46 (**CH$_3$** (OMe)), 45.24 (N**CH$_2$**CH_3), 44.28 (N**CH$_2$**CH_3), 12.75 (NCH_2**CH$_3$**), 11.32 (NCH_2**CH$_3$**).

MS (*m/z*): 459.1 $[M+H]^+$, 934.3 $[2M+NH_4]^+$, 1392.4 $[3M+NH_4]^+$.

HRMS (*m/z*): for $C_{21}H_{23}N_4O_6S$ calculated 459.1333 measured 459.1322.

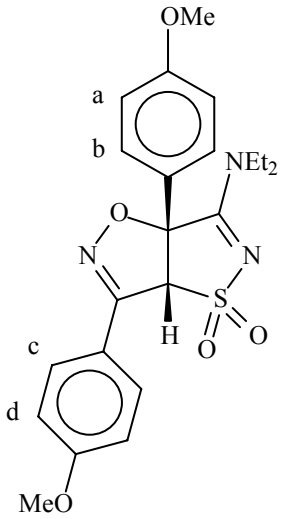
3.4.1.5 Synthesis of (+/-)-3-diethylamino-3a,6-di(4-methoxyphenyl)isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg; 0.34 mmol) and 4-methoxybenzohydroximoyl chloride (**268**) (63 mg; 0.34 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (47 μL; 34 mg; 0.34 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture over 4-5 hours. The mixture was stirred overnight (20 hours) under nitrogen. It was filtered, and the solvent was evaporated under reduced pressure to give the crude product as a yellow solid (185 mg). It was purified by gravity silica chromatography (PE 40-60˚C / AcOEt: gradient elution 3/1 to 2/1) to give the product as a white solid (**108 mg; 71%; m.p.=83-85°C**).

IR υ_{max} (cm^{-1}) 2978 (w), 1594 (s, **C=N**), 1514 (s), 1443 (m), 1422 (w) 1353 (m), 1320 (s, **SO_2**), 1253 (s), 1211 (w), 1178 (s, **SO_2**), 1137 (m), 1096 (w), 1030 (m), 968 (m), 948 (w), 920 (m), 890 (w), 833 (m), 781 (w), 734 (w).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.9 Hz, **CH**$_c$ (Ar)), 7.37 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 6.98 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 6.94 (2H, d, *J*=8.9 Hz, **CH**$_d$ (Ar)), 5.09 (1H, s, **CH** (ring junction)), 3.84 (3H, s, O**CH$_3$**), 3.83 (3H, s, O**CH$_3$**), 3.69 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3)), 3.42 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.26 (2H, m, N**CH$_2$**CH_3), 1.28 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.86 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

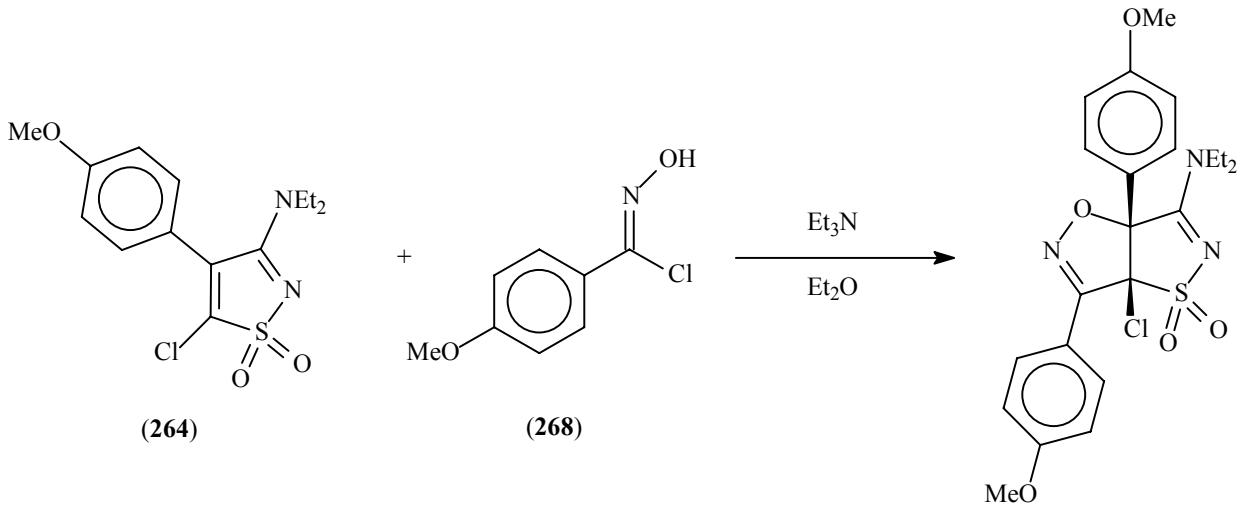
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.69 (Et_2N-**C**=N), 161.76 (**C**-OMe (Ar)), 160.34 (**C**-OMe (Ar)), 151.97 (Ar-**C**=N-O), 129.23 (**CH**$_c$ (Ar)), 129.03 (**C** (Ar)), 125.12 (**CH**$_b$ (Ar)), 119.22 (**C** (Ar)), 115.00 (**CH**$_a$ (Ar)), 114.34 (**CH**$_d$ (Ar)), 98.86 (**C** (ring junction)), 79.57 (**CH** (ring junction)), 55.43 (O**CH$_3$**), 55.38 (O**CH$_3$**), 44.99 (N**CH$_2$**CH_3), 44.17 (N**CH$_2$**CH_3), 12.74 (NCH_2**CH$_3$**), 11.37 (NCH_2**CH$_3$**).

MS (*m/z*): 466.1 ($[M+Na]^+$), 909.3 ($[2M+Na]^+$), 1352.4 ($[3M+Na]^+$).

HRMS (*m/z*): $[M+Na]^+$ for $C_{22}H_{25}N_3NaO_5S$ calculated 466.1407 measured 466.1409.

3.4.2 Reaction of 5-substituted-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxides with 4-methoxybenzonitrile oxide

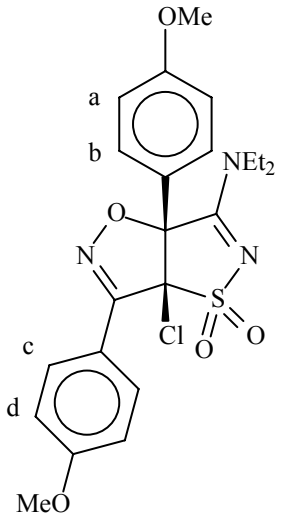
3.4.2.1 Synthesis of (+/-)-6a-chloro-3-diethylamino-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



5-Chloro-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1dioxide (**264**) (27 mg; 0.08 mmol) and 4-methoxybenzohydroximoyl chloride (**268**) (15 mg; 0.08 mmol; 1 eq) were suspended in dry diethyl ether (5 mL). Triethylamine (12 µL; 8.7 mg; 0.09 mmol; 1 eq) in dry diethyl ether (5 mL) was added dropwise to the mixture under nitrogen over 4 to 5 hours. The whole was stirred for 21 hours. The reaction mixture was filtered, and the solvent was removed *in vacuo* to give the crude product as a white oily solid (85 mg). Purification by gravity silica chromatography (PE 60-80˚C/EtOAc : 3/1) afforded the product as a yellow oil (**22 mg; 56%**).

IR υ_{max} (cm^{-1}) 2926 (w), 2853 (w), 1593 (s, **C=N**), 1513 (s), 1441 (m), 1420 (w), 1383 (w), 1335 (s, **SO_2**), 1306 (m), 1256 (s), 1209 (w), 1180 (s), 1162 (s, **SO_2**), 1122 (w), 1101 (w), 1068 (w), 1028 (m), 981 (m), 963 (m), 945 (w), 918 (m), 833 (m), 810 (w), 794 (w), 770 (w), 732 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



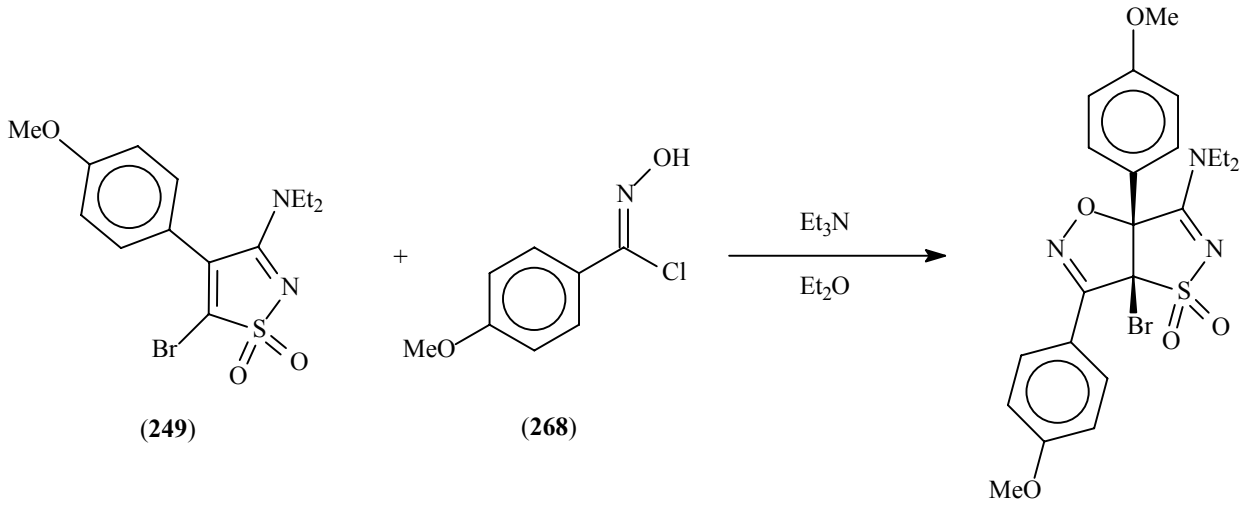
^{1}H NMR δ (500 MHz, $CDCl_3$) 7.99 (2H, d, *J*=8.8 Hz, **CH**$_c$ (Ar)), 7.57 (1H, bs, **CH**$_b$ (Ar)), 7.00 (3H, bs, **CH**$_{b,a}$ (Ar)), 6.93 (2H, d, *J*=8.8 Hz, CH (Ar)), 3.85 (3H, s, O**CH$_3$**), 3.85 (3H, s, O**CH$_3$**), 3.77 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.40 (1H, dq, *J*=14.2 and 7.0 Hz, N**CH$_2$**CH_3), 3.36 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.15 (1H, dq, *J*=14.2 and 7.0 Hz, N**CH$_2$**CH_3), 1.26 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 1.03 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 162.94 (N=**C**-NEt_2), 161.74 (**C**-OMe (Ar)), 160.94 (**C**-OMe (Ar)), 154.81 (Ar-**C**=N), 130.42 (**CH**$_c$ (Ar)), 127.95 (**CH**$_b$ (Ar)), 127.22 (**CH**$_b$ (Ar)), 123.70 (**C** (Ar)), 117.36 (**C** (Ar)), 114.51 (**CH**$_a$ (Ar)), 113.77 (**CH**$_d$ (Ar)), 101.01 (**C** (ring junction)), 90.36 (**C**-Cl (ring junction)), 55.36 (O**CH$_3$**), 55.33 (O**CH$_3$**), 44.80 (N**CH$_2$**CH_3), 44.10 (N**CH$_2$**CH_3), 12.81 (NCH_2**CH$_3$**), 11.17 (NCH_2**CH$_3$**).

MS (*m/z*): 500.1 (^{35}Cl) ($[M+Na]^+$), 977.2 (^{35}Cl) ($[2M+Na]^+$).

HRMS (^{35}Cl) (*m/z*): $[M+Na]^+$ for $C_{22}H_{24}ClN_3NaO_5S$ calculated 500.1017 measured 500.1016.

3.4.2.2 Synthesis of (+/-)-6a-bromo-3-diethylamino-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide

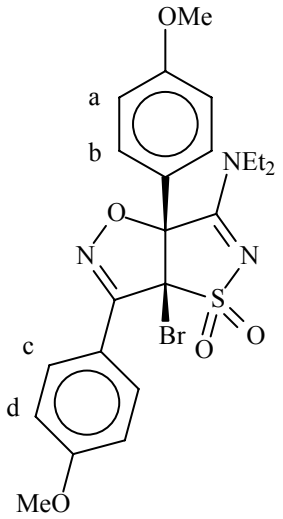


(315g)
$C_{22}H_{24}BrN_3O_5S$
MW = 522.41 g/mol

5-Bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**249**) (102 mg; 0.27 mmol) and 4-methoxybenzohydroximoyl chloride (**268**) (51 mg; 0.27 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (38 μL; 27 mg; 0.27 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture under nitrogen over 4-5 hours. The whole was stirred overnight (21 hours). The reaction mixture was filtered, and the solvent was removed *in vacuo* to give the crude product as a white oily solid (195 mg). Purification by gravity silica chromatography (PE 60-80˚C/EtOAc : 3/1) gave the product as an orange oil (**77 mg; 54%**).

IR υ_{max} (cm^{-1}) 2935 (w), 2840 (w), 1591 (s, **C=N**), 1512 (s), 1440 (m), 1419 (w), 1383 (w), 1359 (w), 1333 (s, **SO_2**), 1305 (m), 1254 (s), 1208 (w), 1179 (s), 1159 (s, **SO_2**), 1121 (w), 1100 (w), 1062 (m), 1026 (m), 978 (m), 959 (m), 936 (m), 910 (m), 831 (s), 804 (m), 792 (m), 728 (s).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



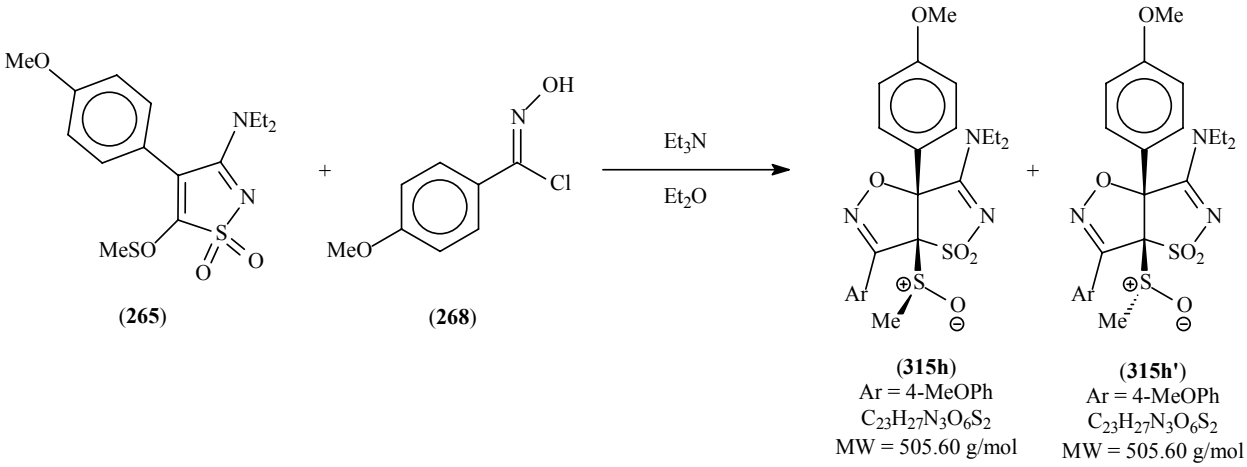
^{1}H NMR δ (500 MHz, $CDCl_3$) 8.05 (2H, d, *J*=9.0 Hz, **CH**$_c$ (Ar)), 7.61 (1H, bs, **CH**$_b$ (Ar)), 7.02 (1H, bs, **CH**$_b$ (Ar)), 6.98 (2H, bs, **CH**$_a$ (Ar)), 6.91 (2H, d, *J*=9.0 Hz, **CH**$_d$ (Ar)), 3.84 (3H, s, O**CH$_3$**), 3.84 (3H, s, O**CH$_3$**), 3.76 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.41 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH_3), 3.35 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.13 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH_3), 1.25 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 1.03 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 163.35 (N=**C**-NEt_2), 161.67 (**C**-OMe (Ar)), 160.88 (**C**-OMe (Ar)), 155.44 (Ar-**C**=N), 130.80 (**CH**$_c$ (Ar)), 128.17 (**CH**$_b$ (Ar)), 127.08 (**CH**$_b$ (Ar)), 125.36 (**C** (Ar)), 117.60 (**C** (Ar)), 114.33 (**CH**$_a$ (Ar)), 113.56 (**CH**$_d$ (Ar)), 101.21 (**C** (ring junction)), 81.77 (**C**-Br (ring junction)), 55.32 (O**CH$_3$**), 55.29 (O**CH$_3$**), 44.77 (N**CH$_2$**CH_3), 44.05 (N**CH$_2$**CH_3), 12.82 (NCH_2**CH$_3$**), 11.12 (NCH_2**CH$_3$**).

MS (*m/z*): (^{79}Br) 522.1 ($[M+H]^+$), (^{81}Br) 524.1 ($[M+H]^+$), (^{79}Br) 544.1 ($[M+Na]^+$), (^{81}Br) 546.1 ($[M+Na]^+$).

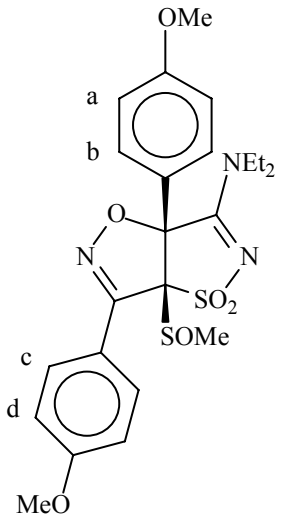
HRMS (^{79}Br) (*m/z*): $[M+H]^+$ for $C_{22}H_{25}BrN_3O_5S$ calculated 522.0693 measured 522.0693.

3.4.2.3 Synthesis of (+/-)-3-diethylamino-6a-methanesulfinyl-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



3-Diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**265**) (100 mg; 0.28 mmol) and 4-methoxybenzohydroximoyl chloride (**268**) (52 mg; 0.28 mmol; 1 eq.) were suspended in dry diethyl ether (5 mL). Triethylamine (39 µL; 28 mg; 0.28 mmol; 1 eq.) in dry diethyl ether (10 mL) was added dropwise to the mixture under nitrogen over 4 to 5 hours. The whole was stirred overnight (21 hours). The resulting precipitate was filtered off, and the solvent was evaporated under reduced pressure to give the crude product as a yellow oil (m=141 mg). Purification by gravity silica chromatography (hexane/EtOAc: 2/1) afforded the two diastereoisomers as a yellow solid (**315h**) (**48 mg; 34%; m.p. = 192-193°C**) and a yellow oil (**315h'**) (**26 mg, 18%**) in a ~2:1 ratio.

The assignment for NMR was established from HSQC and HMBC data and is as follows:



Diastereoisomer (**315h**):

IR υ_{max} (cm^{-1}) 2938 (w), 2839 (w), 1602 (s, **C=N**), 1512 (s), 1440 (w), 1325 (s, **SO_2**)*, 1306 (s)*, 1256 (s), 1208 (w), 1181 (s), 1156 (s, **SO_2**), 1072 (m)#, 1028 (m, **SO**)#, 964 (m), 912 (m), 836 (m).

* Assignments may be interchanged

Assignments may be interchanged

^{1}H NMR δ (500 MHz, $CDCl_3$) 8.02 (2H, d, *J*=8.8 Hz, **CH_c** (Ar)), 7.83 (1H, m, **CH_b** (Ar)), 7.13 (1H, m, **CH_b** (Ar)), 7.05 (1H, m, **CH_a** (Ar)), 6.96 (2H, d, *J*=8.8 Hz, **CH_d** (Ar)), 6.96 (overlapping) (1H, m, **CH_a** (Ar)), 3.85 (6H, s, 2x O**CH_3**), 3.78 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH_2**CH_3), 3.43 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH_2**CH_3), 3.36 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH_2**CH_3), 3.11 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH_2**CH_3), 2.56 (3H, s, **CH_3**SO) 1.29 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**), 1.05 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**).

^{13}C NMR (500 MHz, $CDCl_3$) 165.01 (Et_2N-**C**=N), 161.53 (**C**-OMe (Ar)), 161.15 (**C**-OMe (Ar)), 151.70 (Ar-**C**=N-O), 133.05 (**CH_c** (Ar)), 129.41 (**CH_b** (Ar)), 127.64 (**CH_b** (Ar)), 121.41 (**C** (Ar)), 119.56 (**C** (Ar)), 114.51 (**CH_a** (Ar)), 114.16 (**CH_a** (Ar)), 113.76 (**CH_d** (Ar)), 102.49 (**C**-Ar (ring junction)), 95.34 (**C**-SOMe), 55.31 (O**CH_3**), 55.26 (O**CH_3**), 45.16 (N**CH_2**CH_3), 43.94 (N**CH_2**CH_3), 35.41 (SO**CH_3**), 12.82 (NCH_2**CH_3**), 11.12 (NCH_2**CH_3**).

MS (*m/z*): 528.1 $[M+Na]^+$, 1033.3 $[2M+Na]^+$, 1538.4 $[3M+Na]^+$

HRMS (*m/z*): $[M+Na]^+$ for $C_{23}H_{27}N_3NaO_6S_2$ calculated 528.1233 measured 528.1248.

Crystal data: appendix XVI

Crystal structure: appendix XV

Diastereoisomer (**315h'**):

IR υ_{max} (cm^{-1}) 2938 (w), 2840 (w), 1597 (s, **C=N**), 1513 (s), 1441 (m), 1420 (w), 1333 (s, **SO_2**), 1308 (s), 1258 (s), 1208 (w), 1183 (s), 1158 (s, **SO_2**), 1061 (m), 1032 (m, **SO**), 981 (w), 953 (m), 912 (m), 836 (m).

^{1}H NMR δ (400 MHz, $CDCl_3$) 8.23 (2H, d, *J*=9.0 Hz, **CH**$_c$ (Ar)), 7.55 (1H, m, **CH**$_b$ (Ar)), 7.50 (1H, m, **CH**$_b$ (Ar)), 6.99 (2H, m, **CH**$_a$ (Ar)), 6.94 (2H, d, *J*=9.0 Hz, **CH**$_d$ (Ar)), 3.86 (3H, s, O**CH$_3$**), 3.84 (3H, s, O**CH$_3$**), 3.67 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.33 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH_3), 3.28 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH_3), 3.15 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH_3), 2.33 (3H, s, **CH$_3$**SO), 1.20 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 0.91 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

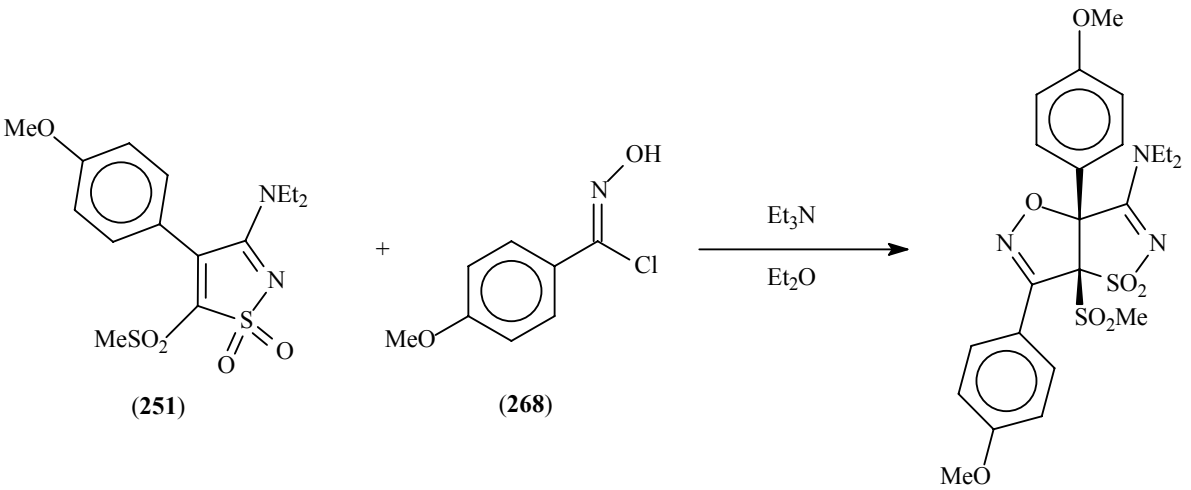
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.73 (Et_2N-**C**=N), 162.03 (**C**-OMe (Ar)), 161.07 (**C**-OMe (Ar)), 154.67 (Ar-**C**=N-O), 132.22 (**CH**$_c$ (Ar)), 129.16 (**CH**$_b$ (Ar)), 126.71 (**CH**$_b$ (Ar)), 120.05 (**C** (Ar)), 118.26 (**C** (Ar)), 115.02 (**CH**$_a$ (Ar)), 114.35 (**CH**$_a$ (Ar)), 113.79 (**CH**$_d$ (Ar)), 100.03 (**C**), 93.85 (**C**), 55.43 (O**CH$_3$**), 55.33 (O**CH$_3$**), 45.45 (N**CH$_2$**CH_3), 43.22 (N**CH$_2$**CH_3), 35.51 (**CH$_3$**SO), 12.81 (NCH_2**CH$_3$**), 11.08 (NCH_2**CH$_3$**).

MS (*m/z*): 528.1 $[M+Na]^+$, 1033.3 $[2M+Na]^+$, 1538.4 $[3M+Na]^+$

HRMS (*m/z*): $[M+Na]^+$ for $C_{23}H_{27}N_3NaO_6S_2$ calculated 528.1233 measured 528.1243.

Crystal data: appendix XVI

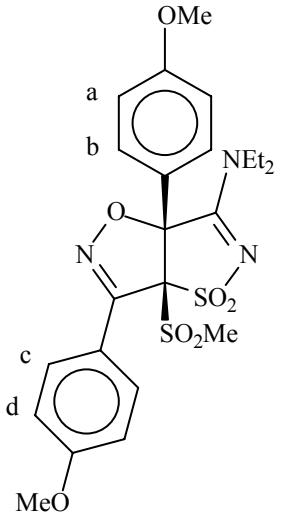
3.4.2.4 Synthesis of (+/-)-3-diethylamino-6a-methanesulfonyl-3a,6-di(4-methoxyphenyl)-isothiazolino[4,5-*d*]isoxazolin-1,1-dioxide



3-Diethylamino-5-methanesulfonyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**251**) (101 mg; 0.27 mmol) and 4-methoxybenzohydroximoyl chloride (**268**) (50 mg; 0.27 mmol; 1 eq.) were dissolved in dry diethyl ether (5 mL). Triethylamine (38 µL; 28 mg; 0.27 mmol; 1 eq.) in dry diethyl ether (10 mL) was added to the mixture under nitrogen over 4 hours. The whole was stirred overnight (23 hours). The resulting suspension was filtered off, and the solvent was removed under reduced pressure to give the crude product as a yellow solid (m=159 mg). Purification by gravity silica chromatography (PE 60-80˚C/EtOAc: 2/1) afforded the product as a white solid (**96 mg; 68%; m.p.=198-199˚C**).

IR υ_{max} (cm^{-1}) 2935 (w), 1603 (s, **C=N**), 1513 (s), 1442 (w), 1332 (s, **SO_2**), 1308 (s), 1259 (s), 1183 (s, **SO_2**), 1169 (s, **SO_2**), 1161 (s, **SO_2**), 1144 (s, **SO_2**), 1026 (m), 985 (w), 966 (m), 916 (w), 835 (m).

The assignment for NMR was established from HSQC and HMBC data and is as follows:



^{1}H NMR δ (400 MHz, $CDCl_3$) 8.19 (2H, d, *J*=9.1 Hz, **CH**$_c$ (Ar)), 7.87 (1H, dd, *J*= 8.8 and 2.6 Hz, **CH**$_b$ (Ar)), 7.19 (1H, dd, *J*= 8.8 and 2.6 Hz, **CH**$_b$ (Ar)), 7.09 (1H, dd, *J*=8.8 and 2.6 Hz, **CH**$_a$ (Ar)), 6.98 (1H, dd, *J*=8.8 and 2.6 Hz, **CH**$_a$ (Ar)), 6.93 (2H, d, *J*=9.1 Hz, **CH**$_d$ (Ar)), 3.87 (3H, s, O**CH$_3$**), 3.84 (3H, s, O**CH$_3$**), 3.80 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 3.40 (1H, dq, *J*=14.2 and 7.0 Hz, N**CH$_2$**CH_3), 3.31 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH$_2$**CH_3), 2.99 (1H, dq, *J*= 14.2 and 7.0 Hz, N**CH$_2$**CH_3), 1.28 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 1.13 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

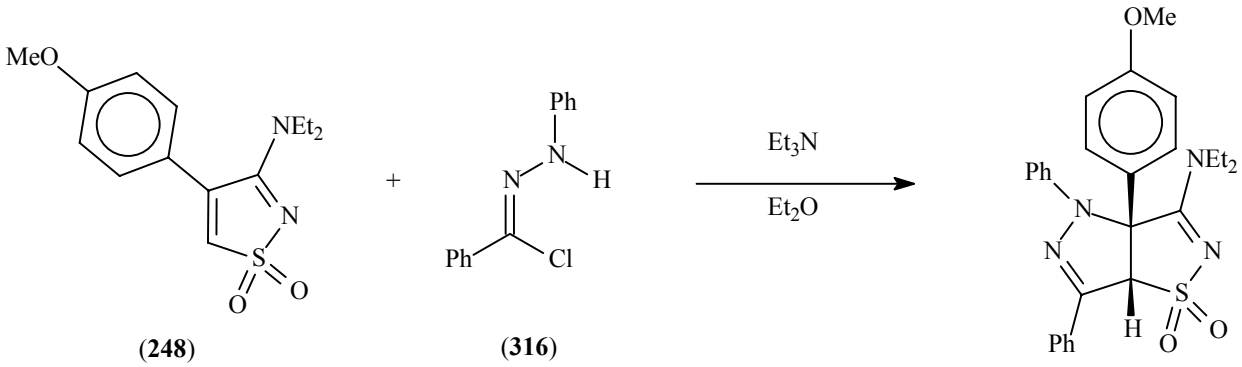
^{13}C NMR δ (400 MHz, $CDCl_3$) 163.73 (Et_2N-**C**=N), 161.76 (**C**-OMe (Ar)), 161.74 (**C**-OMe (Ar)), 152.71 (Ar-**C**=N-O), 133.00 (**CH**$_c$ (Ar)), 129.99 (**CH**$_b$ (Ar)), 128.57 (**CH**$_b$ (Ar)), 120.03 (**C** (Ar)), 118.67 (**C** (Ar)), 114.88 (**CH**$_a$ (Ar)), 113.42 (**CH**$_d$ (Ar)), 99.87 (**C** (ring junction)), 98.44 (**C**-SO_2Me), 55.50 (O**CH$_3$**), 55.28 (O**CH$_3$**), 45.21 (N**CH$_2$**CH_3), 43.94 (N**CH$_2$**CH_3), 42.76 (SO_2**CH$_3$**), 12.92 (NCH_2**CH$_3$**), 11.02 (NCH_2**CH$_3$**).

MS (*m/z*): 544.1 $[M+Na]^+$, 1065.3 $[2M+Na]^+$.

HRMS (*m/z*): $[M+Na]^+$ for $C_{23}H_{27}N_3NaO_7S_2$ calculated 544.1183 measured 544.1197.

Crystal data: appendix XVI

3.4.3 Cycloaddition of 3-diethylamino-4-(4-methoxyphenyl)isothiazol-1,1-dioxide with *N*-phenylbenzonitrile imine: synthesis of (+/-)-3-diethylamino-4,6-diphenyl-3a-(4-methoxyphenyl)isothiazolino[4,5-*d*]pyrazolin-1,1-dioxide



(**248**) (**316**)

(**318**)
$C_{27}H_{28}N_4O_3S$
MW = 488.60 g/mol

3-Diethylamino-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**248**) (100 mg, 0.34 mmol) and *α*-chlorobenzaldehyde phenylhydrazone (**316**) (78 mg, 0.34 mmol, 1 eq.) were suspended in dry ether (5 mL). Triethylamine (47 μL, 34 mg, 0.34 mmol, 1 eq.) in dry ether (10 mL) was added dropwise to the mixture over 4 to 5 hours. The whole was stirred under nitrogen at RT for 4 days and 17 hours. Then, it was refluxed for 28 hours. The mixture was filtered off, and the solvent evaporated to give the crude product as a pale brown oil (183 mg). It was purified by

gravity silica chromatography (PE 40-60˚C / EtOAc: gradient elution 3/1, 2/1) to give the product as a yellow solid (**45 mg, 27 %, m.p. = 210-211˚C**).

IR υ_{max} (cm^{-1}) 2979 (w), 1574 (s, **C=N**), 1508 (m), 1492 (m), 1463 (w), 1444 (m), 1357 (m), 1308 (s, **SO_2**), 1250 (s), 1210 (w), 1171 (s, **SO_2**), 1133 (s, **SO_2**), 1096 (m), 1075 (w), 1031 (m), 977 (m), 950 (w), 911 (m), 894 (m), 836 (m), 781 (m), 755 (m), 729 (s), 705 (m), 692 (m).

^{1}H NMR δ (500 MHz, $CDCl_3$) 7.80 (2H, m, **CH** (Ph)), 7.51 (2H, m, **CH** (Ph)), 7.36 (8H, m, **CH** (Ph)), 7.00 (2H, d, *J*=9.00 Hz, **CH_a** (Ar)), 4.90 (1H, s, **CH** (ring junction)), 3.82 (3H, s, O**CH_3**), 3.56 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH_2**CH_3), 3.01 (1H, dq, *J*=13.6 and 7.0 Hz, N**CH_2**CH_3), 2.96 (1H, dq, *J*=14.2 and 7.0 Hz, N**CH_2**CH_3), 1.99 (1H, dq, *J*=14.2 and 7.0 Hz, N**CH_2**CH_3), 0.78 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**), 0.33 (3H, t, *J*=7.0 Hz, NCH_2**CH_3**).

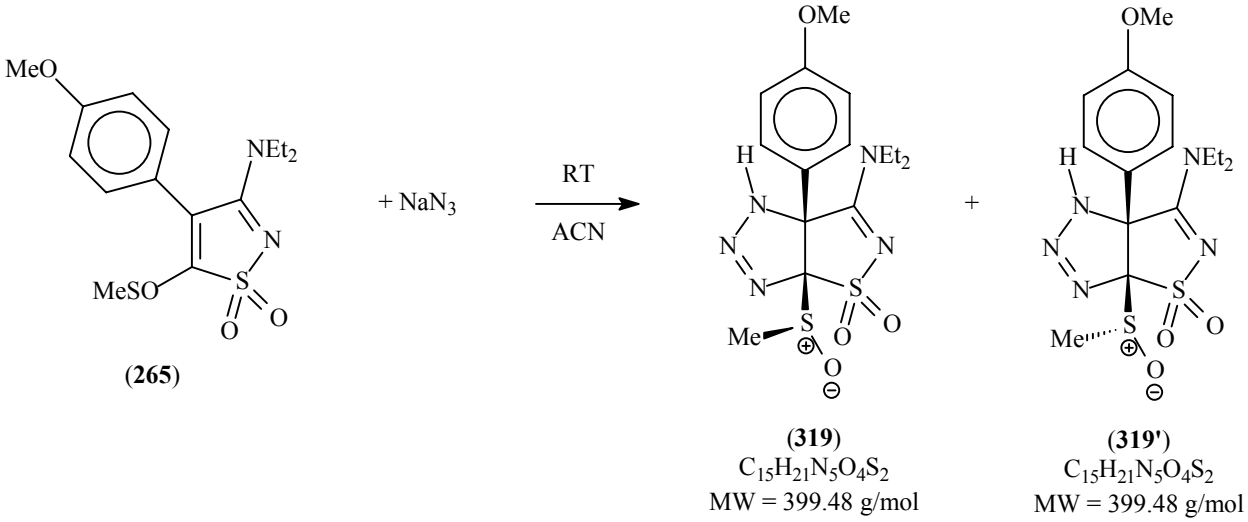
^{13}C NMR δ (500 MHz, $CDCl_3$) 162.11 (Et_2N-**C**=N), 159.87 (**C**-OMe (Ar)), 144.26 (**C**), 143.01 (**C**), 132.02 (**C**), 130.23 (**C**), 129.76 (**CH** (Ar)), 129.61 (**CH** (Ar)), 129.13 (**CH** (Ar)), 128.92 (**CH** (Ar)), 128.74 (**CH** (Ar)), 126.49 (**CH** (Ar)), 125.98 (**C**), 115.05 (**CH_a** (Ar)), 85.19 (**C** (ring junction)), 82.84 (**CH** (ring junction)), 55.43 (O**CH_3**), 45.28 (N**CH_2**CH_3), 44.16 (N**CH_2**CH_3), 11.24 (NCH_2**CH_3**), 10.51 (NCH_2**CH_3**).

MS (*m/z*): 511.2 $[M+Na]^+$, 999.4 $[2M+Na]^+$.

HRMS (*m/z*): $[M+Na]^+$ for $C_{27}H_{28}N_4NaO_3S$ calculated 511.1774 measured 511.1778.

Crystal data: appendix XVI

3.4.4 Cycloaddition of 3-diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide with sodium azide: synthesis of (+/-)-3-diethylamino-6a-methanesulfinyl-3a-(4-methoxyphenyl)isothiazolino[4,5-*d*]triazolin-1,1-dioxide



3-Diethylamino-5-methanesulfinyl-4-(4-methoxyphenyl)-isothiazol-1,1-dioxide (**264**) (200 mg, 0.56 mmol) was dissolved in dry acetonitrile (10 mL), and sodium azide (38 mg, 0.58 mmol, 1 eq.) was added to the mixture. The whole was stirred at RT under nitrogen, and the reaction was monitored by TLC. After 30 hours, the solvent was removed *in vacuo* to give the crude product as a yellow solid (257 mg). Purifiaction by flash silica chromatography (PE 40-60˚C/EtOAc: gradient elution 1/1, 1/2, 1/4) gave the product as two separable diastereoisomers (**319**) (**50 mg, 22%, m.p.=133˚C**) and (**319'**) (**60 mg, 27%, m.p. = 142-143˚C**) in a 1.2/1 ratio.

Diastereoisomer (**319**):

IR υ_{max} (cm^{-1}) 3080 (br, **NH**), 2964 (w), 2929 (w), 2853 (w), 1638 (w), 1590 (s, **C=N**), 1513 (m), 1425 (w), 1384 (w), 1360 (w), 1327 (s, **SO_2**), 1304 (m), 1257 (s), 1208 (w), 1157 (s, **SO_2**), 1131 (m), 1100 (w), 1029 (s, **SO**), 985 (w), 961 (w), 912 (w), 896 (w), 836 (m).

^{1}H NMR δ (500 MHz, $CDCl_3$) 12.16 (1H, bs, **NH**), 7.45 (1H, m, **CH_b** (Ar)), 7.40 (1H, m, **CH_b** (Ar)), 6.97 (2H, d, *J*=8.7 Hz, **CH_a** (Ar)), 3.85 (3H, s, O**CH_3**), 3.74 (1H, dq, *J*=14.5 and 7.0 Hz, N**CH_2**CH_3), 3.49 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH_2**CH_3), 3.39 (1H, dq, *J*=13.5 and 7.0 Hz,

N**CH$_2$**CH$_3$), 3.37 (1H, dq, *J*=14.5 and 7.0 Hz, N**CH$_2$**CH$_3$), 2.11 (3H, s, **CH$_3$**SO), 1.17 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**), 0.65 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 161.66 (Et_2N-**C**=N), 160.90 (**C**-OMe (Ar)), 128.85 (**CH$_b$** (Ar)), 128.16 (**CH$_b$** (Ar)), 121.67 (**C** (Ar)), 115.03 (**CH$_a$** (Ar)), 98.90 (**C**), 96.43 (**C**-SOMe), 55.43 (O**CH$_3$**), 45.56 (N**CH$_2$**CH$_3$), 43.83 (N**CH$_2$**CH$_3$), 33.27 (**CH$_3$**SO), 12.51 (NCH$_2$**CH$_3$**), 11.28 (NCH$_2$**CH$_3$**).

^{1}H NMR δ (400 MHz, DMSO-D_6) 13.78 (1H, bs, **NH**), 7.44 (1H, m, **CH** (Ar)), 7.19-7.07 (3H, m, **CH** (Ar)), 3.78 (3H, s, O**CH$_3$**), 3.67 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.43-3.32 (3H, m, N**CH$_2$**CH$_3$), 1.99 (3H, s, **CH$_3$**SO), 1.07 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**), 0.56 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**).

^{13}C NMR δ (400 MHz, DMSO-D_6) 161.95 (Et_2N-**C**=N), 160.72 (**C**-OMe (Ar)), 129.02 (**CH$_b$** (Ar)), 128.72 (**CH$_b$** (Ar)), 121.78 (**C** (Ar)), 115.42 (**CH$_a$** (Ar)), 98.50 (**C**), 97.02 (**C**-SOMe), 55.87 (O**CH$_3$**), 45.44 (N**CH$_2$**CH$_3$), 43.93 (N**CH$_2$**CH$_3$), 33.46 (**CH$_3$**SO), 12.74 (NCH$_2$**CH$_3$**), 11.56 (NCH$_2$**CH$_3$**).

MS (*m/z*): 422.1 $[M+Na]^+$, 821.2 $[2M+Na]^+$.

HRMS (*m/z*): $[M+NH_4]^+$ for $C_{15}H_{25}N_6O_4S_2$ calculated 417.1373 measured 417.1367.

Diastereoisomer (**319'**):

IR υ_{max} (cm^{-1}) 3118 (br, **NH**), 3017 (w), 2976 (w), 2935 (w), 2898 (w), 1604 (s, **C=N**), 1510 (m), 1424 (m), 1316 (s, **SO$_2$**), 1299 (s), 1258 (m), 1244 (m), 1165 (m), 1153 (s, **SO$_2$**), 1128 (m), 1045 (m), 1025 (s, **SO**), 1002 (m), 957 (m), 911 (m), 836 (s).

^{1}H NMR δ (400 MHz, $CDCl_3$) 10.64 (1H, bs, **NH**), 7.35 (1H, d, *J*=8.6 Hz, **CH$_b$** (Ar)), 7.16 (1H, d, *J*=8.6 Hz, **CH$_b$** (Ar)), 7.02 (1H, d, *J*=8.6 Hz, **CH$_a$** (Ar)), 6.99 (1H, d, *J*=8.6 Hz, **CH$_a$** (Ar)), 3.86 (3H, s, O**CH$_3$**), 3.67 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.57 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.50 (1H, dq, *J*=14.3 and 7.0 Hz, N**CH$_2$**CH$_3$), 3.39 (1H, dq, *J*=13.5 and 7.0 Hz, N**CH$_2$**CH$_3$), 2.87 (3H, s, **CH$_3$**SO), 1.27 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**), 0.90 (3H, t, *J*=7.0 Hz, NCH$_2$**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 162.59 (Et_2N-**C**=N), 160.92 (**C**-OMe (Ar)), 129.67 (**CH**$_b$ (Ar)), 127.82 (**CH**$_b$ (Ar)), 121.71 (**C** (Ar)), 114.95 (**CH**$_a$ (Ar)), 114.40 (**CH**$_a$ (Ar)), 102.77 (**C**), 95.66 (**C**-SOMe), 55.35 (O**CH$_3$**), 45.16 (N**CH$_2$**CH_3), 44.42 (N**CH$_2$**CH_3), 34.72 (**CH$_3$**SO), 12.87 (NCH_2**CH$_3$**), 11.25 (NCH_2**CH$_3$**).

^{1}H NMR δ (400 MHz, DMSO-D_6) 13.22 (1H, bs, **NH**), 7.21 (1H, d, *J*=8.7 Hz, **CH** (Ar)), 7.10 (1H, d, *J*=8.7 Hz, **CH** (Ar)), 7.06-7.02 (2H, m, **CH** (Ar)), 3.79 (3H, s, O**CH$_3$**), 3.54-3.44 (3H, m, N**CH$_2$**CH_3), 3.35 (1H, m, N**CH$_2$**CH_3), 2.73 (3H, s, **CH$_3$**SO), 1.12 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**), 0.77 (3H, t, *J*=7.0 Hz, NCH_2**CH$_3$**).

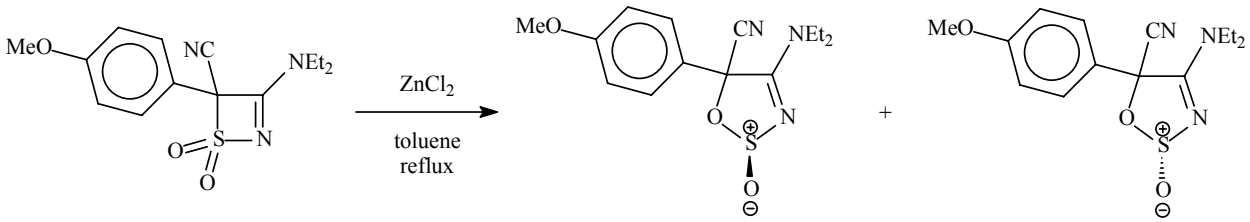
^{13}C NMR δ (400 MHz, DMSO-D_6) 163.03 (Et_2N-**C**=N), 160.75 (**C**-OMe (Ar)), 130.12 (**CH**$_b$ (Ar)), 128.25 (**CH**$_b$ (Ar)), 122.43 (**C**), 114.92 (**CH**$_a$ (Ar)), 114.88 (**CH**$_a$ (Ar)), 101.35 (**C**), 96.21 (**C**-SOMe), 55.82 (O**CH$_3$**), 45.17 (N**CH$_2$**CH_3), 44.40 (N**CH$_2$**CH_3), 34.10 (**CH$_3$**SO), 13.10 (NCH_2**CH$_3$**), 11.53 (NCH_2**CH$_3$**).

MS (*m/z*): 422.1 $[M+Na]^+$, 821.2 $[2M+Na]^+$.

HRMS (*m/z*): $[M+NH_4]^+$ for $C_{15}H_{25}N_6O_4S_2$ calculated 417.1373 measured 417.1379.

Crystal data: appendix XVI

3.5 Synthesis of 1,2,3-oxathiazolin-2-oxide



(**252**)

(**274**)
$C_{14}H_{17}N_3O_3S$
MW = 307.36 g/mol

(**274'**)
$C_{14}H_{17}N_3O_3S$
MW = 307.36 g/mol

3-Diethylamino-1,2-thiazetin-1,1-dioxide (**251**) (155 mg, 0.50 mmol) and zinc chloride (250 µL of a 1M sol. in diethyl ether, 0.25 mmol, 0.5 eq.) were dissolved in toluene (2 mL). The whole was stirred under nitrogen at 60˚C for 22 hours. The mixture was then heated at reflux for

a further 25 hours. The solvent was removed *in vacuo* to give the crude product as a dark brown oil (m=96 mg). Purification by gravity silica chromatography (hexane/EtOAc: 2/1) gave the product as two diastereoisomers (**274**) (**25 mg, 16 %**) and (**274'**) (**10 mg, 6 %**) in a 2.5/1 ratio, one as a pure fraction, the other one as mixed fractions.

Pure fraction of diastereoisomer (**274**)*:

IR υ_{max} (cm^{-1}) 2975 (w), 2938 (w), 2838 (w), 2055 (w, **C**N), 1595 (vs, **C**=**N**), 1514 (m), 1442 (w), 1359 (w), 1309 (w), 1261 (m), 1209 (w), 1183 (s), 1066 (w), 1030 (w), 968 (w), 884 (w), 836 (w).

^{1}H NMR δ (400 MHz, $CDCl_3$) 7.60 (2H, d, *J*=8.9 Hz, **CH**$_b$ (Ar)), 7.00 (2H, d, *J*=8.9 Hz, **CH**$_a$ (Ar)), 3.85 (3H, s, O**CH$_3$**), 3.58 (2H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 3.25 (1H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 3.24 (1H, q, *J*=7.1 Hz, N**CH$_2$**CH_3), 1.30 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.83 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (400 MHz, $CDCl_3$) 164.72 (Et_2N-**C**=N), 161.23 (**C**-OMe (Ar)), 128.81 (**CH**$_b$ (Ar)), 125.25 (**C** (Ar)), 115.01 (**CH**$_a$ (Ar)), 114.55 (**C**N), 84.16 (**C**), 55.51 (O**CH$_3$**), 45.47 (N**CH$_2$**CH_3), 44.15 (N**CH$_2$**CH_3), 12.30 (NCH_2**CH$_3$**), 11.15 (NCH_2**CH$_3$**).

MS (*m/z*): 330.1 $[M+Na]^+$, 637.2 $[2M+Na]^+$.

Mixed fractions of diastereoisomer (**274'**)*:

^{1}H NMR δ (500 MHz, $CDCl_3$) 7.37 (2H, d, *J*=8.8 Hz, **CH**$_b$ (Ar)), 6.99 (2H, d, *J*=8.8 Hz, **CH**$_a$ (Ar)), 3.84 (3H, s, O**CH$_3$**), 3.73 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.50 (1H, dq, *J*=13.6 and 7.1 Hz, N**CH$_2$**CH_3), 3.24 (1H, m (overlapping), N**CH$_2$**CH_3), 3.18 (1H, dq, *J*=14.4 and 7.1 Hz, N**CH$_2$**CH_3), 1.31 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**), 0.88 (3H, t, *J*=7.1 Hz, NCH_2**CH$_3$**).

^{13}C NMR δ (500 MHz, $CDCl_3$) 166.34 (Et_2N-**C**=N), 161.45 (**C**-OMe (Ar)), 127.52 (**CH**$_b$ (Ar)), 124.75 (**C** (Ar)), 115.11 (**CH**$_a$ (Ar)), 114.63 (**C** (CN)), 81.68 (**C**), 55.53 (O**CH$_3$**), 45.47 (N**CH$_2$**CH_3), 44.75 (N**CH$_2$**CH_3), 12.35 (NCH_2**CH$_3$**), 11.23 (NCH_2**CH$_3$**).

* The two diastereoisomers may be interchanged.

References

[1] Black, J. G. In *Microbiology: Principles and Explorations*; 5th ed.; Wiley: New York, 2002, p 77-79.

[2] Schrechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.

[3] Pauling, L. *Chem. Eng. News* **1946**, *24*, 1375.

[4] Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10.

[5] Frère, J. M.; Nguyen-Distèche, M.; Coyette, J.; Joris, B. In *The Chemistry of β-Lactams*; Page, M. I., Ed.; Blackie: Glagow, 1992, p 148-197.

[6] Page, M. I. *Adv. Phys. Org. Chem.* **1987**, *23*, 165-270.

[7] Martin, H. H. *J. Gen. Microbiol.* **1964**, *36*, 441.

[8] Tipper, D. J.; Stominger, J. L. *Proc. Natl. Acad. Sci. USA* **1965**, *54*, 1133.

[9] Frère, J. M.; Duez, C.; Ghuysen, J. M.; Vandekerkhove, J. *Febs Letters* **1976**, *70*, 257-260.

[10] Tomasz, A. *Annu. Rev. Microbiol.* **1979**, *33*, 113-137.

[11] Helfand, M. S.; Bonomo, R. A. *Curr. Drug Target-Infectious Disorders* **2003**, 9.

[12] Tsurukato, Y.; Fukushima, K.; Nishizaki, K.; Takata, T.; Ogawa, T.; Nakashima, T.; Sugata, K.; Yorizane, S.; Ogawara, T.; Masuda, Y. *Acta Oto-Laryngol. Suppl.* **1999**, *540*, 67.

[13] Saier, M. H.; Paulsen, I. T.; Sliwinski, M. K.; Pao, S. S.; Skurray, R. A.; Nikaido, H. *The FASEB Journal* **1998**, *12*, 265.

[14] Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395-424.

[15] Staudinger, H. *Liebigs Ann. Chem.* **1908**, *356*, 51.

[16] Morin, R. B.; Gorman, M. In *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982; Vol. 1, p 500.

[17] Davis, J. *Science* **1994**, *264*, 375.

[18] Levy, S. B. *Sci. Am.* **1998**, *278*, 46-53.

[19] Normark, B. H.; Normark, S. *J. Intern. Med.* **2002**, *252*, 91.

[20] Walsh, C. *Nature* **2000**, *406*, 775-781.

[21] Knowles, J. R. *Acc. Chem. Res.* **1985**, *18*, 97-104.

[22] Deziel, R.; Malenfant, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1437.

[23] Yoakim, C.; Ogilive, W.; Cameron, D.; Chabot, C.; Grande-Marte, C.; Guse, I.; Hache, B.; Naud, J.; Kawai, S.; O'Meara, J.; Plante, R.; Deziel, R. *Chem. Chemother.* **1998**, *9*, 379.

[24] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 19.

[25] Page, M. I. In *Comprehensive Medicinal Chemistry*; Sammes, P. G., Ed.; Pergamon: Oxford, 1990; Vol. 2, p 61-67.

[26] King, J. F.; Rathore, R.; Lam, J. Y. L.; Guo, Z. R.; Klassen, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3028-3033.

[27] Wood, J. M.; Page, M. I. *Trends in Heterocyclic Chemistry* **2002**, *8*, 19.

[28] Baxter, J.; Laws, A. P.; Rigoreau, L. J.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1996**, *2*, 245.

[29] Chanet-Ray, J.; Vessiere, R. *Org. Prep. Proced. Int.* **1986**, *18*, 157-178.

[30] Iwama, T.; Kataoka, T. *Rev. Heteroat. Chem.* **1996**, *15*, 25-60.

[31] Enders, D.; Wallert, S. *Tetrahedron Lett.* **2002**, *43*, 5109-5111.

[32] Enders, D.; Wallert, S.; Runsink, J. *Synthesis* **2003**, 1856-1868.

[33] Enders, D.; Wallert, S. *Synlett* **2002**, 304-306.

[34] Enders, D.; Moll, A. *Synthesis* **2005**, 1807-1816.

[35] Enders, D.; Moll, A.; Schaadt, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2003**, 3923-3938.

[36] Schwenkkraus, P.; Merkle, S.; Otto, H.-H. *Liebigs Ann.* **1997**, 1261-1266.

[37] Meinzer, A.; Breckel, A.; Abu Thaher, B.; Manicone, N.; Otto, H. H. *Helv. Chim. Acta* **2004**, *87*, 90-105.

[38] Lewis, A. K. D.; Mok, B. J.; Tocher, D. A.; Wilden, J. D.; Caddick, S. *Org. Lett.* **2006**, *8*, 5513-5515.

[39] Caddick, S.; Bush, H. D. *Org. Lett.* **2003**, *5*, 2489-2492.

[40] Barton, W. R. S.; Paquette, L. A. *Can. J. Chem.* **2004**, *82*, 113-119.

[41] Brienne, M. J.; Varech, D.; Leclercq, M.; Jacques, J.; Radembino, N.; Dessalles, M. C.; Mahuzier, G.; Gueyouche, C.; Bories, C.; Loiseau, P.; Gayral, P. *J. Med. Chem.* **1987**, *30*, 2232-2239.

[42] Truce, W. E.; Abraham, D. J.; Son, P. *J. Org. Chem.* **1967**, *32*, 990-997.

[43] Baldoli, C.; Del Buttero, P.; Perdicchia, D.; Pilati, T. *Tetrahedron* **1999**, *55*, 14089-14096.

[44] Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177-8181.

[45] Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2869-2872.

[46] Iwama, T.; Kataoka, T.; Muraoka, O.; Tanabe, G. *J. Org. Chem.* **1998**, *63*, 8355-8360.

[47] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.

[48] Iwama, T.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 5507-5522.

[49] Kataoka, T. *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *153-154*, 193-207.

[50] Kataoka, T.; Iwama, T.; Takagi, A. *Tetrahedron Lett.* **1996**, *37*, 2257-2260.

[51] Zajac, M.; Peters, R. *Org. Lett.* **2007**, *9*, 2007-2010.

[52] Mihova, T. R.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1996**, *79*, 2067-2074.

[53] Todorova, T. R.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1999**, *82*, 354-371.

[54] Le Berre, A.; Etienne, A.; Desmazières, B. *Bull. Soc. Chim. Fr.* **1975**, 807.

[55] Le Berre, A.; Etienne, A.; Desmazières, B. *Bull. Soc. Chim. Fr.* **1976**, 277.

[56] Hu, W. Q.; Hesse, M. *Helv. Chim. Acta* **1996**, *79*, 548-559.

[57] Huang, T. L.; Dredar, S. A.; Manneh, V. A.; Blankenship, J. W.; Fries, D. S. *J. Med. Chem.* **1992**, *35*, 2414-2418.

[58] Khoukhi, M.; Vaultier, M.; Benalil, A.; Carboni, B. *Synthesis* **1996**, 483.

[59] Khoukhi, N.; Vaultier, M.; Carrie, R. *Tetrahedron* **1987**, *43*, 1811-1822.

[60] Glasl, D.; Rihs, G.; Otto, H. H. *Helv. Chim. Acta* **1997**, *80*, 671-683.

[61] Nicolaus, B. J. R.; Bellasio, E.; Testa, E. *Helv. Chim. Acta* **1962**, *84*, 717-728.

[62] Iwama, T.; Ogawa, M.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 8941-8974.

[63] Kataoka, T.; Iwama, T. *Tetrahedron Lett.* **1995**, *36*, 5559-5562.

[64] Anastassiou, A. G.; Hammer, R. B. *J. Am. Chem. Soc.* **1972**, *94*, 303-305.

[65] Hall, J. H.; Huisgen, R.; Ross, C. H.; Scheer, W. *J. Chem. Soc. , Chem. Commun.* **1971**, 1188-1190.

[66] Plagge, H.; Manicone, N.; Otto, H. H. *Helv. Chim. Acta* **2004**, *87*, 1574-1590.

[67] Buynak, J.; Rao, V.; Nidamarthy, S.; Adams, G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 847.

[68] Crichlow, G.; Nukaga, M.; Doppalapudi, V.; Buynak, J.; Knox, J. *Biochemistry* **2001**, *40*, 6233.

[69] Underwood, D. J.; Green, B. G.; Chabin, R.; Mills, S.; Doherty, J. B.; Finke, P. E.; Maccoss, M.; Shah, S. K.; Burgey, C. S.; Dickinson, T. A.; Griffin, P. R.; Lee, T. E.; Swiderek, K. M.; Covey, T.; Westler, W. M.; Knight, W. B. *Biochemistry* **1995**, *34*, 14344.

[70] Beardsell, M.; Hinchliffe, P. S.; Wood, J. M.; Wilmouth, R. C.; Schofield, C. J.; Page, M. I. *Chem. Commun.* **2001**, 497.

[71] Schwenkkraus, P.; Otto, H.-H. *Arch. Pharm.* **1993**, *326*, 437.

[72] Luheshi, A. B. N.; Smalley, R. K.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1990**, *31*, 123-126.

[73] Luheshi, A. B. N.; Smalley, R. K.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1990**, *31*, 127-130.

[74] Harnisch, J.; Szeimies, G. *Chem. Ber.* **1979**, *112*, 3914-3933.

[75] Szeimies, G.; Siefken, U.; Rinck, R. *Angew. Chem. Int. Ed.* **1973**, *12*, 161-162.

[76] Jorritsma, R.; Steinberg, H.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 307-312.

[77] Marchand-Brynaert, J.; Moya-Portuguez, M.; Lesuisse, D.; Ghosez, L. *J. Chem. Soc., Chem. Comm.* **1980**, 173-174.

[78] Hassner, A.; Currie, J. O.; Steinfel, A. S.; Atkinson, R. F. *Angew. Chem. Int. Ed.* **1970**, *9*, 731-732.

[79] Hassner, A.; Currie, J. O.; Steinfel, A. S.; Atkinson, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2982-2987.

[80] Hoshina, H.; Kubo, K.; Morita, A.; Sakurai, T. *Tetrahedron* **2000**, *56*, 2941-2951.

[81] Yang, N. C.; Kim, B.; Chiang, W.; Hamada, T. *J. Chem. Soc., Chem. Comm.* **1976**, 729-730.

[82] Bestian, H.; Biener, H.; Clauss, K.; Heyn, H. *Liebigs Ann.* **1968**, *718*, 94-100.

[83] Bormann, D. *Liebigs Ann.* **1969**, *725*, 124-129.

[84] Graf, R. *Liebigs Ann.* **1963**, *661*, 111-157.

[85] Pifferi, G.; Consonni, P.; Pelizza, G.; Testa, E. *J. Heterocycl. Chem.* **1967**, *4*, 619-624.

[86] Hemming, K.; Redhouse, A. D.; Smalley, R. K.; Thompson, J. R.; Kennewell, P. D.; Westwood, R. *Tetrahedron Lett.* **1992**, *33*, 2231-2234.

[87] Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437.

[88] Durst, T.; O'Sullivan, M. J. *J. Org. Chem.* **1970**, *35*, 2043-2044.

[89] Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett.* **2004**, *45*, 3589-3592.

[90] Singh, G. S. *Tetrahedron* **2003**, *59*, 7631-7649.

[91] Brillon, D. *Sulfur Rep.* **1992**, *12*, 297-338.

[92] Polshettiwar, V.; Kaushik, M. P. *J. Sulf. Chem.* **2006**, *27*, 353-386.

[93] Brillon, D. *Synth. Commun.* **1990**, *20*, 3085-3095.

[94] Curphey, T. J. *Tetrahedron Lett.* **2000**, *41*, 9963-9966.

[95] Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461-6473.

[96] Curphey, T. J. *Tetrahedron Lett.* **2002**, *43*, 371-373.

[97] Nivsarkar, M.; Gupta, A. K.; Kaushik, M. P. *Tetrahedron Lett.* **2004**, *45*, 6863-6866.

[98] Polshettiwar, V.; Nivsarkar, M.; Paradashani, D.; Kaushik, M. R. *J. Chem. Res.* **2004**, 474-476.

[99] Polshettiwar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2004**, *45*, 6255-6257.

[100] Polshettiwar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2006**, *47*, 2315-2317.

[101] Elwahy, A. H. M.; Masaret, G. S. *J. Heterocycl. Chem.* **2004**, *41*, 711-715.

[102] Heravi, M. M.; Rajabzadeh, G.; Rahimizadeh, M.; Bakavoli, M.; Ghassemzadeh, M. *Synth. Commun.* **2001**, *31*, 2231-2234.

[103] Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061-5087.

[104] Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929-1958.

[105] Nicolaus, B. J. R.; Bellasio, E. *Helv. Chim. Acta* **1962**, *33*, 211.

[106] Hitotsuyanagi, Y.; Matsumoto, Y.; Sasaki, S.; Suzuki, J.; Takeya, K.; Yamaguchi, K.; Itokawa, H. *J. Chem. Soc., Perkin Trans I* **1996**, 1749-1755.

[107] Nieschalk, J.; Schaumann, E. *Liebigs Ann.* **1996**, 141-145.

[108] Braverman, S.; Cherkinsy, M.; Kedrova, L. *Tetrahedron Lett.* **1998**, *39*, 9259-9262.

[109] Wipf, P.; Jenny, C.; Heimgartner, H. *Helv. Chim. Acta* **1987**, *70*, 1001-1011.

[110] Charette, A. B.; Grenon, M. *J. Org. Chem.* **2003**, *68*, 5792-5794.

[111] Ilankumaran, P.; Ramesha, A. R.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, *36*, 8311-8314.

[112] Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 348-354.

[113] Bodine, J. J.; Kaloustian, M. K. *Synth. Commun.* **1982**, *12*, 787-793.

[114] Brain, C. T.; Hallett, A.; Ko, S. Y. *J. Org. Chem.* **1997**, *62*, 3808-3809.

[115] Chowdhury, S. K. D.; Sarkar, M.; Chatterjee, A.; Mahalanabis, K. K. *Ind. J. Chem. B* **2003**, *42*, 2563.

[116] Coats, S. J.; Link, J. S.; Hlasta, D. J. *Org. Lett.* **2003**, *5*, 721-724.

[117] Kodama, Y.; Ori, M.; Nishio, T. *Helv. Chim. Acta* **2005**, *88*, 187-193.

[118] Mendez, L.; Delpiccolo, C. M. L.; Mata, E. G. *Synlett* **2005**, 1563-1566.

[119] Neilson, D. G. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley: 1975, p 385-489.

[120] Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, *33*, 1679-1681.

[121] Bock, M. G.; Dipardo, R. M.; Pitzenberger, S. M.; Homnick, C. F.; Springer, J. P.; Freidinger, R. M. *J. Org. Chem.* **1987**, *52*, 1644-1646.

[122] Venkatesan, A. M.; Agarwal, A.; Abe, T.; Ushirogochi, H.; Yamamura, I.; Ado, M.; Tsuyoshi, T.; Dos Santos, O.; Gu, Y.; Sum, F. W.; Li, Z.; Francisco, G.; Lin, Y. I.; Petersen, P. J.; Yang, Y.; Kumagai, T.; Weiss, W. J.; Shlaes, D. M.; Knox, J. R.; Mansour, T. S. *J. Med. Chem.* **2006**, *49*, 4623-4637.

[123] Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Galy, A. M.; Barbe, J. *J. Heterocycl. Chem.* **1982**, *19*, 503-507.

[124] Blanchard, C.; Fabre, J. M.; Montginoul, C.; Chaffia, B. A.; Torreilles, E.; Giral, L. *J. Heterocycl. Chem.* **1978**, *15*, 149-153.

[125] Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040-4044.

[126] Chung, N. M.; Tieckelm.H *J. Org. Chem.* **1970**, *35*, 2517-2520.

[127] Brzozowski, Z.; Saczewski, F.; Gdaniec, M. *Bioorg. Med. Chem.* **2003**, *11*, 3673-3681.

[128] Janin, Y. L.; Huel, C.; Flad, G.; Thirot, S. *Eur. J. Org. Chem.* **2002**, 1763-1769.

[129] Ludek, O. R.; Meier, C. *Synlett* **2006**, 324-326.

[130] Comins, D. L.; Gao, J. H. *Tetrahedron Lett.* **1994**, *35*, 2819-2822.

[131] Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier: 1984; Vol. 2, p 165-314.

[132] Uff, B. C. In *Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier: 1984; Vol. 2, p 315-364.

[133] Bausch, M. J.; Wang, L. H. *J. Phys. Org. Chem.* **1993**, *6*, 601-608.

[134] Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 2246-2250.

[135] Meislich, H. *Chem. Heterocycl. Compd.* **1962**, *14-3*, 509.

[136] Podlech, J. *J. Prakt. Chem.* **1998**, *340*, 679-682.

[137] Julia, M.; Mestdagh, H. *Tetrahedron* **1983**, *39*, 433-442.

[138] Eicher, T.; Abdesaken, F.; Franke, G.; Weber, J. L. *Tetrahedron Lett.* **1975**, *45*, 3915-3918.

[139] Eicher, T.; Rohde, R. *Synthesis* **1985**, 619-625.

[140] Eicher, T.; Weber, J. L.; Chatila, G. *Liebigs Ann.* **1978**, *8*, 1203-1221.

[141] Stierli, F.; Prewo, R.; Bieri, J. H.; Heimgartner, H. *Helv. Chim. Acta* **1983**, *66*, 1366-1375.

[142] Allen, C. F. H.; Ryan Jr, R. W.; Van Allan, J. A. *J. Org. Chem.* **1962**, *27*, 778-779.

[143] Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1982**, *47*, 3736-3743.

[144] Jikyo, T.; Eto, M.; Harano, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3463-3470.

[145] Jikyo, T.; Eto, M.; Harano, K. *Tetrahedron* **1999**, *55*, 6051-6066.

[146] Knolker, H. J.; Baum, E.; Heber, J. *Tetrahedron Lett.* **1995**, *36*, 7647-7650.

[147] Kumar, U.; Neenan, T. X. *Macromolecules* **1995**, *28*, 124-130.

[148] Pearson, A. J.; Kim, J. B. *Tetrahedron Lett.* **2003**, *44*, 8525-8527.

[149] Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272-7276.

[150] Sato, S.; Isobe, H.; Tanaka, T.; Ushijima, T.; Nakamura, E. *Tetrahedron* **2005**, *61*, 11449-11455.

[151] Thomas, A.; Anilkumar, G.; Nair, V. *Tetrahedron* **1996**, *52*, 2481-2488.

[152] Jäger, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: 2002, p 361-472.

[153] Ferwanah, A. R. S.; Awadallah, A. M. *Molecules* **2005**, *10*, 492-507.

[154] Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598.

[155] Huisgen, R. In *The Adventure Playground of Mechanism and Novel Reactions*; American Chemical Society: Washington DC, 1994, p 91-123.

[156] Sahoo, M. K. *Synlett* **2007**, 2142-2143.

[157] Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240.

[158] Moody, C. J.; Whitham, G. H. In *Reactive Intermediates*; Davies, S. G., Ed.; Oxford University Press: Oxford, 1992, p 51-67.

[159] Duvall, J. R.; Wu, F. H.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579-8590.

[160] Snider, B. B.; Duvall, J. R.; Sattler, I.; Huang, X. S. *Tetrahedron Lett.* **2004**, *45*, 6725-6727.

[161] Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2007**, *9*, 4375-4378.

[162] Angle, S. R.; Bensa, D.; Belanger, D. S. *J. Org. Chem.* **2007**, *72*, 5592-5597.

[163] Tang, M. Y.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818-7824.

[164] Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741-1744.

[165] Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896-3898.

[166] Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615-3618.

[167] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 49-72.

[168] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 64.

[169] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 72.

[170] Tsang, W.-Y.; Ahmed, N.; Hemming, K.; Page, M. I. *Org. Biomol. Chem.* **2007**, *5*, 3993-4000.

[171] Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.

[172] Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.

[173] Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1984**, *106*, 139-143.

[174] Clerici, F.; Gelmi, M. L.; Soave, R.; Lo Presti, L. *Tetrahedron* **2002**, *58*, 5173-5178.

[175] Cromwell, N. H. *J. Am. Chem. Soc.* **1940**, *62*, 1672-1673.

[176] Cromwell, N. H. *J. Org. Chem.* **1940**, *62*, 2897-2900.

[177] Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959-1964.

[178] Clerici, F.; Marazzi, G.; Taglietti, M. *Tetrahedron* **1992**, *48*, 3227-3238.

[179] Pocar, D.; Rossi, L. M.; Trimarco, P. *J. Heterocycl. Chem.* **1979**, *16*, 925-927.

[180] Pocar, D.; Trimarco, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 622-624.

[181] Oka, K. *Synthesis* **1981**, 661-681.

[182] El-Sakka, I. A.; Hassan, N. A. *J. Sulf. Chem.* **2005**, *26*, 33-97.

[183] Clerici, F.; Erba, E.; Gelmi, M. L.; Valle, M. *Tetrahedron* **1997**, *53*, 15859-15866.

[184] Beccalli, E. M.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **1999**, *55*, 2001-2012.

[185] King, J. F. *Acc. Chem. Res.* **1975**, *8*, 10-17.

[186] Tanabe, T.; Shingaki, T.; Nagai, T. *Chem. Lett.* **1975**, 679-682.

[187] King, J. F.; Baines, K. M.; Netherton, M. R.; Dave, V. *Can. J. Chem.* **2000**, *78*, 1642-1646.

[188] King, J. F.; Beatson, R. P.; Buchshriber, J. M. *Can. J. Chem.* **1977**, *55*, 2323-2330.

[189] Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1962**, *84*, 313.

[190] Paquette, L. A.; Freeman, J. P.; Maiorana, S. *Tetrahedron* **1971**, *27*, 2599-2606.

[191] Petukhova, N. P.; Aristova, N. E.; Stepanyants, A. U.; Prilezhaeva, E. N. *Bull. Acad. Sci. USSR Chem. Science* **1976**, *25*, 119-123.

[192] Koch, F. M.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 2685-2689.

[193] Hiraoka, T.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 480-483.

[194] Truce, W. E.; Allison, J. R. *J. Org. Chem.* **1975**, *40*, 2260-2261.

[195] Truce, W. E.; Dean, B. D. *Heterocycles* **1982**, *18*, 343-356.

[196] Menozzi, G.; Bargagna, A.; Mosti, L.; Schenone, P. *J. Heterocycl. Chem.* **1986**, *23*, 455-458.

[197] Bard, M.; Meslin, J. C.; Quiniou, H. *J. Chem. Soc., Chem. Comm.* **1973**, 672.

[198] Block, E. In *Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R., Rees, C. W., Eds.; Elsevier: 1984; Vol. 7, p 403-447.

[199] Harris, P. A. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: 1996; Vol. 1B, p 1009-1039.

[200] King, J. F.; Harding, D. R. K. *Can. J. Chem.* **1976**, *54*, 2652-2657.

[201] King, J. F.; Harding, D. R. K.; Luinstra, E. A. *J. Chem. Soc., Chem. Comm.* **1972**, 1313-1315.

[202] Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1967**, *89*, 2502-2503.

[203] Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744-4745.

[204] Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 6135-6141.

[205] Burgess, E. M.; Williams, W. M. *J. Am. Chem. Soc.* **1972**, *94*, 4386-4387.

[206] Burgess, E. M.; Williams, W. M. *J. Org. Chem.* **1973**, *38*, 1249-1250.

[207] Tornus, I.; Schaumann, E. *Tetrahedron* **1996**, *52*, 725-732.

[208] Lwowski, W.; Scheiffele, E. *J. Am. Chem. Soc.* **1965**, *87*, 4359-4365.

[209] Schaumann, E. *Tetrahedron* **1988**, *44*, 1827-1871.

[210] Moltzen, E. K.; Senning, A.; Lutjens, H.; Krebs, A. *J. Org. Chem.* **1991**, *56*, 1317-1318.

[211] Gupta, R. C.; Win, T.; Bittner, S. *Curr. Med. Chem.* **2005**, *12*, 2021-2039.

[212] Barbeau, A.; Donaldson, J. *Arch. Neurol.* **1974**, *30*, 52-58.

[213] Azuma, J.; Hasegawa, H.; Sawamura, A.; Awata, N.; Ogura, K.; Harada, H.; Yamamura, Y.; Kishimoto, S. *Clin. Ther.* **1983**, *5*, 398-408.

[214] Azuma, J.; Sawamura, A.; Awata, N.; Ohta, H.; Hamaguchi, T.; Harada, H.; Takihara, K.; Hasegawa, H.; Yamagami, T.; Ishiyama, T.; Iwata, H.; Kishimoto, S. *Clin. Cardiol.* **1985**, *8*, 276-282.

[215] Singh, R. B.; Kartikey, K.; Charu, A. S.; Niaz, M. A.; Schaffer, S. *Adv. Exp. Med. Biol.* **2003**, *526*, 41-48.

[216] Fujita, T.; Ando, K.; Noda, H.; Ito, Y.; Sato, Y. *Circulation* **1987**, *75*, 525-532.

[217] Chauncey, K. B.; Tenner, T. E.; Lombardini, J. B.; Jones, B. G.; Brooks, M. L.; Warner, R. D.; Davis, R. L.; Ragain, R. M. *Adv. Exp. Med. Biol.* **2003**, *526*, 91-96.

[218] McCarty, M. F. *Med. Hypotheses* **1997**, *49*, 143-152.

[219] McCarty, M. F. *Med. Hypotheses* **1999**, *53*, 290-299.

[220] Fennessy, F. M.; Moneley, D. S.; Wang, J. H.; Kelly, C. J.; Bouchier-Hayes, D. J. *Circulation* **2003**, *107*, 410-415.

[221] Wilde, M. I.; Wagstaff, A. J. *Drugs* **1997**, *53*, 1038-1053.

[222] Wallace, D. R.; Dawson, R. *Gerontology* **1990**, *36*, 19-27.

[223] Barbeau, A.; Inoue, N.; Tsukada, Y.; Butterworth, R. F. *Life Sci.* **1975**, *17*, 669-678.

[224] Douglass, I. B.; Farah, B. S. *J. Org. Chem.* **1959**, *24*, 973-975.

[225] Douglass, I. B.; Johnson, T. B. *J. Am. Chem. Soc.* **1938**, *60*, 1486-1489.

[226] Field, L. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977, p 303-382.

[227] Lee, S. W.; Dougherty, C. A. *J. Org. Chem.* **1940**, *5*, 81-85.

[228] Stirling, C. J. M. *J. Chem. Soc.* **1957**, 3597-3604.

[229] Capozzi, G.; Modena, G. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: 1974, p 785-839.

[230] Douglass, I. B.; Poole, D. R. *J. Org. Chem.* **1957**, *22*, 536-537.

[231] Kice, J. L.; Cleveland, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 104-109.

[232] Kharasch, N. In *Organic Sulfur Compounds*; Kharasch, N., Ed.; Pergamon Press: New York, 1961; Vol. 1.

[233] Barnard, D. *J. Chem. Soc.* **1957**, 4675-4676.

[234] Kice, J. L.; Cleveland, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 109-112.

[235] Kice, J. L.; Venier, C. G.; Large, G. B.; Heasley, L. *J. Am. Chem. Soc.* **1969**, *91*, 2028-2035.

[236] Douglass, I. B.; Osborne, C. E. *J. Am. Chem. Soc.* **1953**, *75*, 4582-4583.

[237] Deborde, M.; Von Gunten, U. *Water Res.* **2008**, *42*, 13-51.

[238] Prutz, W. A. *Arch. Biochem. Biophys.* **1996**, *332*, 110-120.

[239] Allen Jr, P.; Brook, J. W. *J. Org. Chem.* **1962**, *27*, 1019-1020.

[240] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 145-146.

[241] Bliss, A. D.; Cline, W. K.; Hamilton, C. E.; Sweeting, O. J. *J. Org. Chem.* **1963**, *28*, 3537-3541.

[242] Pellissier, H. *Tetrahedron* **2007**, *63*, 3235-3285.

[243] Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; 6th ed.; Wiley: 2007, p 1187-1194.

[244] Houk, K. N.; Firestone, R. A.; Munchausen, L. L.; Mueller, P. H.; Arison, B. H.; Garcia, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7227-7228.

[245] Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81-90.

[246] Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291-2297.

[247] Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403-419.

[248] Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401-6402.

[249] Huisgen, R.; Mloston, G.; Langhals, E. *J. Org. Chem.* **1986**, *51*, 4085-4087.

[250] Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285-2290.

[251] Firestone, R. A. *J. Chem. Soc. A* **1970**, 1570-1575.

[252] Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181-2191.

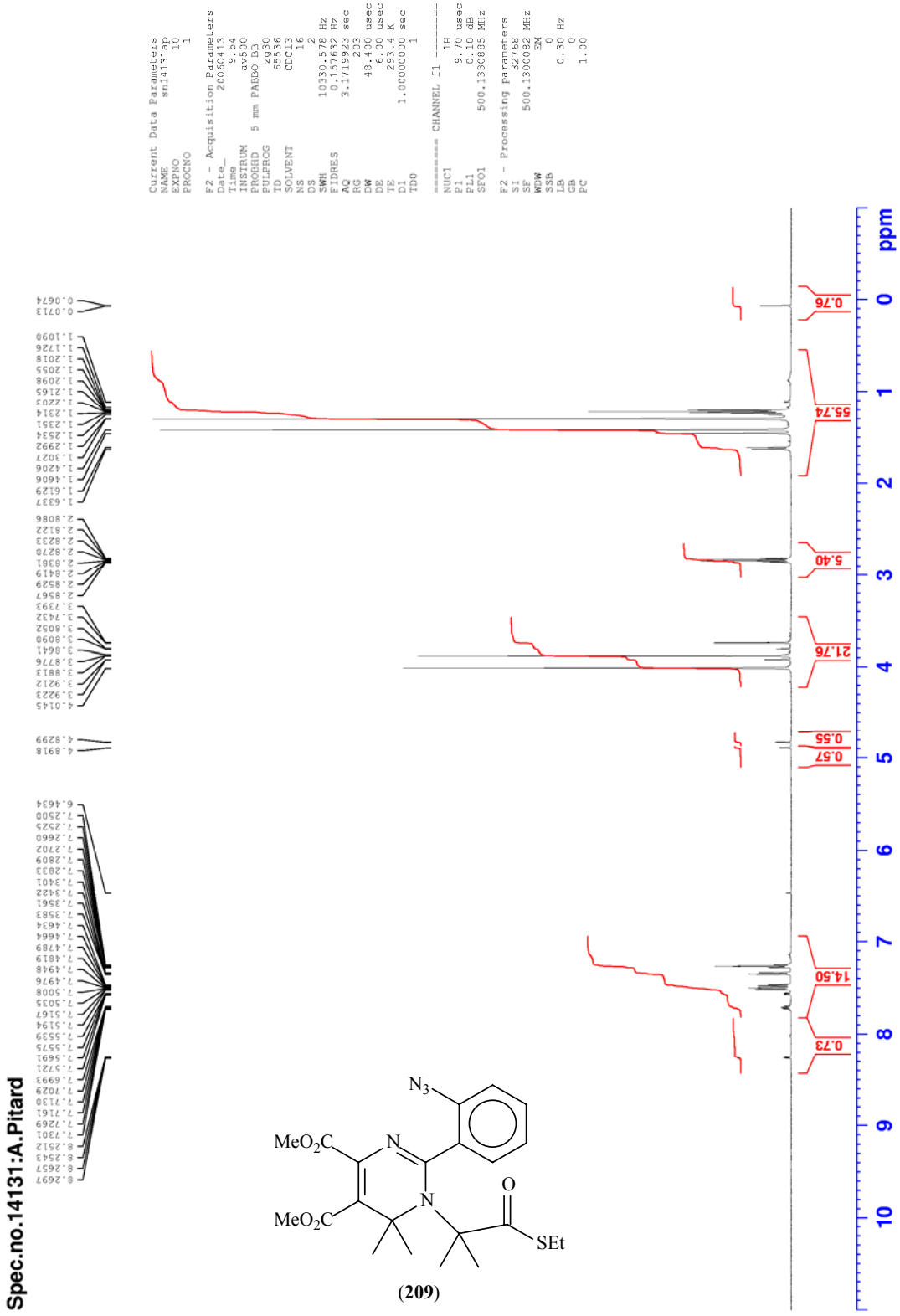
[253] Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009-3039.

[254] Williams, D. H.; Fleming, I. In *Spectroscopic Methods in Organic Chemistry*; 5th ed.; McGraw-Hill: London, 1995, p 63-169.

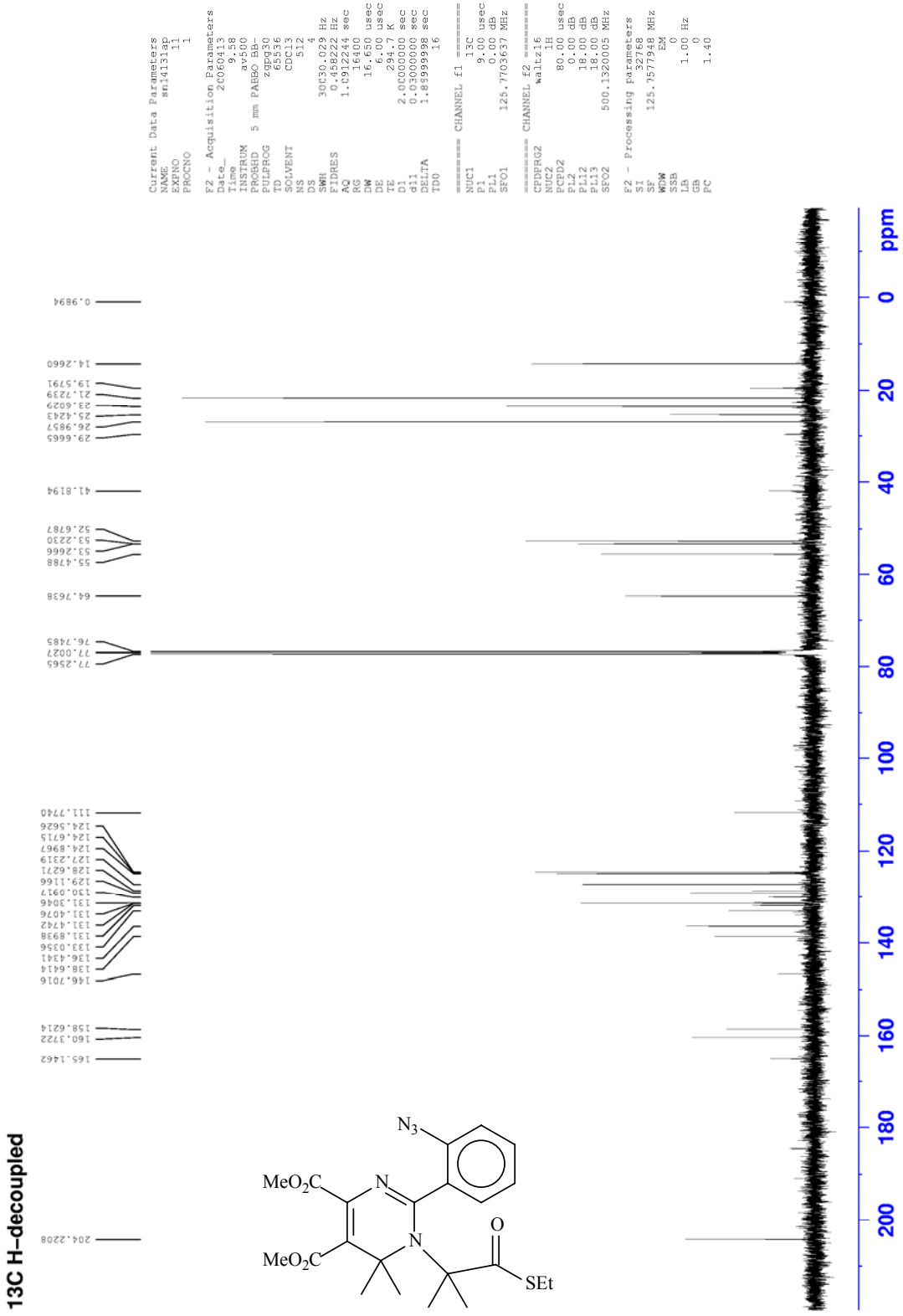
[255] Ahmed, N.; PhD Thesis, University of Huddersfield: 2005, p 69.

[256] Meyle, E.; Otto, H.-H.; Kratky, C. *Monatsh. Chem.* **1985**, *116*, 493-503.

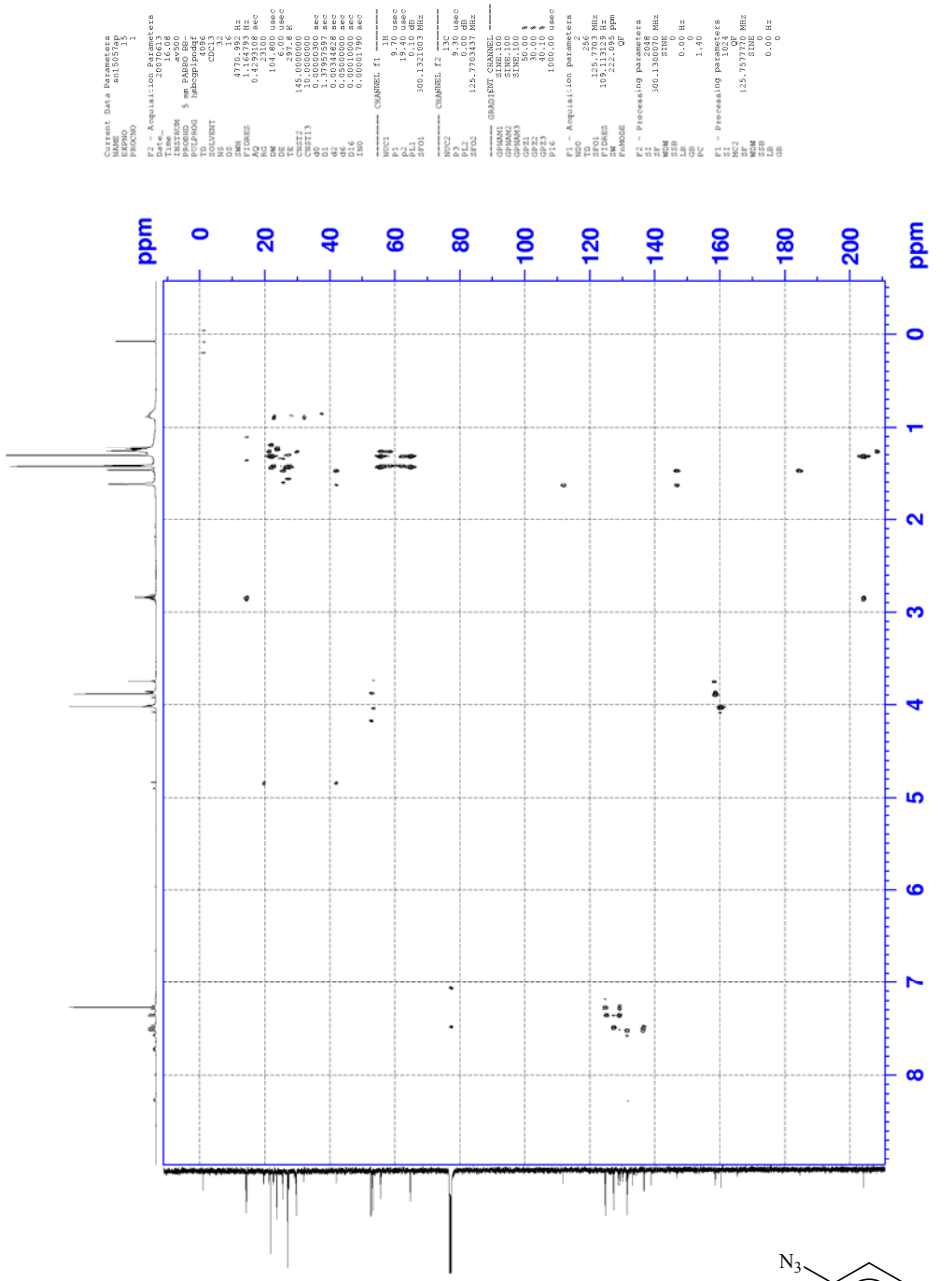
APPENDIX


Spec.no.14131:A.Pitard
Current Data Parameters
NAME sn14131ap
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060413
Time 9.54
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 203
DW 48.400 usec
DE 6.00 usec
TE 293.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.70 usec
PL1 0.10 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300082 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.76
55.74
5.40
21.76
0.57
0.55
14.50
0.73
ppm
N_3
MeO_2C
N
MeO_2C
N
O
SEt

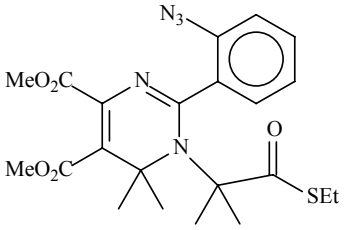
(**209**)


13C H-decoupled
ppm
0
20
40
60
80
100
120
140
160
180
200
N3
MeO2C
MeO2C
N
N
O
SEt

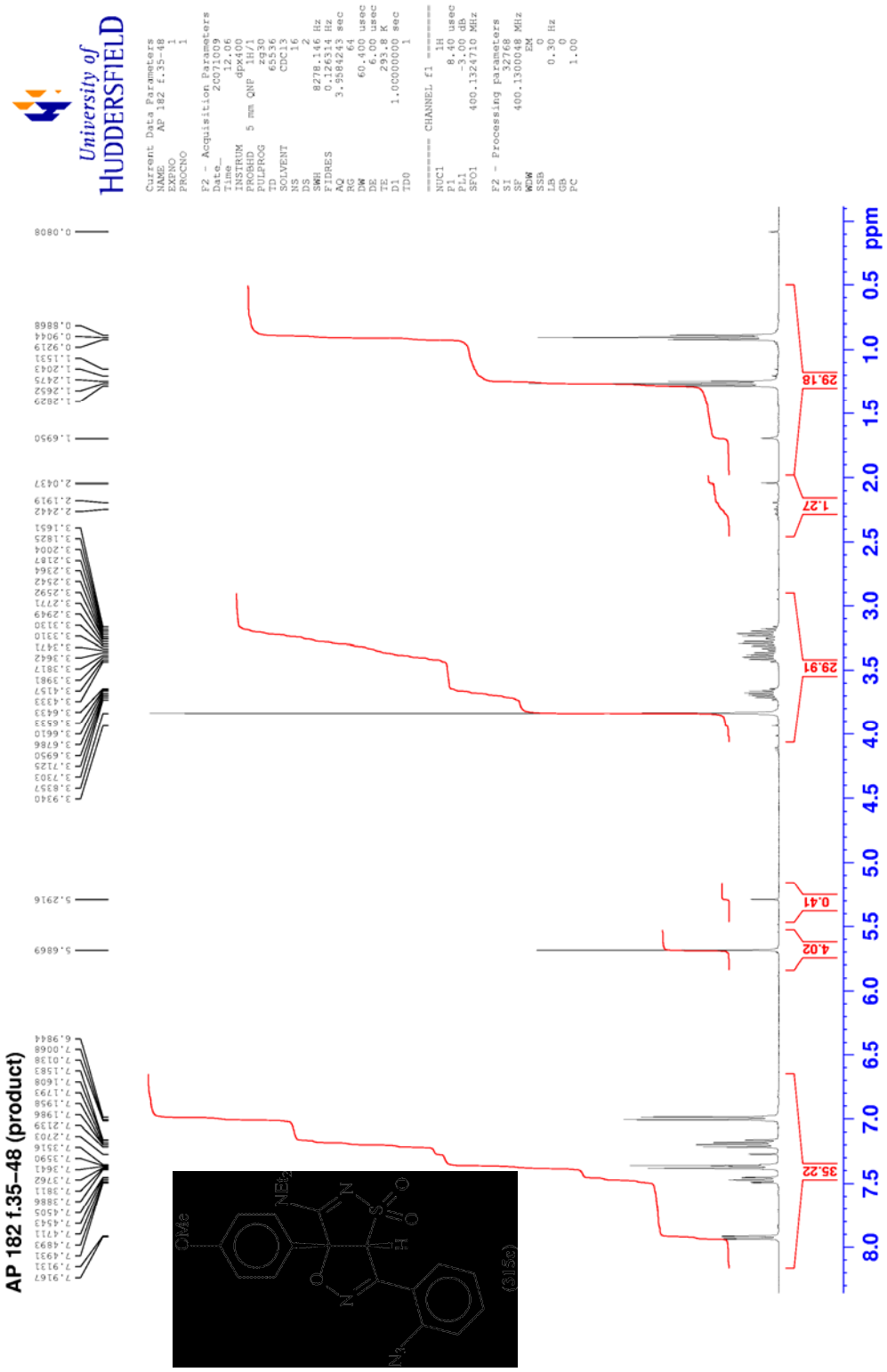
(**209**)

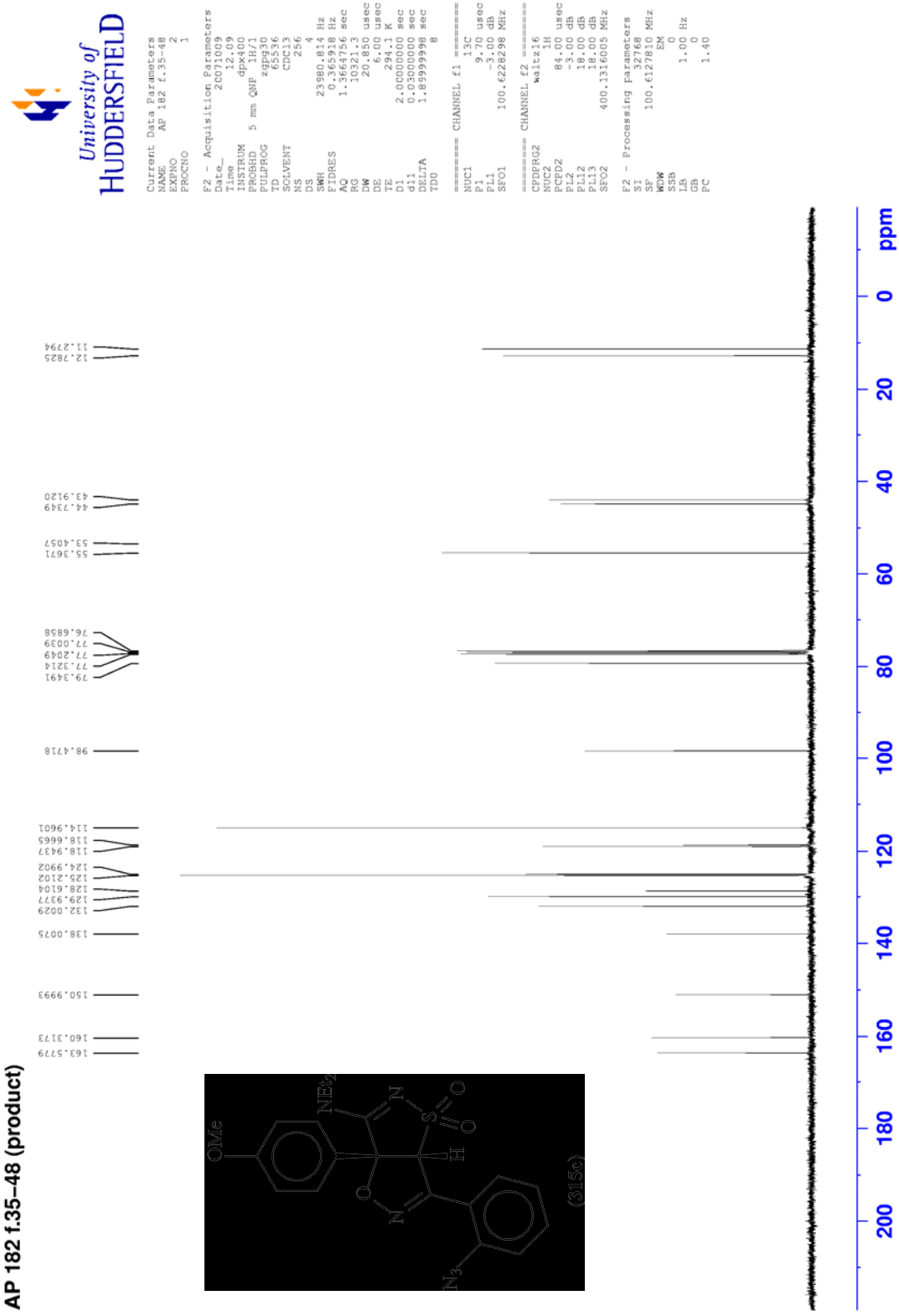

ppm
0
20
40
60
80
100
120
140
160
180
200
ppm
0
1
2
3
4
5
6
7
8

HMBC

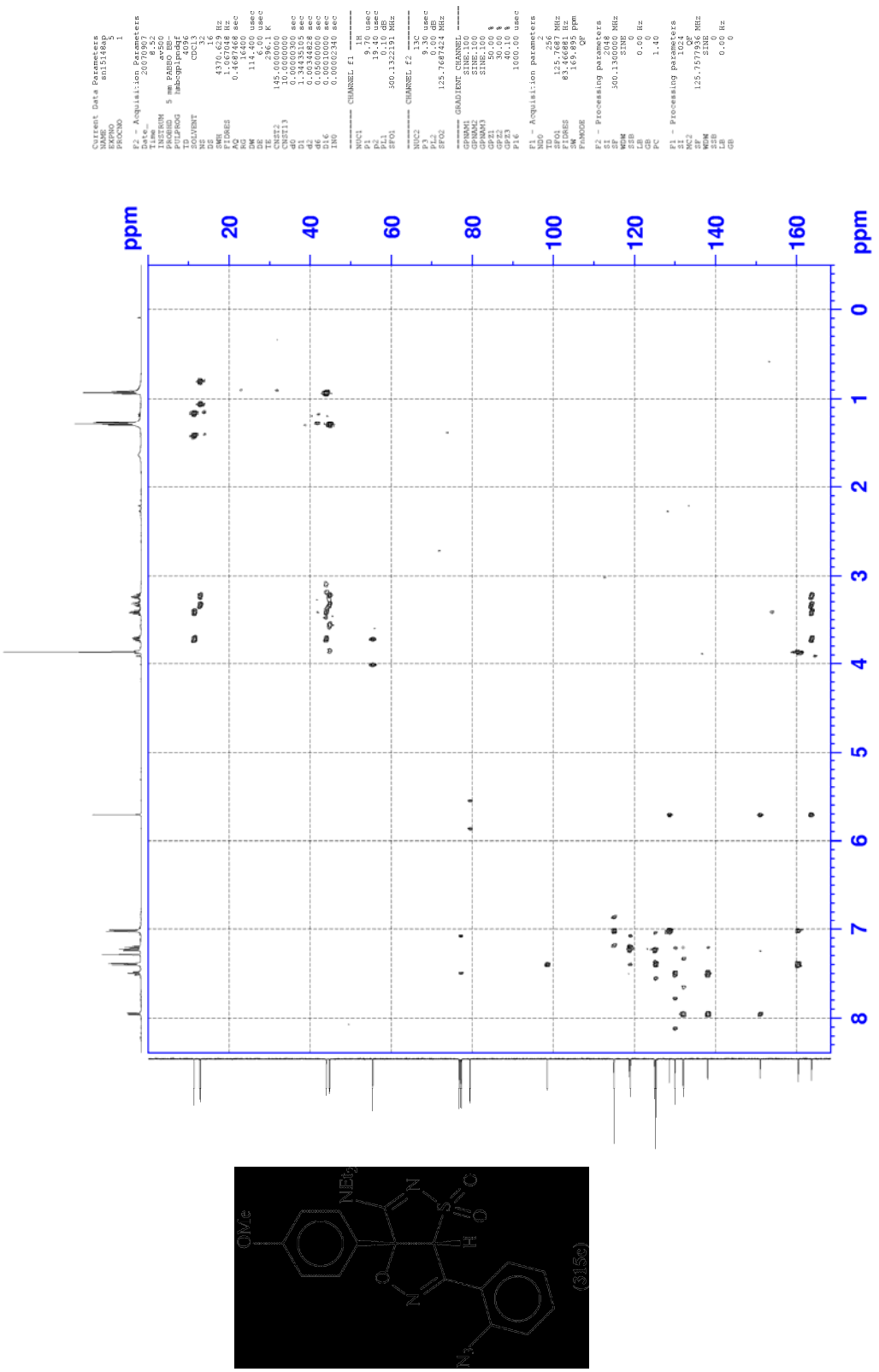

N3
MeO2C
N
MeO2C
N
O
SEt

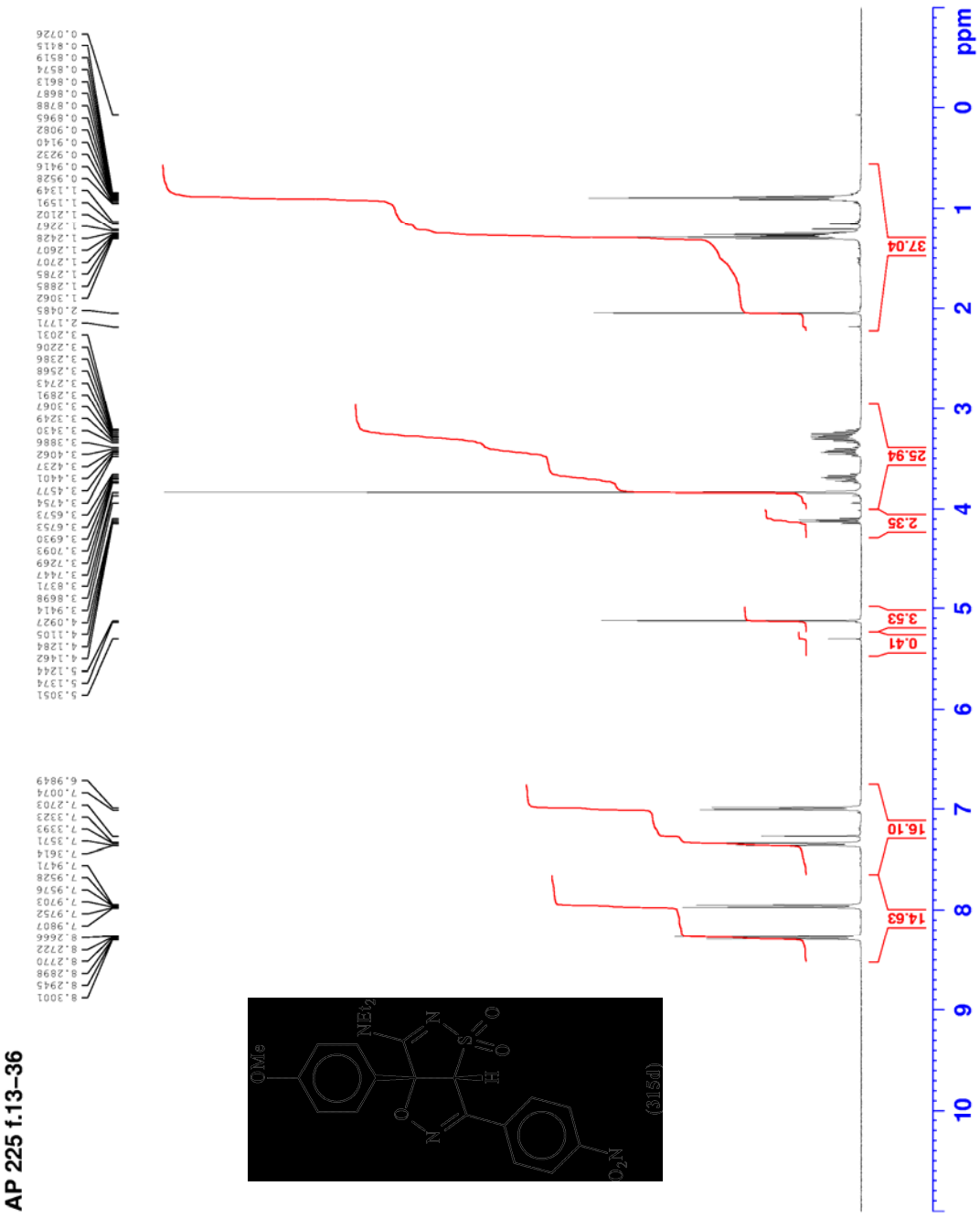
(**209**)

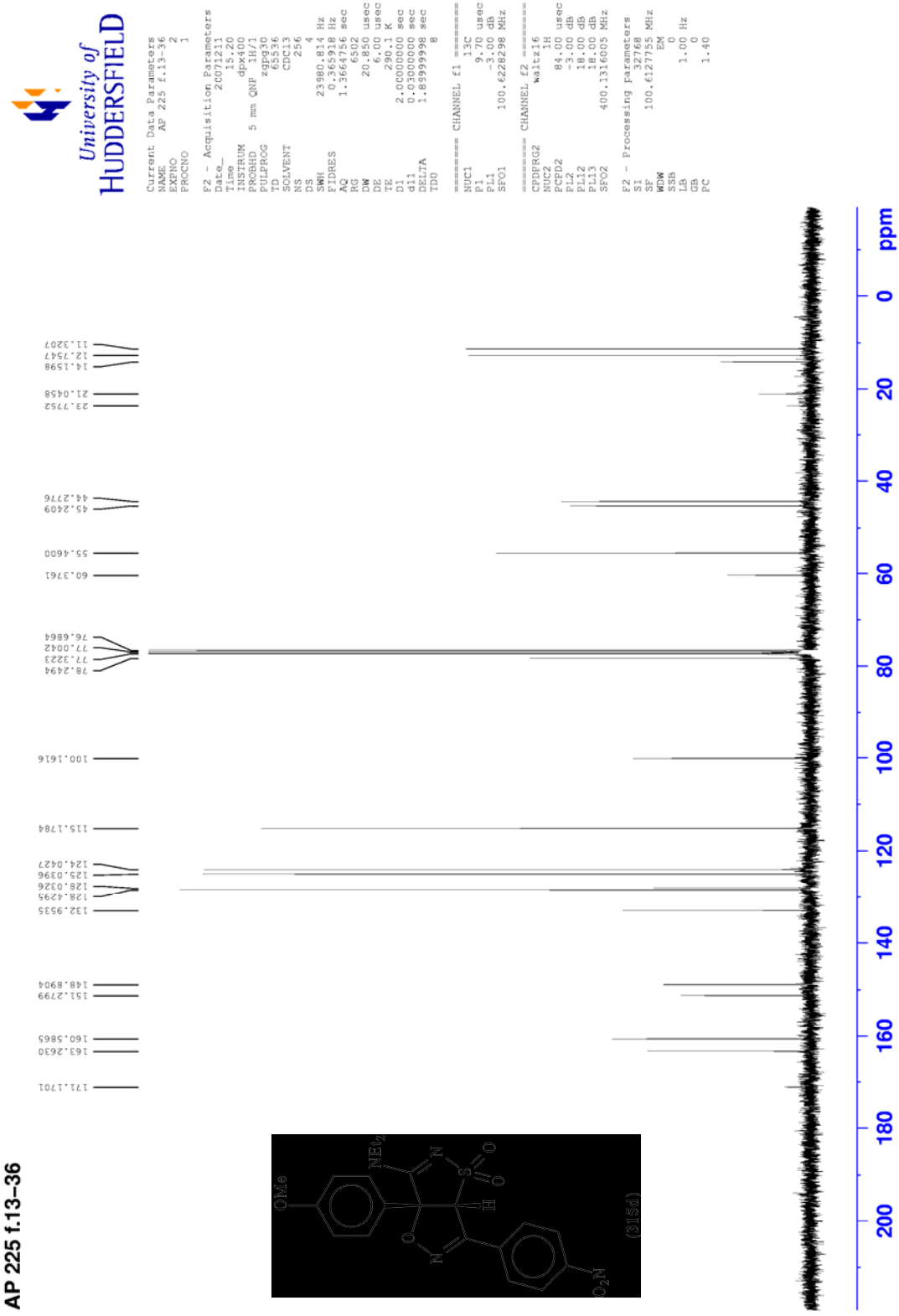

AP 182 f.35–48 (product)
University of HUDDERSFIELD
Current Data Parameters
NAME AP 182 f.35-48
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071009
Time 12.06
INSTRUM dpx400
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 64
DW 60.400 usec
DE 6.00 usec
TE 293.8 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.40 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300048 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
29.18
1.27
29.91
0.41
4.02
35.22
ppm
OMe
NEt2
(S)(S)


AP 182 f.35–48 (product)
University of HUDDERSFIELD
Current Data Parameters
NAME AP 182 f.35-48
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20071009
Time 22.09
INSTRUM dpx400
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 10321.3
DW 20.850 usec
DE 6.00 usec
TE 294.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 8
======== CHANNEL f1 ========
NUC1 13C
P1 9.70 usec
PL1 -3.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 84.00 usec
PL2 3.00 dB
PL12 18.00 dB
PL13 18.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127810 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
163.5779
160.3173
150.9993
138.0075
132.0029
129.9377
128.6104
125.2102
124.9902
118.9437
118.6665
114.9601
98.4718
79.3491
77.3214
77.2049
77.0039
76.6858
55.3671
53.4057
44.7349
43.9120
12.7825
11.2794
OMe
NEt2
(31.5c)
ppm
200
180
160
140
120
100
80
60
40
20
0

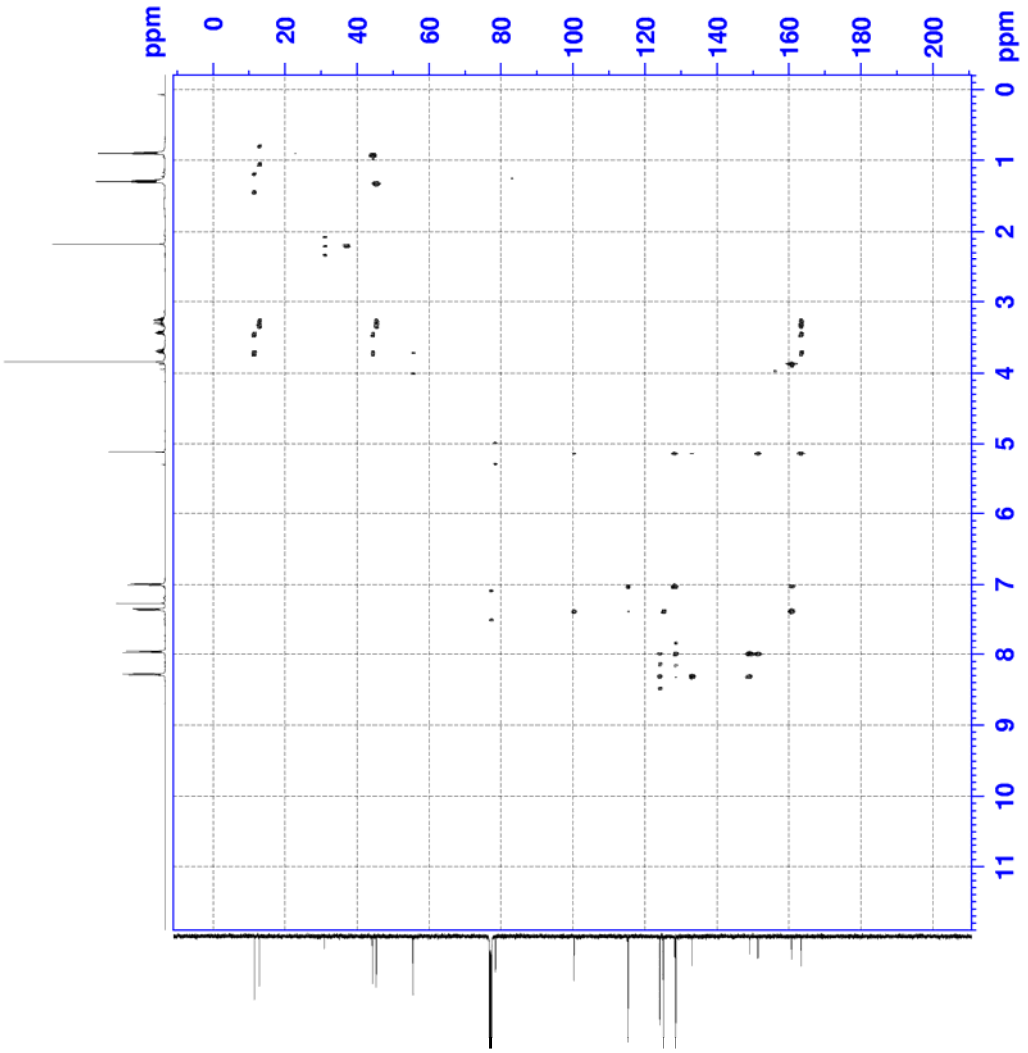
HMBC

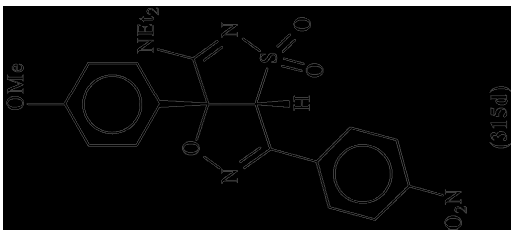


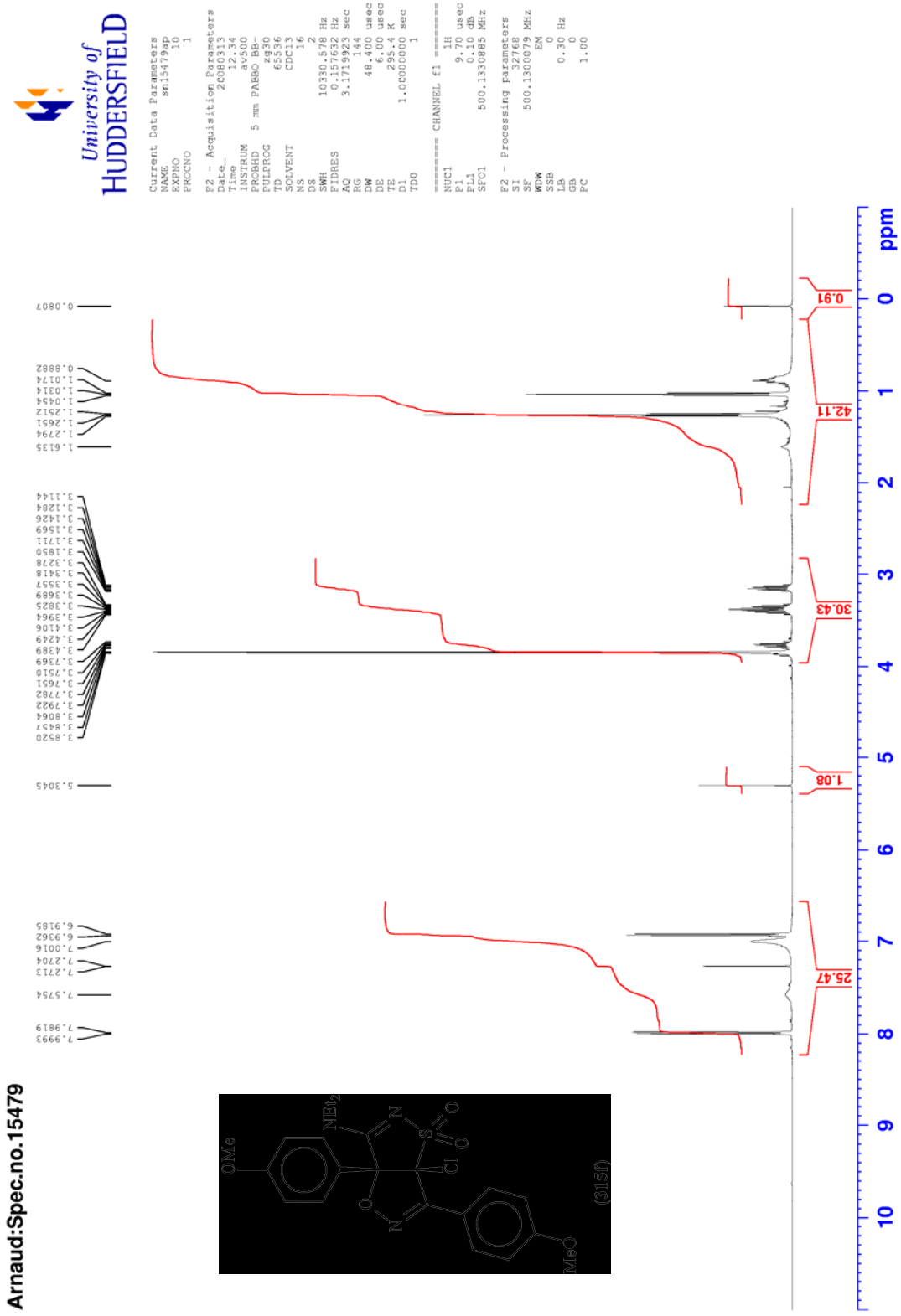

University of
HUDDERSFIELD
AP 225 f.13–36
37.04
25.94
2.35
3.53
0.41
16.10
14.63
ppm

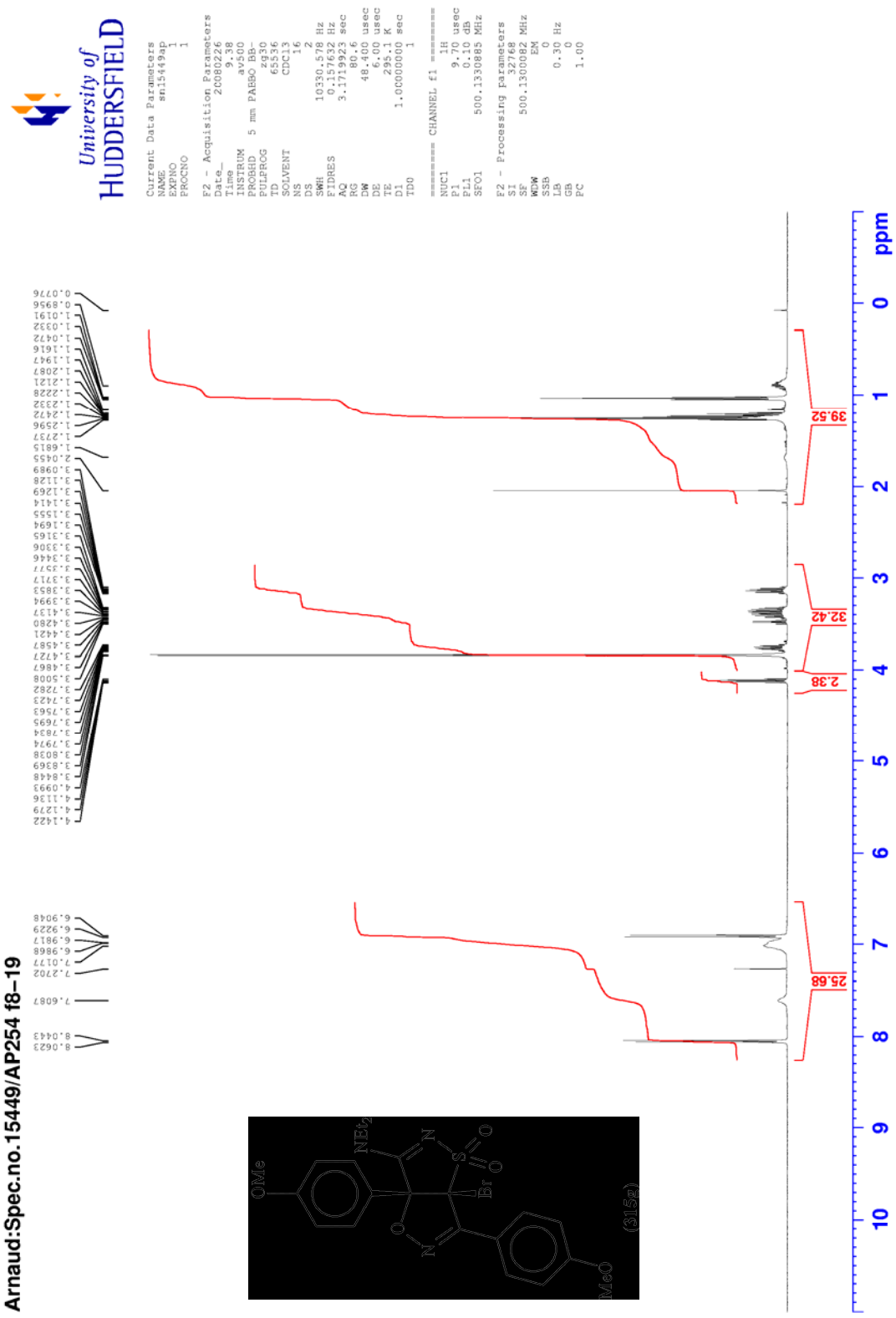

University of
HUDDERSFIELD
AP 225 f.13–36
OMe
NEt2
O2N
(3ISd)
ppm

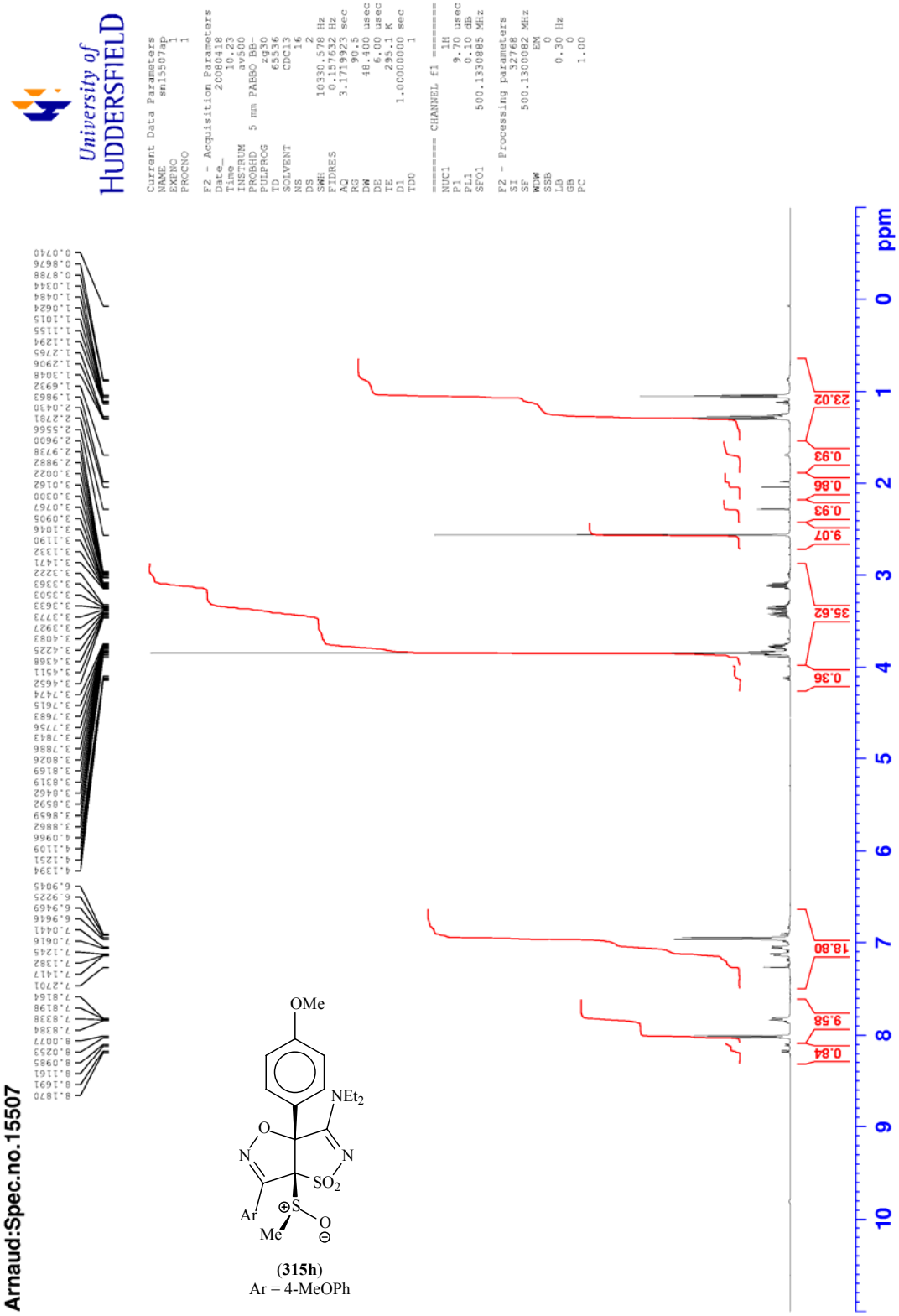
HMBC


ppm
0
20
40
60
80
100
120
140
160
180
200
0 ppm
1
2
3
4
5
6
7
8
9
10
11

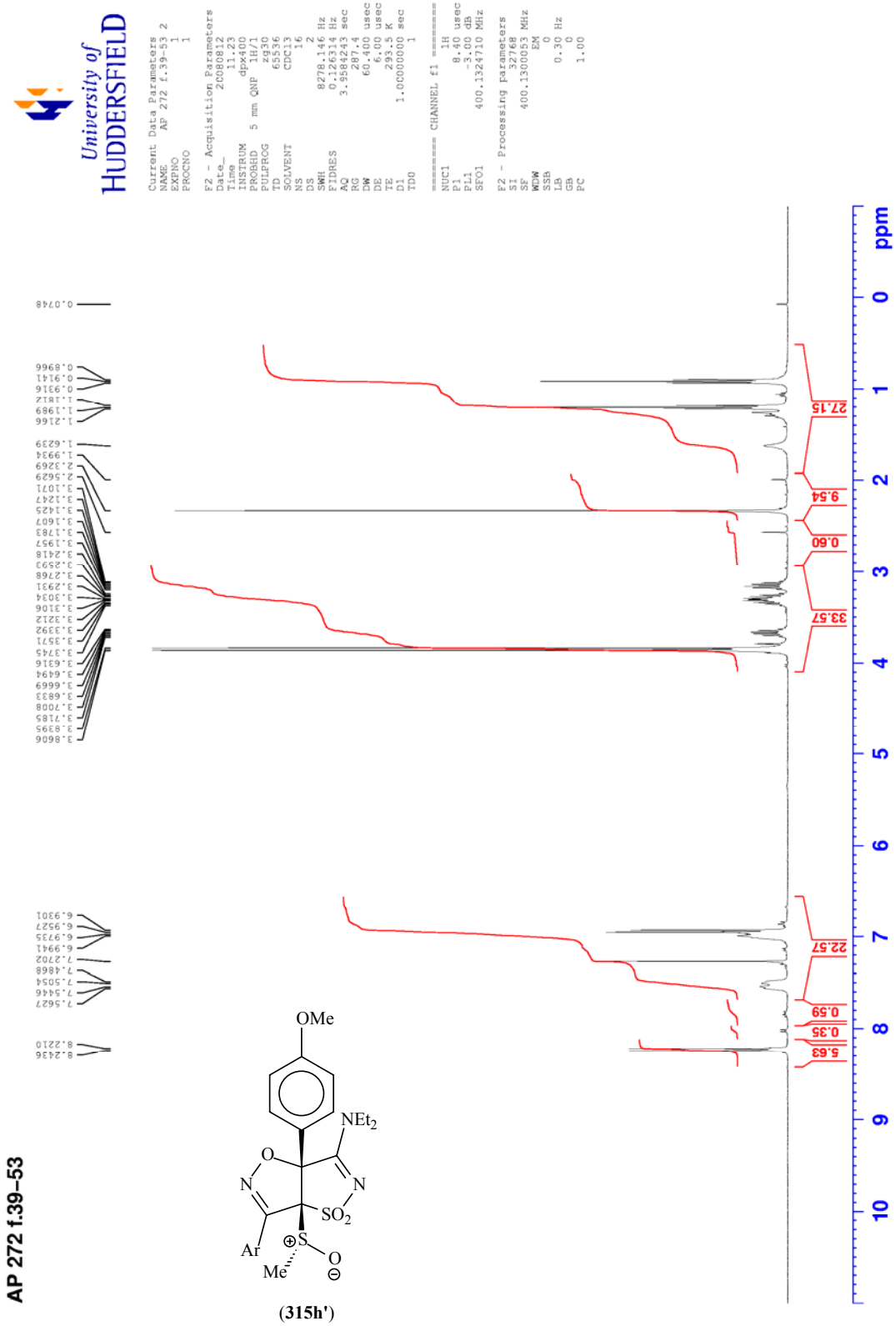

OMe
NEt2
O2N
(31Sd)


University of
HUDDERSFIELD
Arnaud:Spec.no.15479
Current Data Parameters
NAME sn15479ap
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060313
Time 22.34
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 144
DW 48.400 usec
DE 6.00 usec
TE 295.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.70 usec
PL1 0.10 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300079 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.0807
0.8882
1.0174
1.0314
1.0454
1.2512
1.2651
1.2794
1.6135
3.1144
3.1284
3.1426
3.1569
3.1711
3.1850
3.3278
3.3418
3.3557
3.3689
3.3825
3.3964
3.4106
3.4249
3.4389
3.7369
3.7510
3.7651
3.7782
3.7922
3.8064
3.8457
3.8520
5.3045
6.9185
6.9362
7.0016
7.2704
7.2713
7.5754
7.9819
7.9993
0.91
42.11
30.43
1.08
25.47
ppm
0
1
2
3
4
5
6
7
8
9
10
OMe
NEt2
Cl
MeO
(315)

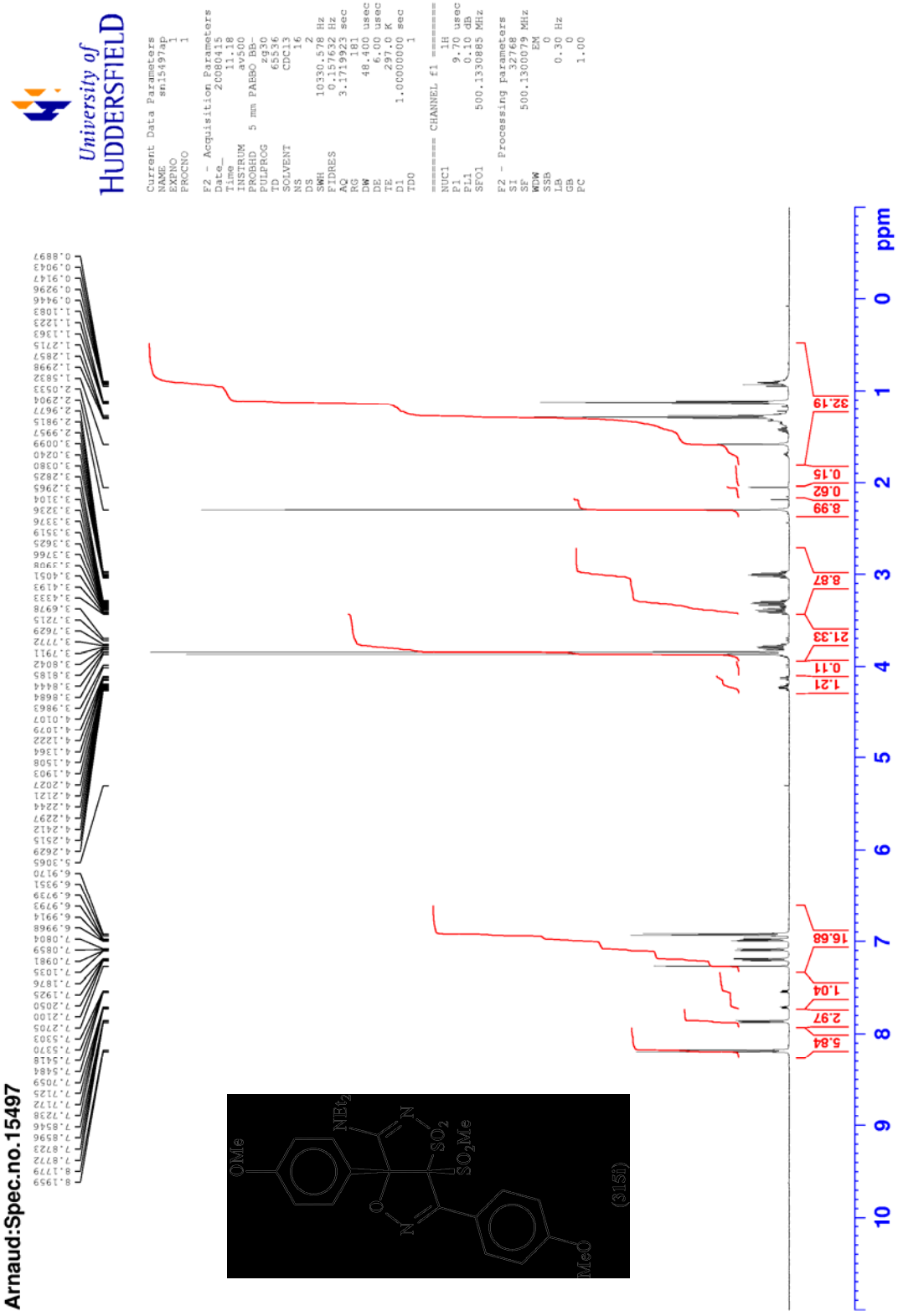

University of HUDDERSFIELD
Arnaud:Spec.no.15449/AP254 f8–19
Current Data Parameters
NAME sn15449ap
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080226
Time 9.38
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 80.6
DW 48.400 usec
DE 6.00 usec
TE 295.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.70 usec
PL1 0.10 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300082 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
39.52
32.42
2.38
25.68
ppm
OMe
NEt2
Br
MeO
(315g)



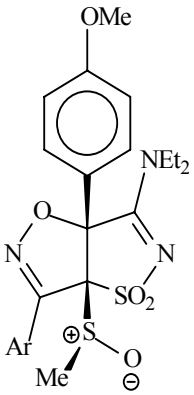
(**315h**)
Ar = 4-MeOPh



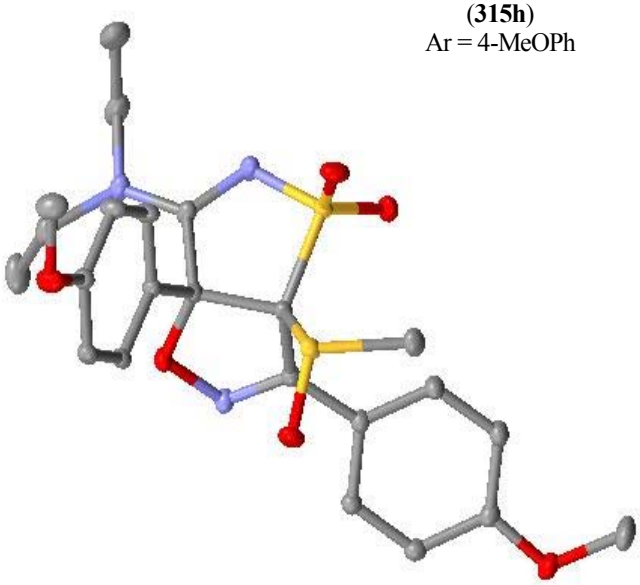
(315h')
Ar = 4-MeOPh


Arnaud:Spec.no.15497
University of HUDDERSFIELD
Current Data Parameters
NAME sn15497ap
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20080415
Time 11.18
INSTRUM av500
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 181
DW 48.400 usec
DE 6.00 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.70 usec
PL1 0.10 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300079 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
32.19
0.15
0.62
8.99
8.87
21.33
0.11
1.21
16.68
1.04
2.97
5.84
ppm
OMe
NBz2
SO2
SO2Me
MeO
(315f)

Crystal structure of compound (**315h**):



(**315h**)
Ar = 4-MeOPh



Crystallographic Data						
	Compounds					
Data	**315a**	**315h**	**315h'**	**315i**	**318**	**319'**
Empirical formula	$C_{18}H_{23}N_3O_6S$	$C_{23}H_{27}N_3O_6S_2$	$C_{23}H_{27}N_3O_6S_2$	$C_{23}H_{27}N_3O_7S_2$	$C_{27}H_{28}N_4O_3S$	$C_{15}H_{21}N_5O_4S_2$
Molecular weight (g/mol)	409,45	505,60	505,60	521,60	488,59	399,48
Temperature (K)	120(2)	100(2)	100(2)	100(2)	120(2)	100(2)
Wavelength (Å)	0,71073	0,71073	0,71073	0,71073	0,71073	0,71073
Crystal system	Orthorhombic	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	Pbca	P-1	P2(1)/n	P-1	P2(1)/c	P2(1)/n
Unit cell dimensions						
a (Å)	12.9462(7)	8.9873(5)	11.789(1)	8.9413(4)	8.9260(8)	9.3651(3)
b (Å	14.7915(7)	11.0990(6)	14.752(2)	11.7201(5)	15.4665(7)	19.5330(6)
c (Å)	21.2167(8)	13.0584(7)	14.574(2)	13.5584(6)	17.789(1)	12.7944(4)
α (°)	90,00	70.595(1)	90,00	95.727(1)	90,00	90,00
β (°)	90,00	76.291(1)	113,86	94.027(1)	99.900(3)	109.830(1)
γ (°)	90,00	83.975(2)	90,00	105.992(1)	90,00	90,00
Volume (Å^3)	4062.9(3)	1193.1(1)	2318.0(6)	1351.9(1)	2419.3(3)	2201.6(1)
Z	8	2	4	4	4	4
Density (calculated) (mg/m^3)	1,339	1,491	1,42	1,352	1,341	1,272
Absorption coefficient (mm^{-1})	0,198	0,276	0,274	0,429	0,171	0,272
Crystal	cut block, colourless	cut block, colourless	cut block, colourless	cut block, colourless	cut block, colourless	cut block, colourless
θ range for data collection (°)	3.15-27.48	1.69-35.63	2.06-28.48	1.82-29.63	2.99-27.21	1.99-29.22
Index ranges	$-14 \le h \le 16$ $-19 \le k \le 19$ $-27 \le l \le 27$	$-14 \le h \le 14$ $-18 \le k \le 18$ $-21 \le l \le 21$	$-15 \le h \le 15$ $-19 \le k \le 18$ $-19 \le l \le 8$	$-12 \le h \le 12$ $-16 \le k \le 16$ $-18 \le l \le 12$	$-11 \le h \le 11$ $-19 \le k \le 18$ $-22 \le l \le 22$	$-12 \le h \le 12$ $-26 \le k \le 26$ $-17 \le l \le 17$
Reflections collected	26596	43008	15611	28474	31632	23543
Independent collections	4656 $R_{int} = 0.0769$	10964 $R_{int} = 0.0348$	4259 $R_{int} = 0.0702$	7503 $R_{int} = 0.0258$	5360 $R_{int} = 0.1765$	5953 $R_{int} = 0.0357$
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4656 / 0 / 258	10964 / 0 / 312	4259 / 0 / 312	7503 / 0 / 348	5360 / 0 /316	5953 / 0 / 281
Goodness-of-fit on F^2	1,054	1,013	0,760	1,028	1,010	0,970
Final R indices $[F^2 > 2\sigma(F^2)]$	$R1 = 0.0558$ $wR2 = 0.1281$	$R1 = 0.0379$ $wR2 = 0.1026$	$R1 = 0.0402$ $wR2 = 0.0822$	$R1 = 0.0307$ $wR2 = 0.0793$	$R1 = 0.0749$ $wR2 = 0.1418$	$R1 = 0.0321$ $wR2 = 0.0813$
R indices (all data)	$R1 = 0.0982$ $wR2 = 0.1467$	$R1 = 0.0502$ $wR2 = 0.1100$	$R1 = 0.0769$ $wR2 = 0.0916$	$R1 = 0.0358$ $wR2 = 0.0828$	$R1 = 0.1647$ $wR2 = 0.1743$	$R1 = 0.0432$ $wR2 = 0.0874$
Extinction coefficient	0.0017(5)	-	-	-	-	-
Largest diff. peak and hole (e/Å^3)	0.755 and -0.363	1.579 and -0.309	0.256 and -0.502	0.447 and -0.508	0.481 and -0.481	0.519 and -0.397