Towards Understanding the Synthesis and Reactivity of Alkynyl Sulfonamides

A dissertation presented by

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Declaration

I, Yi Luo, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that it has been indicated and acknowledged.

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Acknowledgements

Firstly, I would like to thank my supervisor Dr. Jon Wilden, and my sponsor, the Leverhulme Trust for their support, as this project would not have been possible without their kindness. I'd also like to thank the other members of the Wilden lab, both past and present, for helping me get through thick and thin and for entertaining me in times of catastrophe - Vincent, James, Roomi, Peter, Tom, Alex, Mark, and Theo. Klaudia, you are my kindred spirit and I thank you from the bottom of my heart for all of our conversations and for the emotional strength that you have given me towards the end of my research. Shaun and Elliott, I am eternally grateful for everything you have taught me so thank you both for keeping me grounded, for being excellent mentors, and for humouring me on our respective lunchtime and bar pool forays. In the words of Mae West, *"You only live once, but if you do it right, once is enough."* Whilst I certainly cannot say that I have done this PhD "right", I am glad that all of you have been here for me on this journey.

A special thank you goes to Dr. Abil Aliev for his help with interpreting NMR spectra, to Kersti, Xiaoping and Vincent again for providing me with an efficient mass spectrometry service, and to Niccolo for collaborating to test my compounds on his cell cultures. Their assistance has been invaluable for this research.

Finally, to my family, especially my dear mother and father, my brother and my grandparents, and to my friends outside of academia - I would not be who I am today without you to lift me up, so thank you all for believing in me.

Abstract

This thesis discusses the importance of the sulfonamide motif both in medicinal chemistry and as a synthetic tool. Particular focus is given to the alkynyl sulfonamide, a useful alkyne that first attracted the attention of this research group when it was shown to possess potential in the synthesis of ynol ethers. As the reactivity of alkynyl sulfonamides is relatively unexplored, there is interest in expanding the knowledge base of reactions that the alkynyl sulfonamide can undergo with medical applications in mind.

With that being the case, this project has explored routes towards a one pot synthesis of alkynyl sulfonamides, which, whilst successful, proved to be largely unscalable. However, this led to the development of other analogues that demonstrated similar reactivity to alkynyl sulfonamides in addition-elimination reactions to form ynol ethers.

Secondly, a range of novel "drug-like" 2,3-dihydroisoxazoles was developed by reacting alkynyl sulfonamides with nitrones in a 1,3-dipolar cycloaddition reaction. The reactions are rapid and lead to the formation of one regioisomer in good yields, with several of these compounds exhibiting promising biological activity *in vitro*. Novel 4,5-dihydroisoxazoles were also synthesized by reacting alkenyl sulfonamides with nitrile oxides in a 1,3-dipolar cycloaddition to form one regioisomer in good yields.

Lastly, a small range of novel isoxazoles was synthesized through two routes: a 1,3-dipolar cycloaddition between alkynyl sulfonamides and nitrile oxides; and a 1,3-dipolar cycloaddition between alkenyl sulfonamides and nitrile oxides, followed by elimination of the sulfonamide.

Contents

List of Figures

List of Tables

Abbreviations

a	*antarafacial*
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
an.	Anhydrous
Ar	Aryl
ATG	Autophagy related gene
ax.	Axial
Bn	Benzyl
Bu	Butyl
$CDCl_3$	Deuterated chloroform
CI	Chemical Ionization
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane-bis(sulfur dioxide)
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
dppp	1,3-Bis(diphenylphosphino)propane
DHFS	Dihydrofolate synthase
DHPS	Dihydropteroate synthase
DMA	Dimethylamine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dNGLUC	Gaussia luciferase with deleted N-terminus
EDG	Electron donating group

EI	Electron Ionization
EPR	Electron paramagnetic resonance
eq	Equivalent(s)
eq.	Equatorial
ESI	Electrospray Ionization
Et_2O	Diethyl ether
Et	Ethyl
et al.	*et alia*
EWG	Electron withdrawing group
G	Group
HOMO	Highest occupied molecular orbital
HMG-CoA	(3-hydroxy-3-methyl-glutaryl-coenzyme A
HRMS	High resolution mass spectrometry
HSC	Heat shock cognate
i	*iso*
IR	Infrared
LC	Light chain
LC-MS	Liquid chromatography–mass spectrometry
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
min	Minutes
m.p.	Melting point
Me	Methyl
Ms	Mesyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	Nuclear Magnetic Resonance
o	*ortho*
p	*para*
PABA	*p*-aminobenzoic acid
PG	Protecting Group

Ph	Phenyl
Pr	Propyl
RT	Room temperature
s	*suprafacial*
SET	Single electron transfer
t	Tertiary
tert	Tertiary
Tf	Triflate
TLC	Thin layer chromatography

Chapter 1

Introduction

1.1 The Sulfonamide Functional Group

1.1.1 Importance in Medicinal Chemistry

Discovery

The sulfonamide group (Figure 1.1) consists of a sulfonyl group connected to an amine group, with the general formula $R^1SO_2NR^2R^3$. Historically, sulfonamides are particularly important compounds in medicinal chemistry, as they were the first effective antimicrobial agents to be discovered,[1] and not only do they still show potential for future drug development,[2;3] they also still form the largest class of antimicrobial drugs to this day.

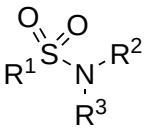

Figure 1.1: The sulfonamide functional group.

Prior to the 1930s, effective antimicrobial drugs were few and far between. The main problem with the compounds in development was that whilst potent *in vitro*, they lost significant activity *in vivo*.[1] As such, the search for an effective antimicro-

bial drug was of utmost importance in order to mitigate the mortality count due to bacterial infections. After years of screening hundreds of compounds with no success, the breakthrough finally came when several dyes prepared by the Bayer laboratories were screened by Domagk.[4;5] Those dyes contained the sulfonamide motif, which was known to bind to wool fibres, and as the fibres were composed of protein, it was thought that perhaps the sulfonamide group would also bind to bacterial proteins.[1]

As shown in Figure 1.2, the red dye **1**, first prepared by Bayer scientists Klarer and Mietzsch,[6] was screened in 1932 and turned out to show remarkable activity against *streptococcal* and *staphylococcal* infections in mice.[1] At the time, this compound was known as Sulfonamidochrysoidine. Since Sulfonamidochrysoidine elicited such positive results from animal testing, it was renamed to Prontosil and introduced into clinical medicine as the first known antibacterial drug.

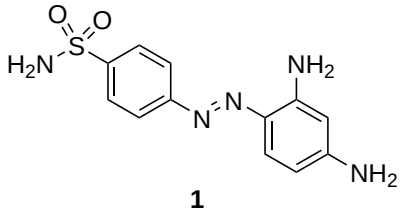

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Figure 1.2: The structure of Sulfonamidochrysoidine (Prontosil).

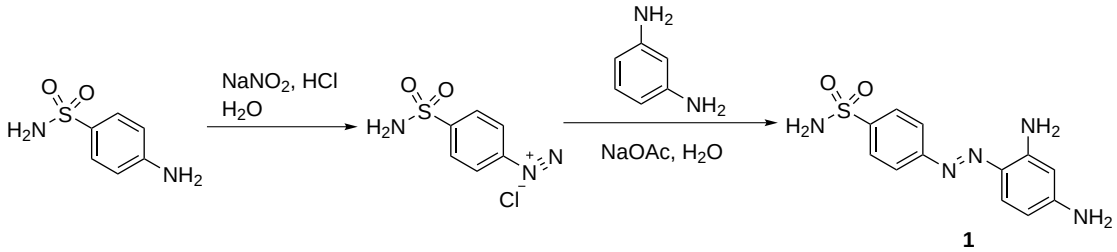

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Figure 1.3: The synthesis scheme for Prontosil by Klarer and Mietzsch.

Further experiments revealed that Prontosil was only active *in vivo* and that it had no effect on bacterial growth *in vitro*. Modifications on the diaminobenzene ring had no significant effect on antibacterial activity, however, urine analysis of patients that ingested the drug showed that the azo linkage had been reductively

cleaved to yield structure **2**, known as *p*-aminobenzenesulfonamide (Figure 1.4). The puzzle had now been solved, and in late 1935, Tréfouël *et al.*[7] at the Pasteur Institute published their result: that the active antimicrobial agent comes from the metabolism of Prontosil into *p*-aminobenzenesulfonamide.

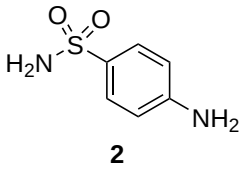

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Figure 1.4: The structure of *p*-aminobenzenesulfonamide, also known as sulfanilamide, turned out to be the active antibacterial agent in the end.

This discovery resulted in an explosion of interest in the development of new sulfonamide compounds (select examples are shown in Figure 1.5) for use in medicine. The first structural analogue of sulfanilamide was prepared shortly after in 1937. Known as sulfapyridine, compound **3** was found to be an extremely effective treatment for pneumonia.[8] Many more structures have since been developed from sulfanilamide that have led to hypoglycemic agents, diuretics, and antihypertensive drugs for example,[9;10] and interest in the sulfonamide group remains to this day.

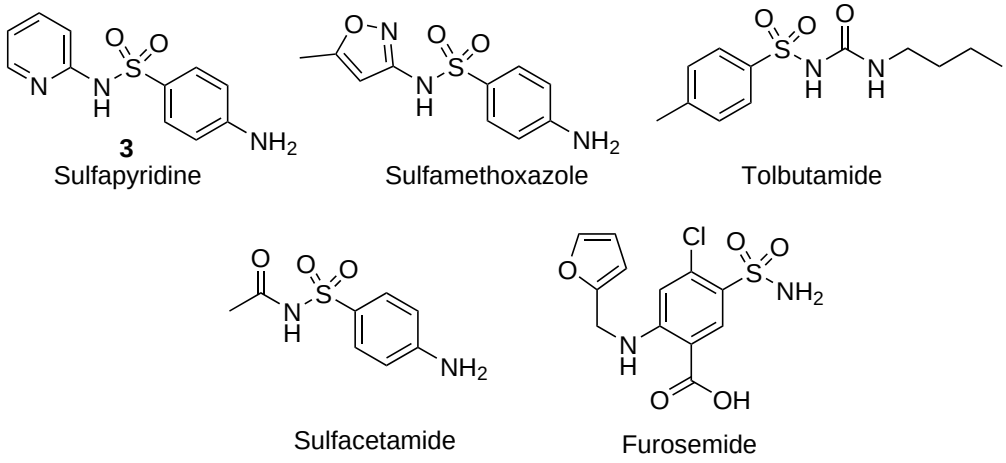
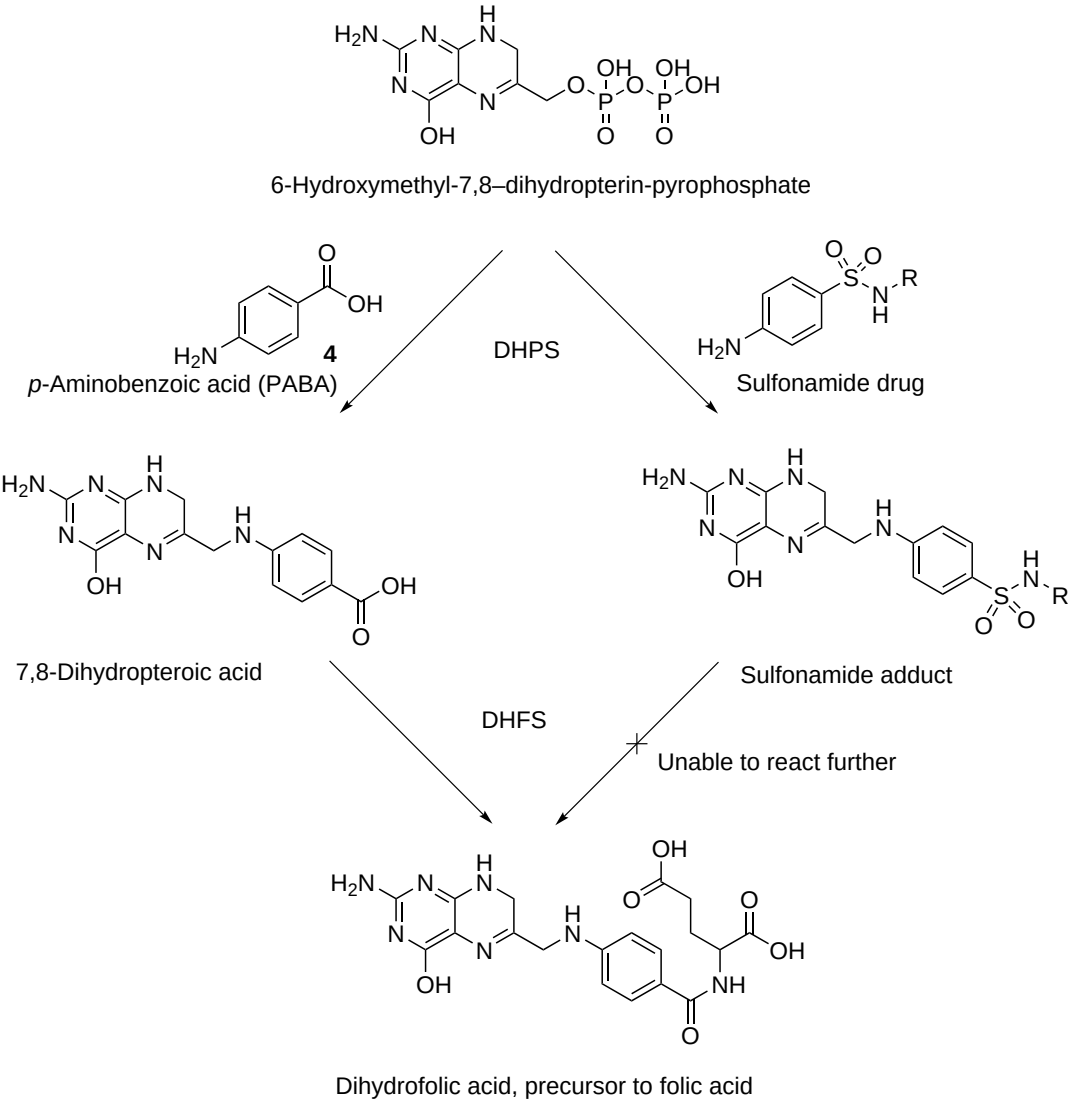


Figure 1.5: Select examples of sulfa drugs that have been developed from sulfanilamide.

Mode of Action

Sulfonamide drugs prevent the conversion of compound **4**, *p*-aminobenzoic acid (PABA), to folate (Scheme 1.1), an essential vitamin required for cell growth.[11] They do this through competitive inhibition, by acting as a transition state analogue to the carboxyl group of PABA when binding to the bacterial enzyme dihydropteroate synthase (DHPS).



Scheme 1.1: The sulfonamide drug interrupts the folate pathway in bacterial metabolic systems.[1]

As such, this prevents all of the biosynthetic pathways that require this vitamin from functioning, ensuring that the bacterial cells stop growing and dividing. This allows the body's immune system to destroy the cells. As the sulfonamides don't

kill the bacterial cells, they are known as bacteriostatic agents. However, in large doses, they can also act as bactericidal compounds. Mammals are safe from the DHPS inhibitory effects of sulfonamide drugs as they are unable to synthesize folate themselves, so must obtain the vitamin from their diets.[1]

Recently, White *et al.* used structural and computational methods to show the mechanism of folate synthesis, which has shed light on how bacterial resistance to sulfonamide drugs arises.[12] It was known that two flexible loops in DHPS hold PABA in place whilst the enzyme catalysed condensation reaction occurs.[13–15] When the sulfonamide compounds were bound to DHPS, White's research shows that part of the molecule "sticks out" of the binding pocket; mutations that occur along the loops near this section impede sulfa drug binding which enables bacteria to develop their resistance.

1.1.2 Chemical Properties

Whilst a survey of the literature reveals that the sulfonamide functional group is mainly synthesized and investigated for its medicinal properties, the group has several interesting reactive properties that have also been investigated by organic chemists. The sulfonamide motif is of particular interest to the Wilden research group, and an extensive review of the chemical reactivity of sulfonamides has already been published by Wilden.[16] This section will offer a brief summary of the more interesting properties exhibited by this motif.

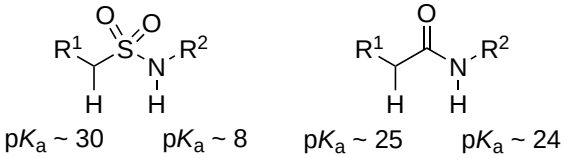


Figure 1.6: The approximate pK_a values of the protons associated with the sulfonamide functional group in contrast to a typical carboxamide.

As can be seen in Figure 1.6, when R^1 = H or an alkyl group, the pK_a of the sulfonamide α proton is approximately 30[16] in contrast to the carbonyl analogue of 25,[17] meaning that it is more difficult to deprotonate α to the sulfonamide than to the carbonyl of amides. This is possibly because the sulfonyl group is less able to stabilise a negative charge than the carbonyl group, which could be due to the difference in energy between the atomic orbitals of the carbon and sulfur atoms, which would result in poorer orbital overlap.

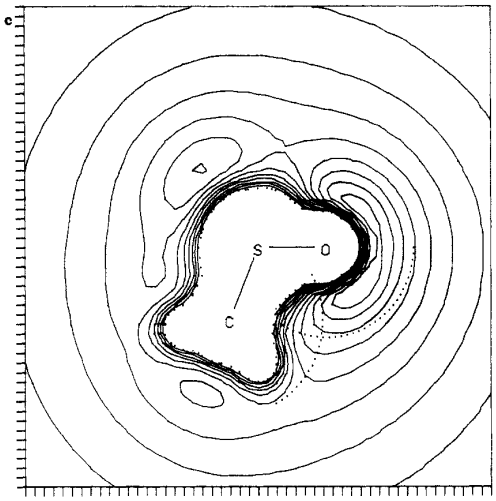


Figure 1.7: Bors and Streitwieser's electrostatic potential contour map of the dimethyl sulfone carbanion for the CSO plane. The dotted lines show normal O-Li and C-Li distances, and the intersection indicates the most stable arrangement for this system.[18]

Bors and Streitwieser's computational model of a lithiated methylsulfonylmethyl anion in Figure 1.7 shows that the most stable configuration is where the lithium cation bridges the carbanion and one of the two oxygen atoms.[18] In comparison, for lithium enolates, several crystal structures show that the lithium cation associates solely with the oxygen anion.[19;20] This suggests that the site of highest electron density on the α deprotonated carbonyl resides fully on the oxygen atom, supporting the case for the carbonyl group being better placed to stabilise a negative charge.

Figure 1.6 also indicates that the pK_a of the N-H bond in sulfonamides is approximately 8.[16] This is significantly lower than the pK_a of the N-H bond in amides, which is approximately 24.[21;22] Roush *et al.* suggests that the lower pK_a of the N-H bond in sulfonamides means that the sulfonamide is often in equilibrium with the deprotonated analogue.[23] This would result in the sulfonamide becoming the least electron withdrawing group in a set of Michael acceptor reactions (Figure 1.8) that compare sulfonamides, sulfones, sulfonate esters and carbonyls. The relative rates for these reactions can be seen in Table 1.1. This equilibrium also explains why the sulfonamide group is somewhat resistant to hydrolysis as approaching nucleophiles are repelled by the high electron density when the sulfonamide is in the deprotonated form.

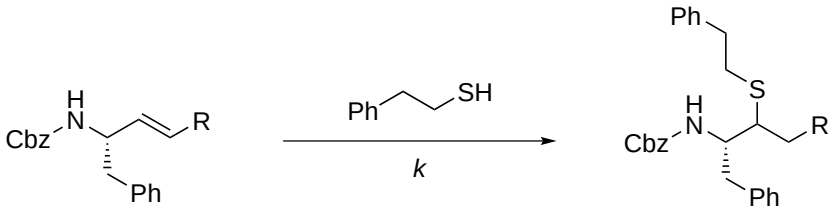


Figure 1.8: Roush's Michael reaction.[23]

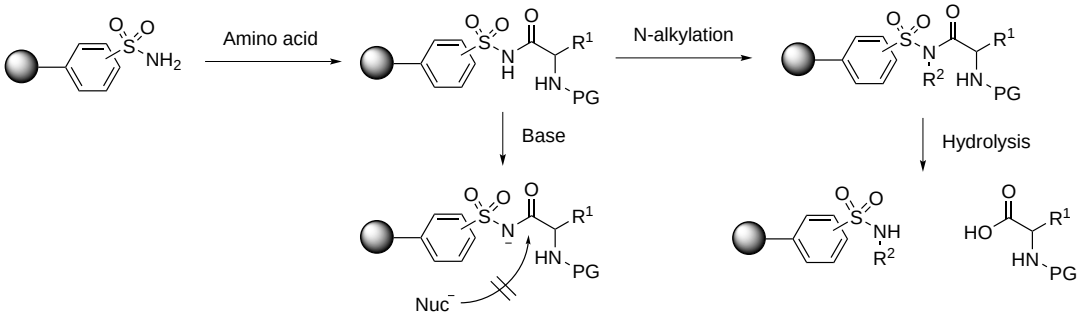
Table 1.1: Relative rates of 1,4-additions to alkenes with various electron withdrawing groups.[16;23]

R	Relative Rate, (k)
SO_3Ph	3000
COMe	2700
$SO_2N(Me)OBn$	150
SO_2Ph	120
SO_3Et	90
SO_2NHOBn	50
CO_2Me	17
$SO_2N(Me)Bn$	3
SO_2NHBn	1

1.1.3 Use in Organic Chemistry

Safety Catch Linker

The sulfonamide group's resistance to hydrolysis has found use in solid phase peptide synthesis as a "safety catch linker", as first demonstrated by Kenner *et al.* in 1971 and summarised in Scheme 1.2.[24] Attached to a solid support, the primary sulfonamide unit acts as a stable platform from which chains of amino acids can be built and purified. This is due to the high acidity of the N-H hydrogen, which ensures that the sulfonamide is deprotonated under mild basic conditions, thus deterring nucleophiles from attacking the unit. In order to remove the sulfonamide unit, the sulfonamide is alkylated at the nitrogen, removing the resistance to hydrolysis, which then allows nucleophiles to attack the adjacent carbonyl.



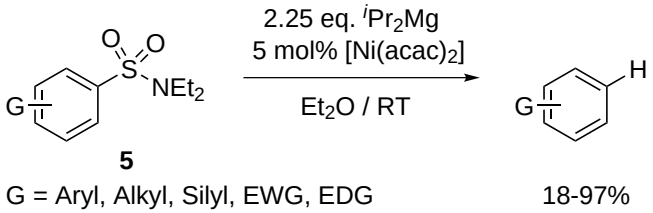
Scheme 1.2: The sulfonamide as a linker in solid phase peptide synthesis[16;25].

Since then, methods have been developed to improve the original procedure,[26–29] which had several disadvantages such as poor loading efficiency and low reactivity as a linker.[25] The improvements have expanded the applicability of Kenner's linker, notably in solid phase organic synthesis for carbon-carbon bond forming reactions to generate large molecules.[26] For more examples, see the extensive review of the sulfonamide linker by Heidler and Link.[25]

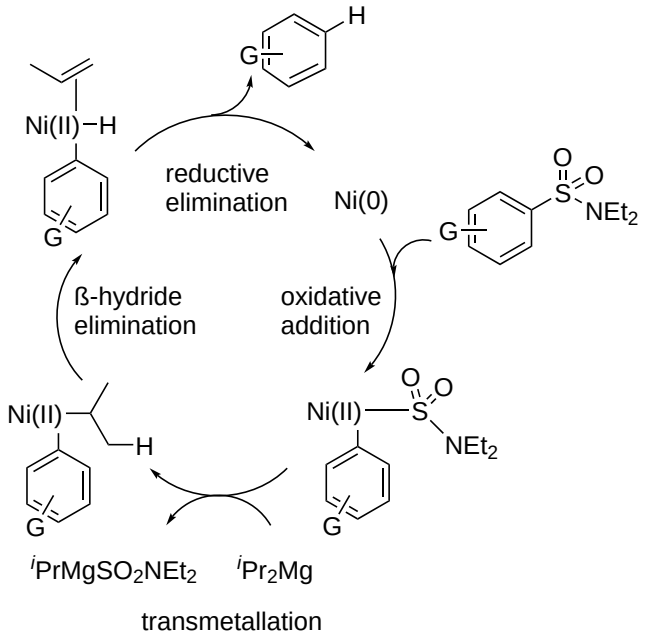
Transformations

The sulfonamide group can undergo several transformations. In 2004, Milburn and Snieckus[30] showed that tertiary aryl sulfonamide **5** can be reduced with $i\text{Pr}_2\text{Mg}$ or iPrMgCl in the presence of a nickel catalyst at room temperature (Scheme 1.3).

It was found that the reaction is sensitive to steric and electronic effects, with large *ortho* substituents and *para* electron donating components giving lower yields, whilst *ortho* groups that were capable of metal co-ordination gave significantly higher yields.



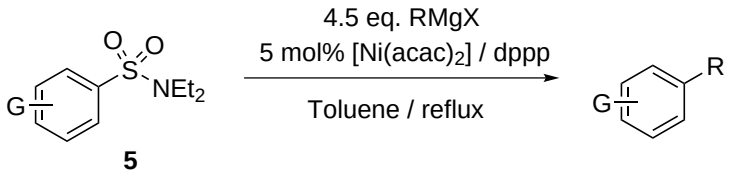
Scheme 1.3: The hydrodesulfamoylation of aryl sulfonamides, catalysed by nickel.[30]



Scheme 1.4: The proposed mechanism for the hydrodesulfamoylation reaction.[30]

Following on from this, they discovered that tertiary aryl sulfonamide **5** can also be cross-coupled with Grignard reagents (Scheme 1.5) in a new carbon-carbon bond forming reaction that is catalysed by Ni(0). The mechanism is presumably similar

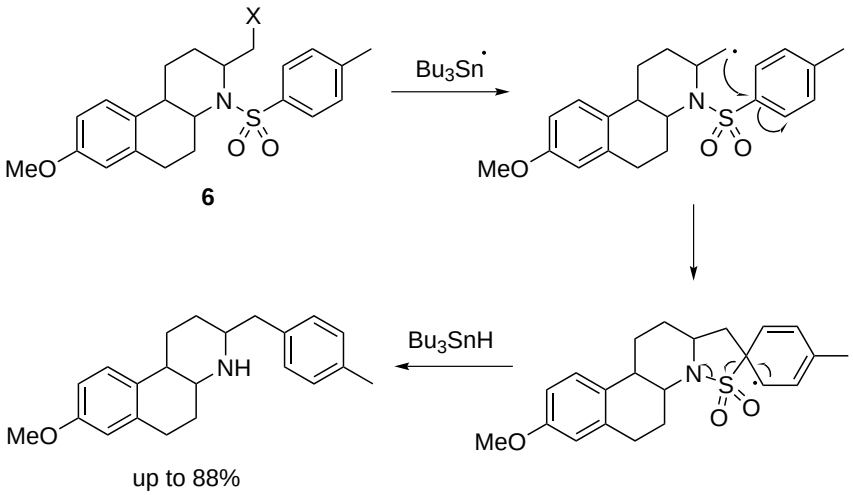
to that in Scheme 1.4, only without the β-hydride elimination step. Whilst Grignard reagents are not known for being mild, this reaction is still useful as it expands the repertoire of currently known methods for cross-coupling reactions.



Scheme 1.5: The cross coupling of aryl sulfonamides, catalysed by nickel.[30]

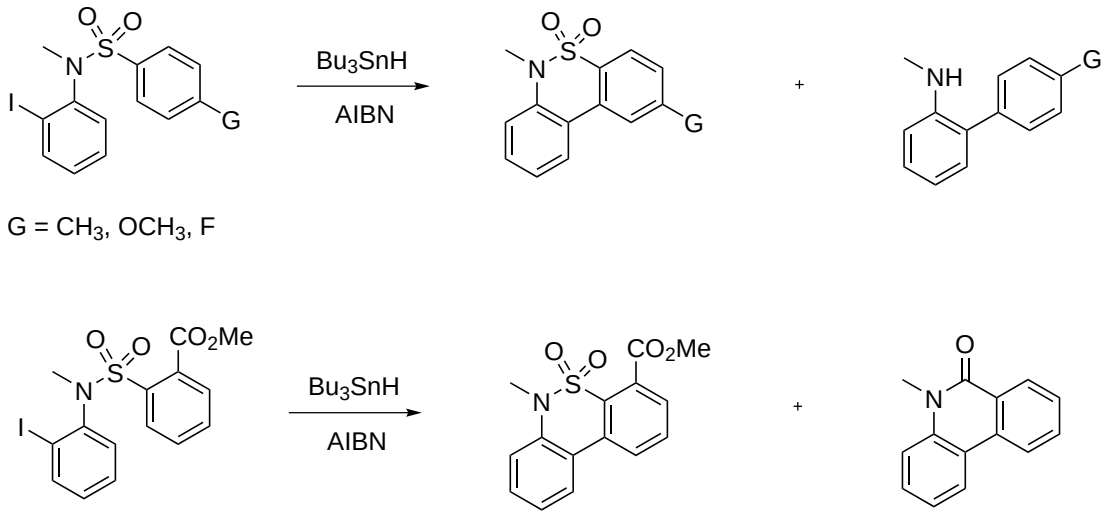
Leaving Group

Another interesting property of the sulfonamide functional group is its propensity to act as a leaving group, with the elimination of SO_2. This was first reported by Loven and Speckamp when, during a synthesis of complex heterocycles,[31] they observed a migration of the aryl group connected to the sulfonamide unit in compound **6**, with the loss of SO_2. Since the reaction mixture contained tributyltin hydride, this was deduced to be a radical process, with the proposed mechanism illustrated in Scheme 1.6.



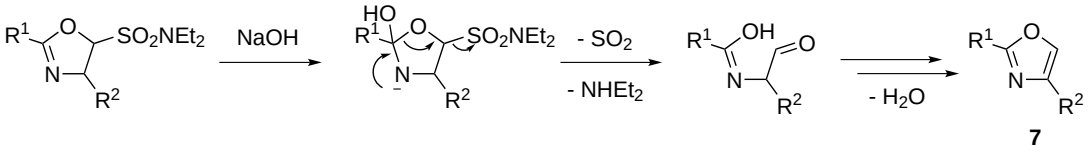
Scheme 1.6: The mechanism illustrating *ipso* attack of the primary radical onto the aromatic ring. This is followed by decomposition of SO_2.[31]

This pathway was also utilised in the work of Pennell and Motherwell when they prepared a series of biaryl and tricyclic compounds in 1991, as shown in Scheme 1.7.[32] They found that there is a competing reaction alongside *ipso* attack: the direct addition of the radical to the aromatic ring.



Scheme 1.7: Examples of Loven and Speckamp's mechanism used in Pennell and Motherwell's work.[32]

The Wilden research group is particularly interested in the chemistry of sulfonamides, and as such, previous work has made use of the sulfonamide's leaving group ability in the development of a novel synthesis of 2,4-substituted oxazole **7**.[33] It was found that the elimination of the group proceeds under basic conditions, implying that the mechanism is ionic rather than radical (Scheme 1.8).



Scheme 1.8: Chudasama and Wilden's synthesis of 2,4-substituted oxazoles.[33]

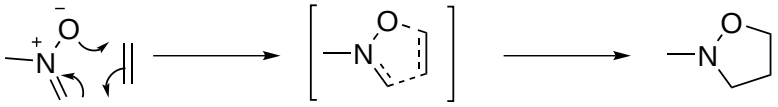
More recently, the Wilden group has developed a novel method for the synthesis of ynol ethers from alkynyl sulfonamides, which also involves the displacement of the sulfonamide unit.[34]

1.2 The 1,3-Dipolar Cycloaddition

Since a key component of this project will focus upon 1,3-dipolar cycloadditions, a brief introduction to cycloadditions will be covered, followed by considerations into orbital theory to explain the underlying mechanisms for these types of reactions.

1.2.1 Introduction

A cycloaddition is an example of a pericyclic reaction, in which two or more unsaturated bonds originating from separate molecules (or different parts of the same molecule) come together to form a cyclic product without any loss of atoms or intermediates formed.[35] Each reaction proceeds through one transition state, with bond breaking and bond forming happening (usually, but not always) simultaneously to create the product. The naming convention for these reactions refers to the number of atoms in each component that is involved in the reaction e.g. the Diels-Alder is a [4+2] cycloaddition because the cycloaddition involves four atoms in the diene, and two atoms of the dienophile.



Scheme 1.9: The 1,3-dipolar cycloaddition reaction between a nitrone and an alkene.

The 1,3-dipolar cycloaddition is a thermal, concerted, suprafacial [3+2] reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring. As can be seen in Scheme 1.9, two new σ bonds are formed, and two π bonds are lost to create the product. As σ bonds are stronger than π bonds, the reaction is thermodynamically favoured. This reaction is also driven by the loss of formal charges in the 1,3-dipole to the electronically neutral product.

Examples of this type of reaction have been known since the late 19th century, but it was the work of Huisgen in the 1960s that led to the popularisation of the 1,3-dipolar cycloaddition. His two reviews,[36;37] published in 1963, show his efforts to understand the mechanistic pathway of the reaction, which is still widely accepted today.

1.2.2 The Reactants

The 1,3-Dipole

The 1,3-dipole consists of a π-system of four electrons shared over three atoms as a zwitterion. In order to stabilize the 1,3-dipole, an available pair of electrons can be donated to the electron deficient centre, allowing the 1,3-dipole to exist in resonance forms. Favoured resonance forms can be obtained from computational calculations and are largely based on dipole moments or electronegativity considerations. Figure 1.9 shows that the 1,3-dipole can also be categorised as allyl-type or propargyl/allenyl-type, depending on the geometry of the central atom. Permutations of C, N and O give rise to 12 allyl-type and 6 propargyl/allenyl-type 1,3-dipoles.

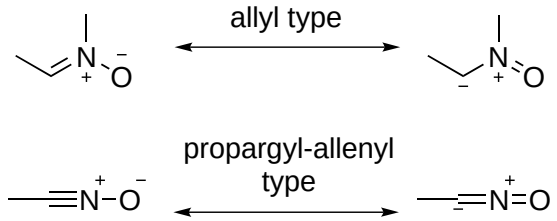
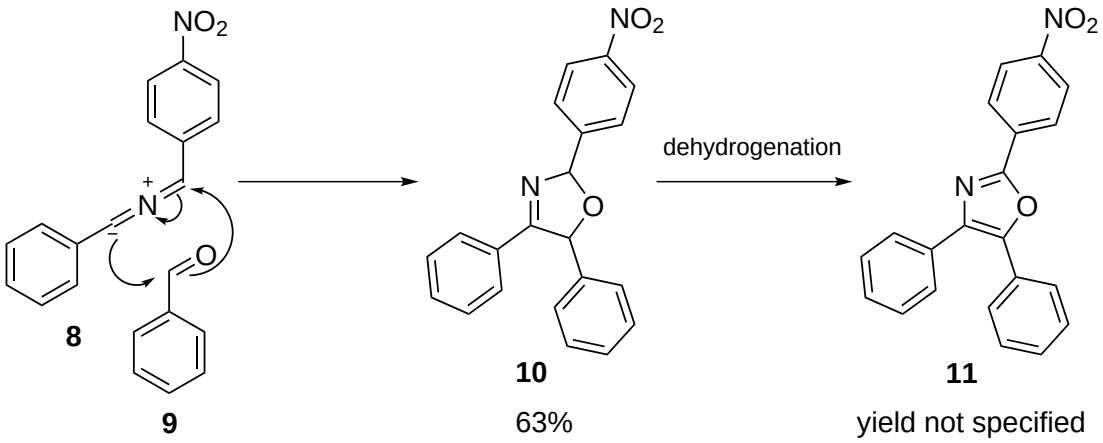


Figure 1.9: Examples of different classifications of 1,3-dipoles.

Examples of 1,3-dipoles include nitrones, nitrile ylides, nitrile imines, nitrile oxides, diazoalkanes, azides, ozone, vinyl carbenes, and vinylazenes, to name but a few. In this work, nitrones and nitrile oxides are the primary 1,3-dipoles used.

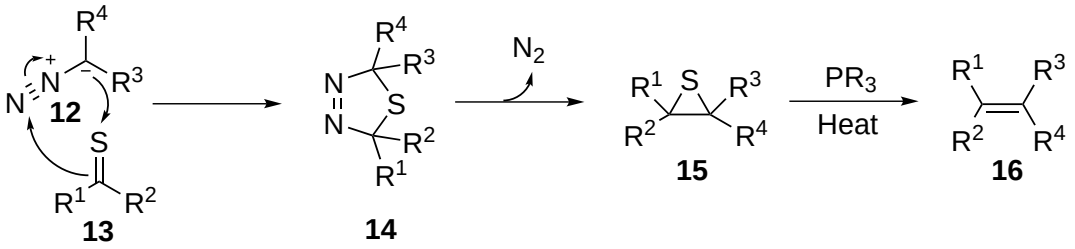
The Dipolarophile

The dipolarophile is a molecule that reacts with the 1,3-dipole and usually contains either a double or triple bond. The most common ones are alkenes and alkynes, but carbonyls, imines and thioketones have also been shown to undergo 1,3-dipolar cycloadditions. For example, benzaldehyde **9** reacts in a 1,3-dipolar cycloaddition with nitrile ylide **8** to give oxazoline **10** in 63% yield, which is then dehydrogenated to form oxazole **11**, as shown in Scheme 1.10.[38]



Scheme 1.10: Huisgen, Stangl, Sturm and Wagenhofer showed in 1962 that the carbonyl bond is able to act as a dipolarophile.

The Barton-Kellog olefination, named after Barton and Kellog who both independently reported this method,[39;40] shows another example of an unusual dipolarophile. The general characteristics of the 1,3-dipolar cycloaddition component of the reaction can be seen below in Scheme 1.11.



Scheme 1.11: The Barton-Kellog reaction is preferably used over the McMurry reaction to prepare asymmetric alkenes.

The first step of the reaction involves a 1,3-dipolar cycloaddition between diazo compound **12** and thioketone **13** to form thiadiazoline ring **14**. This intermediate is extremely unstable and quickly collapses into a thiocarbonyl ylide, which then cyclises into the episulfide, compound **15**. This three-membered ring is opened by a phosphorus nucleophile, following a Wittig-style mechanism to create **16**, the final product.

1.2.3 Mechanistic Considerations

Originally, two mechanisms (Figure 1.10) were proposed to explain 1,3-dipolar cycloadditions:

1) A concerted pericyclic process, proposed by Huisgen.[37]

2) A spin-paired diradical stepwise mechanism, proposed by Firestone.[41]

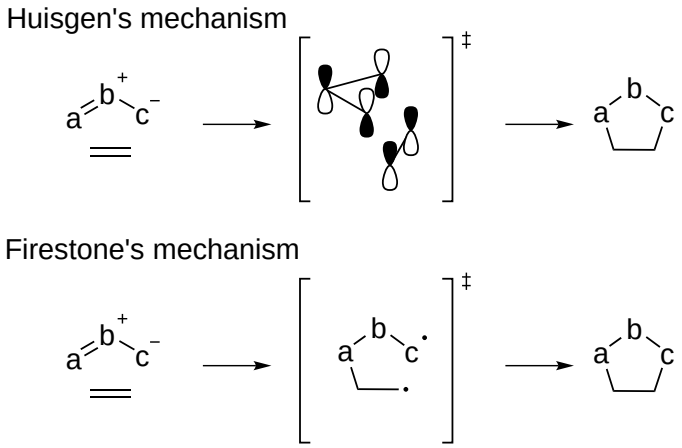


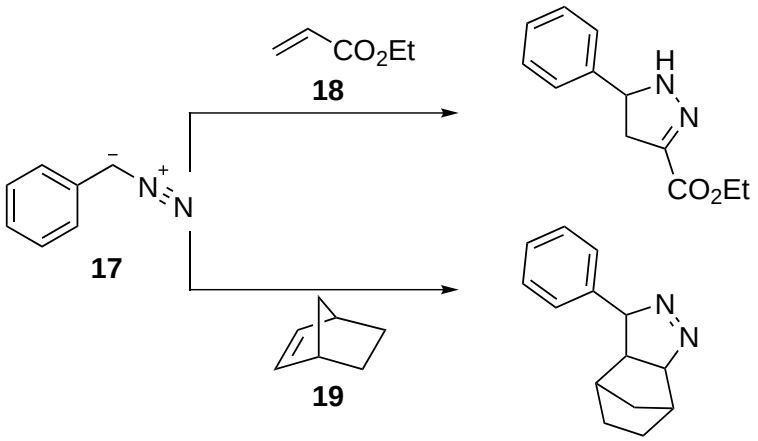
Figure 1.10: Comparison of proposed 1,3-dipolar cycloaddition mechanisms.

Huisgen considered the possibility of a stepwise mechanism, via a zwitterion intermediate, but discounted that during his experiments in favour of the concerted pericyclic process. His mechanism is widely accepted today, as his theory was the only one that could explain all of the observations below in a satisfactory manner.

Solvent Effects

Huisgen carried out a series of experiments on a diazoalkane 1,3-dipole with an alkene dipolarophile,[42] and found that varying the solvent had very little effect on the rate of reaction. If the intermediate was a zwitterion, then the product should be formed more readily in polar solvents, which was not the case. Huisgen acknowledged that if there was a single step mechanism, then there should be an inverse relation of rate to solvent polarity, based on the size of charge dispersal as the charged 1,3-dipole moves towards the neutral product. This was only very weakly observed, and explained by way of resonance between 1,3-dipoles as reducing the dipole moment. Firestone suggests that a diradical representation of the 1,3-dipole could also explain a small dipole moment, and that solvent effects would also be small for a diradical intermediate.[41]

Further kinetic experiments by Huisgen, Geittner and Reissig, conducted later in 1978,[43] showed that reaction rates between phenyl diazomethane **17** and ethyl acrylate **18**, and phenyl diazomethane **17** with norbornene **19** change only slightly upon varying solvents from cyclohexane to methanol. The reactions are illustrated in Scheme 1.12 and the results can be seen in Table 1.2.

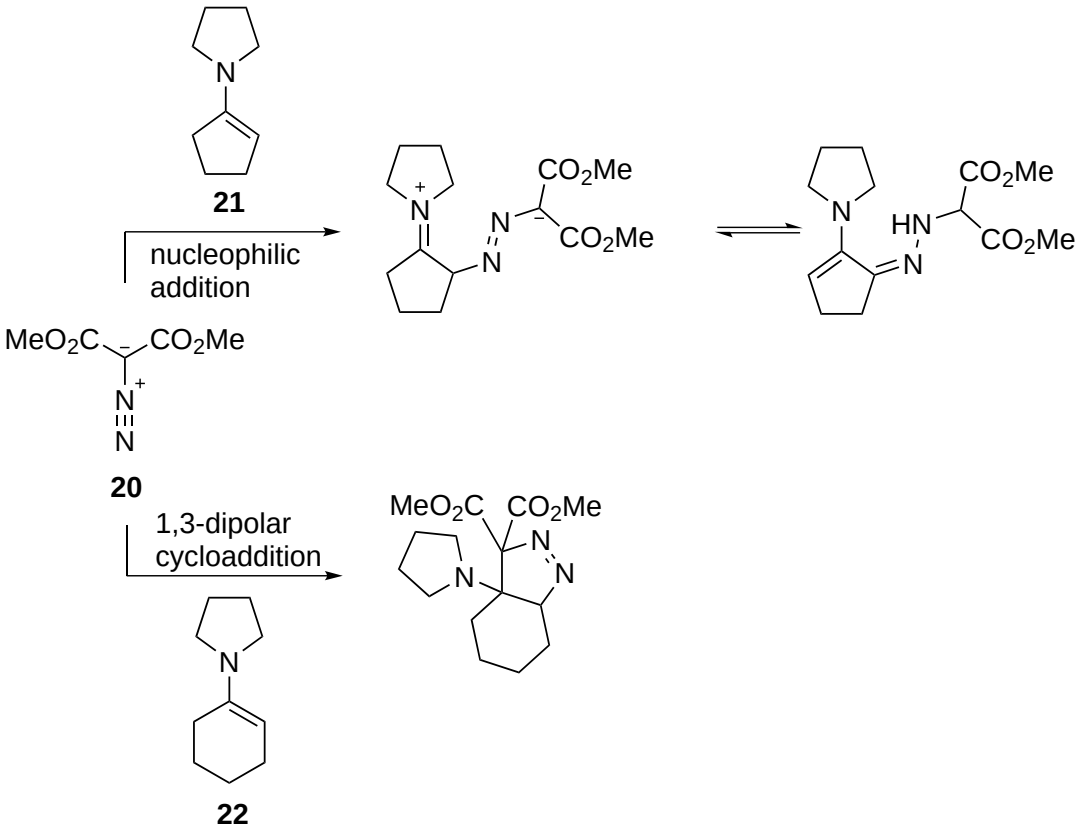


Scheme 1.12: Huisgen carried out reactions with phenyl diazomethane and ethyl acrylate, and phenyl diazomethane with norbornene in different solvents to compare reaction rates.

Table 1.2: Table of results for reaction rates between phenyl diazomethane and ethyl acrylate, and phenyl diazomethane with norbornene in different solvents.[43]

Solvent	Ethyl Acrylate (relative k_1)	Norbornene (relative k_2)
cyclohexane	1	1
dioxane	1.48	0.82
DMF	3.16	1.06
methanol	5.34	0.98

Finally, the lack of solvent effects for 1,3-dipolar cycloadditions was demonstrated elegantly by Huisgen[44] when reacting enamines with dimethyl diazomalonate **20** in Scheme 1.13. The reaction between *N*-cyclopentenyl pyrrolidine **21** and dimethyl diazomalonate **20** proceeds stepwise via a polar intermediate and is 1500 times faster in DMSO as opposed to decalin, whilst the cycloaddition between *N*-cyclohexenyl pyrrolidine **22** and dimethyl diazomalonate **20** only speeds up by 40 times when moving from decalin to DMSO.



Scheme 1.13: Comparing solvent effects when enamines are reacted with dimethyl diazomalonate **20** in different reaction pathways.[44]

Stereospecificity

Retention of configuration in the product for both the 1,3-dipole and dipolarophile was usually observed in experiments, which strongly suggests a concerted mechanism. Firestone acknowledged Huisgen's evidence but also suggests a fit for a two step mechanism if the activation for single-bond rotation in the intermediate is greater than that for either formation of the second bond or reversion to reactants.

Thermodynamic Parameters

Huisgen found that kinetic measurements showed a very high negative entropy of activation, consistent with concerted processes such as the Diels-Alder reaction.[37] This could be due to a highly ordered transition state, which is characteristic of a one step mechanism. Firestone postulated that for every successful collision, there are many where the first bond forms but the orientation is incorrect for the second bond, which would explain the low entropies of activation.[41]

1.2.4 The Woodward-Hoffman Rules

The Woodward-Hoffman rules state that the total number of $(4q+2)_s$ components and $(4r)_a$ components must be odd for a thermal pericyclic reaction, and even for a photochemical pericyclic reaction. The designations (4q+2) and (4r) refer to the number of electrons involved in each component, and *s* and *a* refer to the *suprafacial* and *antarafacial* components of the reaction.

The 1,3-dipole has four electrons in the π system that take part in the reaction, so it is labelled $\pi 4$. The dipolarophile utilises two electrons in a π bond, so it is designated $\pi 2$. From the diagram in Figure 1.11, it can be seen that the reaction takes place at the same side of each component, making both components *suprafacial*.

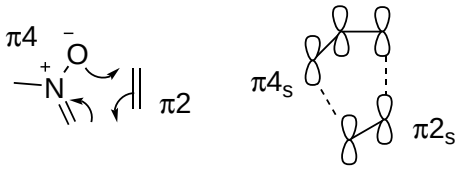


Figure 1.11: The Woodward-Hoffman rules applied to the 1,3-dipolar cycloaddition reaction.

It can be seen that there is one $(4q+2)_s$ component, and no $(4r)_a$ component. Since the sum of these is odd, this reaction is allowed by orbital symmetry.

1.2.5 Frontier Orbital Theory

Frontier orbital theory can be used to explain cycloadditions by considering the possible wavefunctions of each reacting component, where each wavefunction can be interpreted as a molecular orbital with a particular energy level that has the potential to hold two electrons. This approach was first described by Fukui[45] in 1952, when he realized that a good approximation for reactivity could be found by looking at the interactions between frontier orbitals.

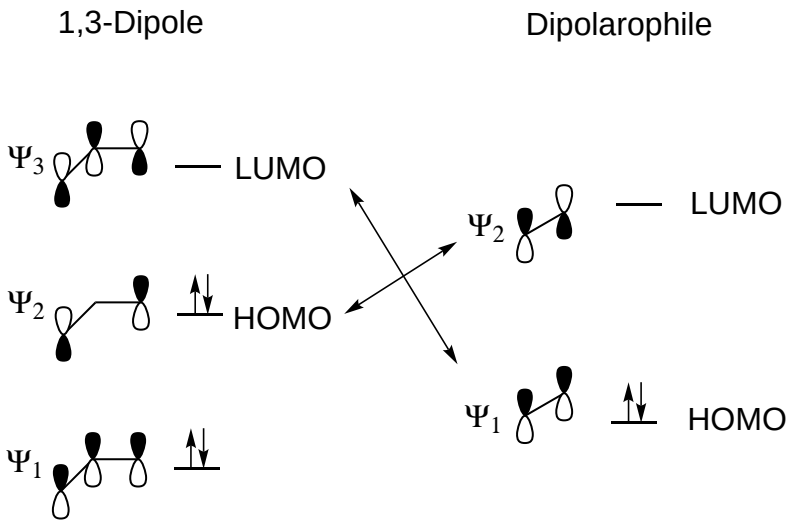


Figure 1.12: The frontier orbital approach towards rationalising the 1,3-dipolar cycloaddition reaction.

Figure 1.12 shows the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for both the 1,3-dipole and dipolarophile, calculated using frontier molecular orbital approaches. When the HOMO of one component and the LUMO of the other interact, one can see that the orbitals that will form the new bonds are in phase with each other, as can be seen in Figure 1.13. As these orbitals interact, the orientation of their interactions will control what the reaction's transition state looks like.

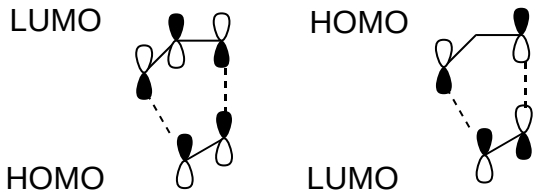


Figure 1.13: Alternative depictions of the interacting orbitals in the 1,3-dipolar cycloaddition reaction.

Issues not dealt with by Woodward-Hoffman rules, such as the influence of substituents on reaction rates and the problem of regioselectivity, can be explained by frontier orbital theory. Within this framework, Sustmann classified Diels-Alder and 1,3-dipolar cycloadditions into three types, based on the relative energies between the dipole and dipolarophile, which would determine the orbitals that interact

with each other.[46] This is summarised in Table 1.3 below and depicted visually in Figure 1.14.

Table 1.3: Classifications of 1,3-dipolar cycloadditions.[46]

Type	1,3-Dipole	Dipolarophile
I	HOMO	LUMO
II	both	both
III	LUMO	HOMO

The types are classed with respect to the dipole, but it must be noted that as it is the relative energies being considered, a traditional type I dipole can shift into another class if the substituent on the dipolarophile affects the energy levels enough.

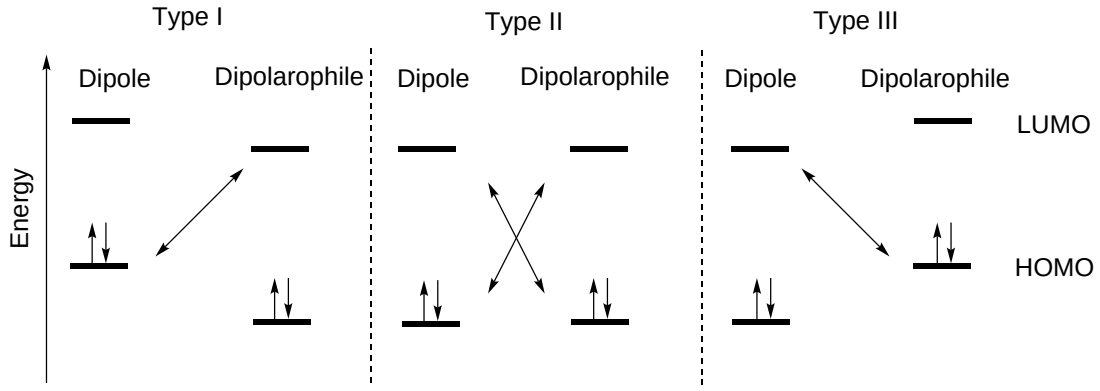


Figure 1.14: The three types of cycloaddition interactions classed by Sustmann.

Type I

In type I reactions, the dominant interaction is between the HOMO of the dipole and the LUMO of the dipolarophile. Closing the energy gap between the reactants will ensure greater stabilisation of the new HOMO in the product and therefore accelerate the rate of reaction. For type I reactions, adding an electron donating group to the 1,3-dipole will raise the HOMO and thus close the energy gap. Examples of 1,3-dipoles that fit into this more nucleophilic class are: azomethine ylides, carbonyl

ylides, nitrile ylides, azomethine imines, carbonyl imines and diazoalkanes. These dipoles are known as HOMO-controlled or nucleophilic dipoles.

Alternatively, adding an electron withdrawing group to the dipolarophile will lower the energy of the LUMO and achieve the same result.

The reaction[47] in Figure 1.15 shows how the addition of electron withdrawing substituents to a dipolarophile affects the rate of cyclisation with diazomethane **23**, which is an example of a HOMO-controlled dipole.

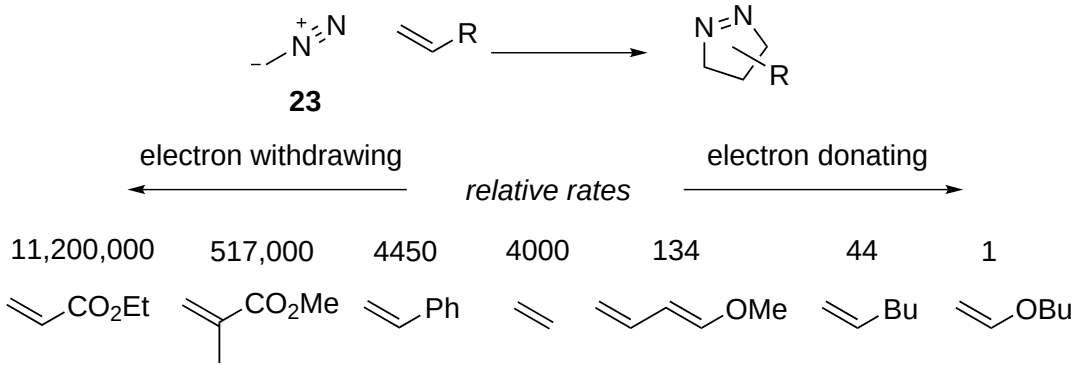


Figure 1.15: Varying the dipolarophile substituents changes the rates of the 1,3-dipolar cycloadditions with diazomethane in such a way as to be consistent with type I trends.[47]

Type II

For type II reactions, the HOMO-LUMO and LUMO-HOMO energy differences between the dipole and dipolarophile are similar enough that both pathways can be considered. Examples of 1,3-dipoles that fit into this class are: nitrile imides, nitrones, carbonyl oxides, nitrile oxides, and azides. These dipoles are known as HOMO-LUMO-controlled or ambiphilic dipoles.

For ambiphilic dipoles, the energy gaps between the HOMO of the dipole with the corresponding LUMO of the dipolarophile and vice versa are small enough such that both energy paths are favourable. This means that any substituent on the dipole would be capable of accelerating the reaction by decreasing the energy gap

for one pathway and increasing the energy gap for the other. For instance, an electron withdrawing group would lower the LUMO of the dipole, which would decrease the energy difference between the LUMO of the dipole and the HOMO of the dipolarophile. Conversely, an electron donating group would raise the HOMO of the dipole and thus decrease the energy difference between the HOMO of the dipole and the LUMO of the dipolarophile.[35] Likewise, the same arguments can be applied when changing substituents on the dipolarophile.

Figure 1.16 shows an example of a type II reaction where benzonitrile oxide **24** will undergo cyclisation with both electron rich and deficient alkenes.[48]

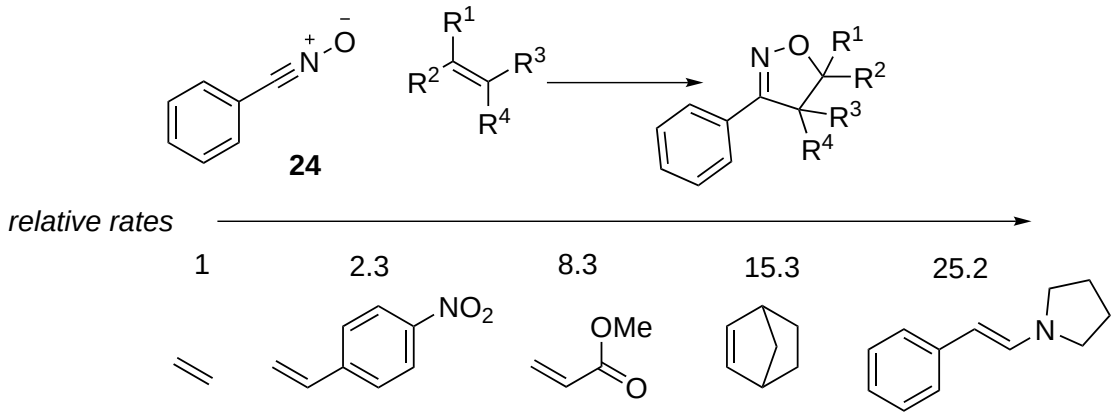


Figure 1.16: Benzonitrile oxide reacts with electron rich and deficient alkenes.[48]

Type III

In type III reactions, the dominant interaction is between the LUMO of the dipole and the HOMO of the dipolarophile. Closing the energy gap between the reactants will ensure greater stabilisation of the new HOMO in the product and therefore accelerate the rate of reaction. There are fewer examples of 1,3-dipoles that fit into this class but they include: nitrous oxide and ozone. These dipoles are known as LUMO-controlled or electrophilic dipoles.

Adding an electron donating group to the dipolarophile will raise the energy of the HOMO and close the energy gap between both reactants. This can be seen

in Figure 1.17 where the addition of electron donating substituents to alkene **25** increases the rate of cyclisation, albeit marginally.

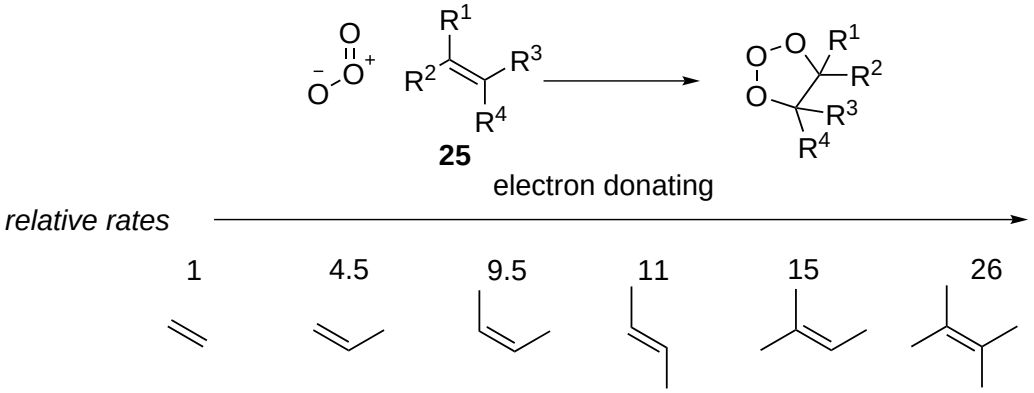


Figure 1.17: Varying the dipolarophile substituents changes the rates of the 1,3-dipolar cycloadditions with ozone in such a way as to be consistent with type III trends.[49;50]

1.2.6 Stereochemistry

Generally, 1,3-dipolar cycloadditions result in retention of configuration with respect to both the dipole and dipolarophile, lending support to the concerted mechanism. The transition state in Figure 1.18 showcases this retention, and it can be seen that *cis* and *trans* configurations are retained throughout the reaction with respect to the dipolarophile. Stereospecificity is more difficult to achieve with respect to dipoles, as bond rotation can often take place. However, Huisgen has shown that dipoles in 1,3-dipolar cycloadditions are also stereospecific.[51]

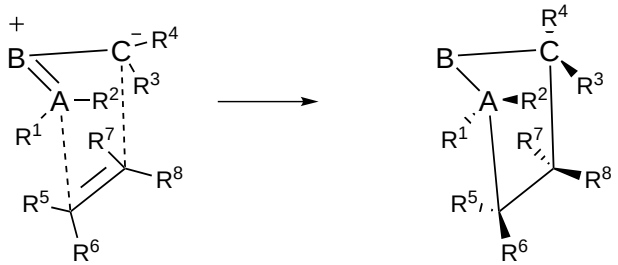


Figure 1.18: Predicting the stereochemistry of the 1,3-dipolar nitrone cycloaddition.

There are three types of selectivities that need to be considered. These are regioselectivity, stereoselectivity and facial selectivity, all of which are illustrated in Figure 1.19.

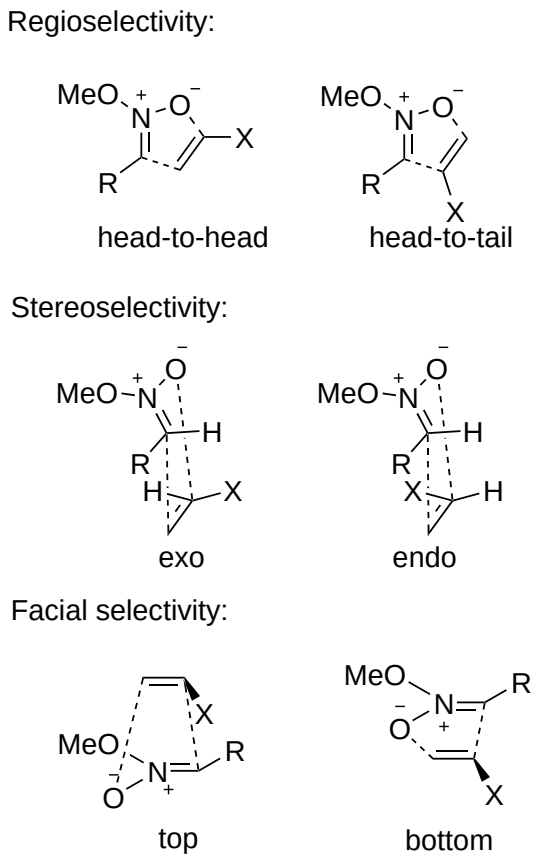
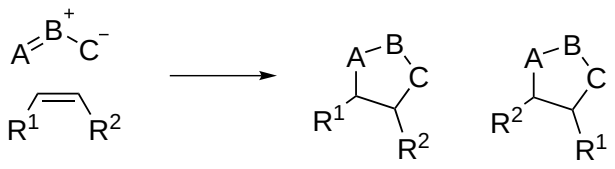


Figure 1.19: The different types of selectivities that are possible for 1,3-dipolar cycloadditions.[52]

Regioselectivity

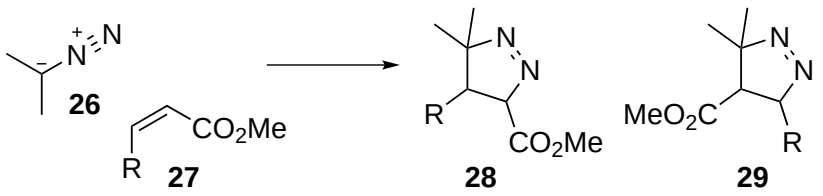
The regioselectivity of a cycloaddition reaction becomes a consideration when both reactants are asymmetrical. Usually, the dipolarophile is the asymmetrical component, making two regioisomers possible, as can be seen in Scheme 1.14.



Scheme 1.14: The two possible regioisomers from a 1,3-dipolar cycloaddition reaction with an asymmetrical dipolarophile.

Both electronic and steric factors need to be taken into account when rationalising the outcome of a reaction. The dominant electronic interaction will be between the atom that holds the largest co-efficient on a HOMO orbital and the atom that holds the largest co-efficient on a LUMO orbital, as described in more detail in Section 1.2.5. Steric factors can either cooperate or compete with this effect, usually to give a mixture of regioisomers. However, the complete opposite regioisomer may be observed if the steric interaction dominates over the electronic interaction.

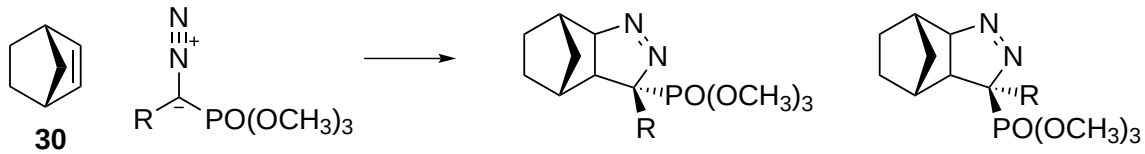
For example, in the reaction below in Scheme 1.15,[53] diazomethane **26** and methyl acrylate **27** react to give pyrazolines **28** and **29**. According to Sustmann's classifications, diazoalkanes are type I HOMO-controlled dipoles, so under normal circumstances will react with the LUMO of the dipolarophile, which has the largest co-efficient on the alkene carbon that is closest to the R group in compound **27**, to give **28**. However, as the R group becomes more sterically hindered, this orientation is no longer favourable, so the reaction proceeds to form compound **29**, the other regioisomer.



R	28	29
H	100%	0%
Me	91%	9%
Et	80%	20%
^{i}Pr	47%	53%
^{t}Bu	0%	100%

Scheme 1.15: Varying the terminal R group illustrates how the steric hindrance overrides the favoured electronic orientation of the cycloaddition with diazomethane.[53]

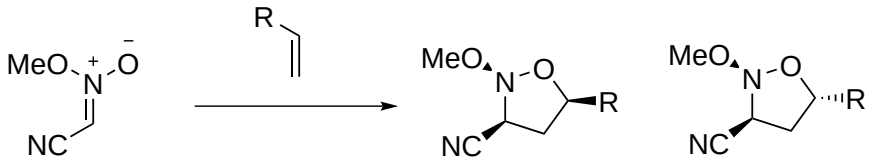
Likewise, the additions of various diazoalkanes to norbornadiene **30** in Scheme 1.16 also illustrates the prevailing dominance of steric factors directing the regioselectivity of the reaction.[54]



R	anti	syn
Me	75%	25%
Et	60%	40%
^{i}Pr	50%	50%
^{t}Bu	0%	100%

Scheme 1.16: In this 1,3-dipolar cycloaddition between a diazoalkane and an alkene, as the R group becomes increasingly bulky, the *syn* product is favoured.[54]

Stereoselectivity



R	endo	exo
CN	50%	50%
CO_2Me	0%	100%
Ph	0%	100%

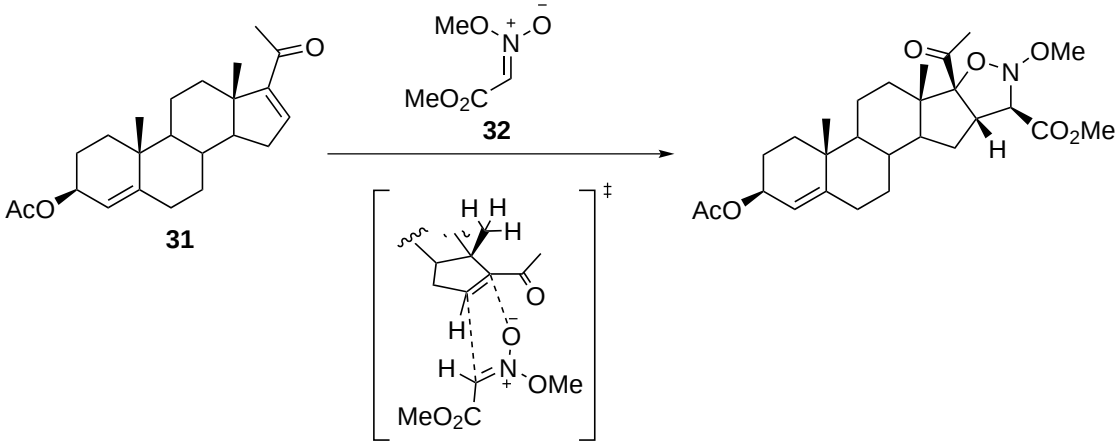
Scheme 1.17: As the R group of the alkene becomes larger, the *exo* product is favoured.[55]

If two or more stereocentres are generated during the reaction, diastereomeric products can be obtained, which are controlled by a balance between attractive π-interactions and repulsive steric clashes. In reactions of nitronates with alkenes, the alkene can approach the 1,3-dipole from two orientations, *endo* and *exo*, akin to Diels-Alder reactions, giving rise to two diastereomers. The *endo* product arises from the stabilisation of the transition state by secondary π orbital interactions, but this is often overruled by steric hindrance in favour of *exo* products (Scheme 1.17).

Facial Selectivity

The two types of facial selectivity are illustrated in Figure 1.19. The main factor that dictates facial selectivity stems from the steric environment about the two faces of each reactant. This can be controlled by using chiral agents through a catalyst, by the chiral nature of the molecule itself, or by physical proximity due to an intramolecular cycloaddition taking place.

For example, in Scheme 1.18, the reaction of the pregnane-like steroid dipolarophile **31** proceeds with nitronate **32** approaching the *Re* face of the alkene, as the *Si* face is blocked by the methyl group.[56]



Scheme 1.18: The use of high pressure induces 1,3-dipolar cycloaddition of the nitronic ester with a pregnane-like scaffold structure.[56]

1.3 Autophagy

Some of the compounds that were synthesized in this research exhibited modest biological activity. As there is a biological component to this work, this section will give a brief overview of autophagy, a cellular process that was being investigated in assays, of which the results will be discussed in Section 2.3.4.

1.3.1 Introduction to Autophagy

Autophagy, from the Greek meaning "eating of self",[57] is a general term to describe a biological process that consists of regulated degradation of unnecessary or dysfunctional cellular components by lysosomes. These are membrane-bound spherical vesicles that contain hydrolytic enzymes which are capable of breaking down a vast array of biological material. Three types of autophagy are recognised: macroautophagy, microautophagy, and chaperone-mediated autophagy.

In macroautophagy, the cytoplasmic contents to be degraded are sequestered into a double membrane bound vesicle called an autophagosome, which then transports the cargo to a lysosome. Both structures fuse together to become an autolysosome and the contents are degraded, as can be seen in Figure 1.20.

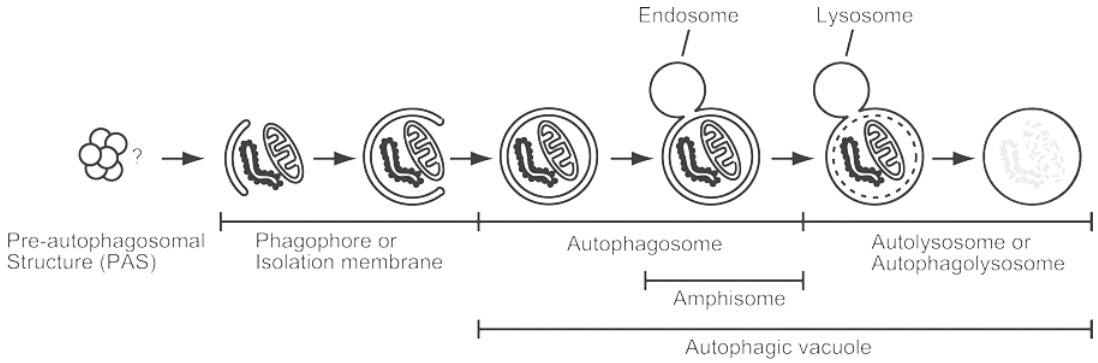


Figure 1.20: The process of macroautophagy in mammalian cells. Image from Mizushima, 2007.[58]

The process for microautophagy differs in that it does not include the transportation step; the lysosome simply engulfs the cytosolic contents directly via invagination of the lysosomal membrane.

Chaperone-mediated autophagy[59] is more complicated, as it involves the use of HSC70 chaperone proteins to target specific substrates. These substrates must contain a recognition site for HSC70, and once the substrate and carrier proteins interact, they form a complex which then translocates the substrate across the lysosome membrane for degradation, as can be seen in Figure 1.21. This method is highly selective and does not require any additional vesicles.

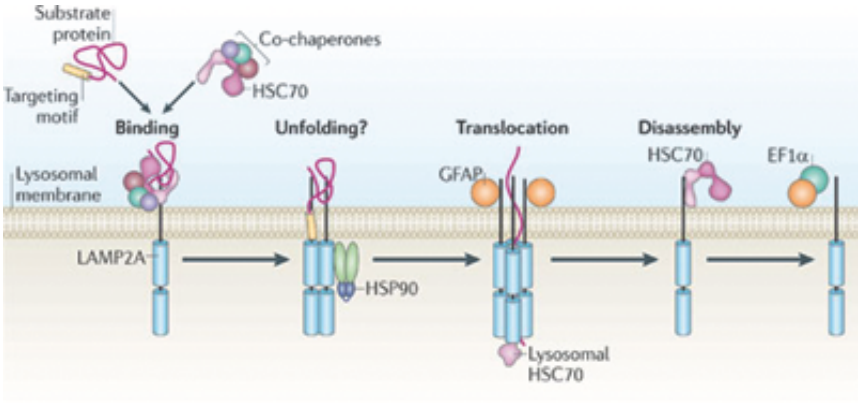


Figure 1.21: Current mechanistic model for chaperone-mediated autophagy. Image adapted from Cuervo, 2011.[60]

Autophagy has been identified as a response to many processes such as cellular starvation, stress response to bacterial or viral infections,[61;62] in neurodegeneration,[63–65] cell repair and anti-aging,[66] and tumour suppression.[67–71]

The term was introduced by de Duve in 1963. It is a cellular process that was first observed in 1962 by Porter and Ashford[72] at the Rockefeller Institute, who noticed that there was an increase in lysosomes when the pancreatic hormone glucagon was added to rat liver cells, and that some of these lysosomes were in the process of degrading other organelles such as mitochondria. They incorrectly believed that this was how lysosomes were formed. It was not until Kleinfield's 1963 "focal cytoplasmic

degradation" study,[73] which shed light on lysosome formation, that de Duve coined the term autophagy to describe Porter and Ashford's observations: that glucagon was an inducer of cell degradation in the liver, which is carried out by lysosomes.

Since then, intensive research has been carried out in this field. Many different names were given to the genes involved in this process, but in 2003, the universally agreed naming protocol to denote autophagy genes became ATG.[74]

Current mechanistic understanding of autophagy has been based largely on breakthroughs in studies on budding yeast.[75;76] For example, Ohsumi *et al.*[77] incubated mutant yeast cells in nutrient deficient media and after an hour, spherical "autophagic bodies" began to appear, which gradually increased in number and were found to contain both cytosolic components and active enzymes. This phenomenon was not only induced by nitrogen depletion, but also by lack of carbon and amino acids. It was found that lack of proteinase B led to the accumulation of the vesicles, suggesting that proteolysis is essential in protein turnover in nutrient deficient conditions.

1.3.2 The Role of ATG4B in Macroautophagy

Previous studies[74] in yeast (*Saccharomyces cerevisiae*) have led to the discovery of a new ubiquitin-like conjugation system called the ATG8 system which is essential for autophagosome formation.[78] In this system, ATG8 is cleaved at the C-terminal arginine residue by ATG4, a novel cysteine protease[79] to expose a glycine. The newly exposed C-terminal glycine is conjugated to the lipid, phosphatidylethanolamine, by the enzymes ATG7 and ATG3. The ATG8-phosphatidylethanolamine complex can then be cleaved at the C-terminal glycine of ATG8 by ATG4. This whole process is

reversible, crucial for autophagy[79] and seems to have been conserved evolutionally across higher eukaryotes.

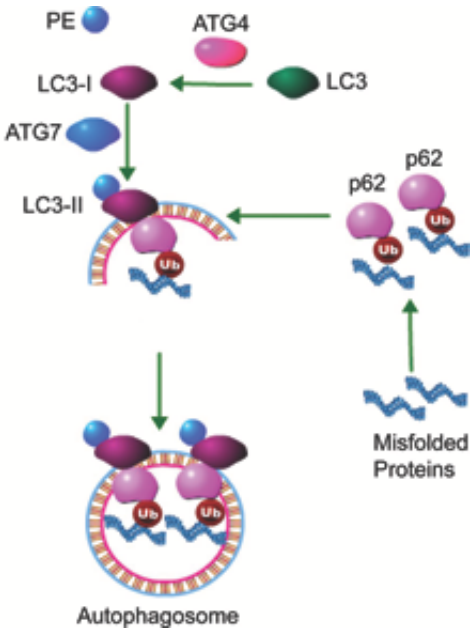


Figure 1.22: Schematic depicting the LC3 system. Image adapted from Banduseela, 2013.[80]

In mammals, an analogous system to the ATG8 system operates. This is known as the LC3 (microtubule-associated protein light chain 3) system[81–83] and is illustrated by the schematic in Figure 1.22. LC3 is the mammalian homologue of ATG8 and was originally identified in the rat brain.[84] The crystal structure can be seen in Figure 1.24.

Similarly to the ATG8 system, the C-terminal region of LC3 is cleaved by the mammalian analogue of ATG4, known as ATG4B (of which the crystal structure can be seen in Figure 1.23), to form LC3-I. This processed form also has a glycine residue at the C-terminus, and exists in the cytosol where it is activated by mammalian homologues of ATG7 and ATG3 before it is modified into LC3-II. LC3-II is found in the autophagosomal membrane so can be used as a probe to monitor autophagosomes and autophagy in mammalian cells.[81]

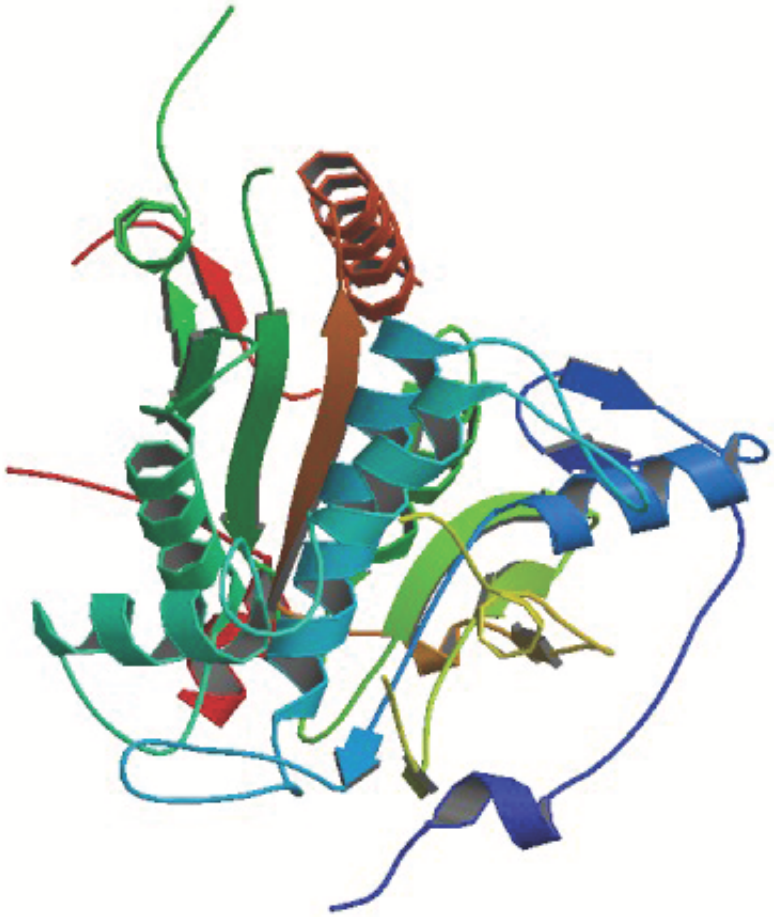


Figure 1.23: Crystal structure of human ATG4B. Image from Sugawara, 2005.[85]

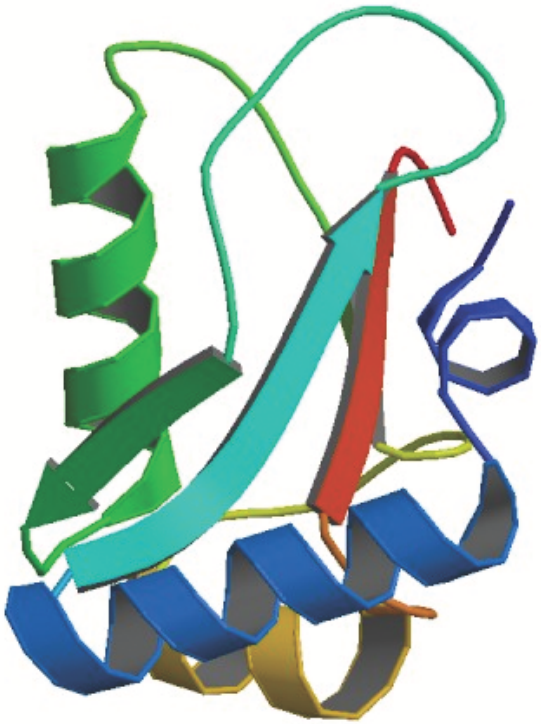
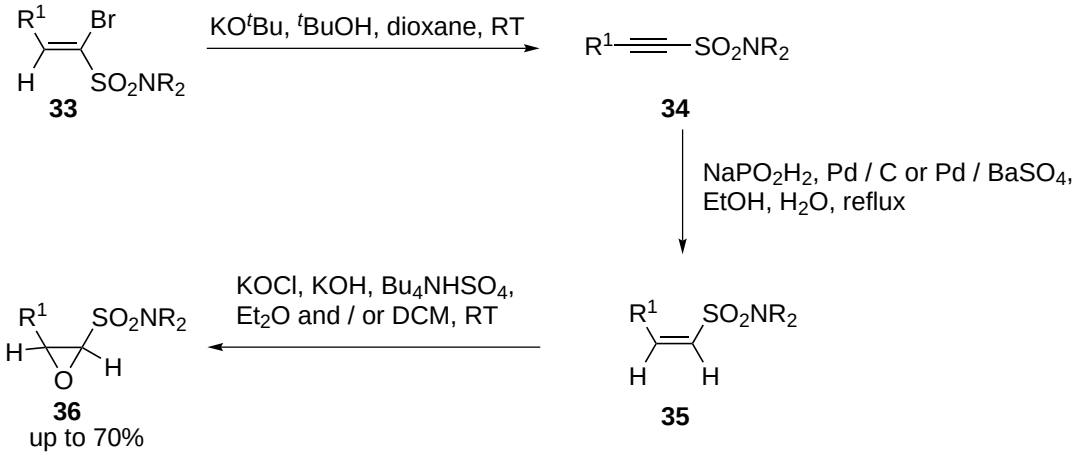


Figure 1.24: Crystal structure of LC3, isolated from *Rattus norvegicus*. Image from Sugawara, 2004.[86]

1.4 Previous Group Work

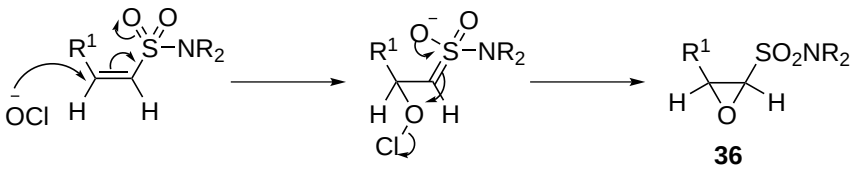
1.4.1 Introduction to the Alkynyl Sulfonamide Motif

One of the research interests within the Wilden group is the synthesis and subsequent investigations into the reactivity of alkynyl sulfonamides,[34] a relatively under-explored compound class. A survey of the literature suggests that this group was first reported by Brienne *et al.* in their search for antifilarial agents[87] in 1987 to treat tropical parasitic infections caused by nematodes.



Scheme 1.19: The alkynyl sulfonamide as an intermediate to epoxy sulfonamides. Alkynyl sulfonamide compounds exhibited antifilarial activity when R^1 = Ph, and R = NMe_2, morpholino, or 4-me-1-piperazinyl.

Brienne initially prepared alkynyl sulfonamides **34** as intermediates to forming epoxy sulfonamides **36** (Scheme 1.19), but found that several of the alkynyl sulfonamides exhibited good *in vivo* activity on treating adult nematodes. In these reactions, a strong tertiary butoxide base undergoes an E2 reaction on vinyl bromide **33** to form alkynyl sulfomanide **34**. This is then reduced on a palladium catalyst to create *cis* alkene **35**, which is finally oxidised by potassium hypochlorite to make **36**, the epoxy compound.

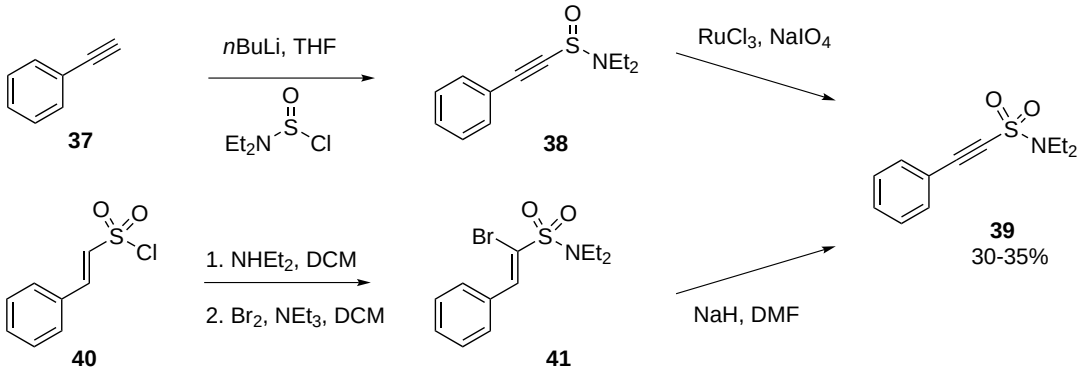


Scheme 1.20: Proposed mechanism for the oxidation step of Brienne's procedure to form epoxy sulfonamides.

The alkynyl sulfonamide unit has also found recognition in more recent medicinal compounds,[88] and several examples of cycloadditions involving this motif have since been reported.[89–91]

1.4.2 Synthetic Routes to Alkynyl Sulfonamides

Two strategies for synthesizing alkynyl sulfonamides are routinely used in the Wilden group to synthesize *N,N*-diethyl-2-phenylethyne-1-sulfonamide **39**, as can be seen in Scheme 1.21.

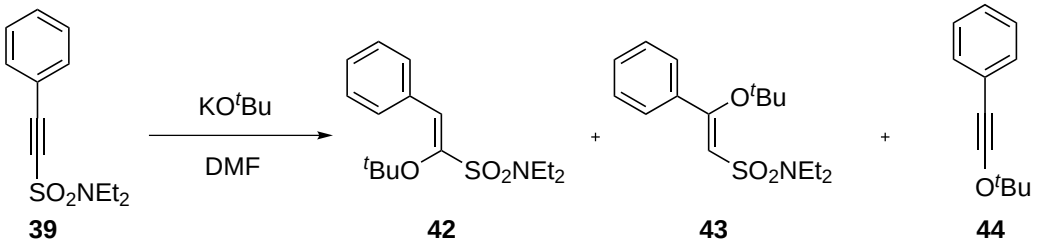


Scheme 1.21: Both routes form the product with overall yields of around 30-35%.

The first method involves the transformation of commercially available phenylacetylene **37** into alkynyl sulfinamide **38**, followed by the subsequent oxidation to compound **39**.[92] The second method involves the nucleophilic substitution of diethylamine on trans-β-styrenesulfonyl chloride **40**, followed by a series of transformations to give vinyl bromide intermediate **41**. The alkynyl sulfonamide is then prepared by eliminating the bromide from **41** to form **39**.

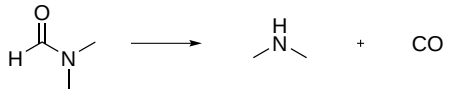
1.4.3 Alkynyl Sulfonamides as Precursors to Ynol Ethers

Previous work in the group[34] has shown that if alkynyl sulfonamide **39** is treated with potassium *tert*-butoxide in the presence of wet dimethylformamide (DMF), then a mixture of products is formed: α-addition **42**, β-addition **43**, and a small amount of ynol ether **44**. This is summarised in Scheme 1.22.



Scheme 1.22: In this reaction, a mixture of products is formed: α-addition **42**, β-addition **43**, and a small amount of ynol ether **44**.

The ratio of α to β product formation was approximately 1:3, with a trace of the ynol ether present. When the reaction was repeated in anhydrous conditions, ynol ether **44** was the sole product. A range of alkynyl sulfonamides was tested, as can be seen in Figure 1.25. Varying the potassium alkoxide base also produced a range of ynol ethers, as shown in Figure 1.26. This was pleasing news for the group as it indicated the existence of a new method for the synthesis of ynol ethers, a class of substrates that are traditionally difficult to synthesize due to complicated synthetic routes, the starting materials being more complicated than the products, and poor atom economy of existing syntheses.[93–95]



Scheme 1.23: Over a period of time, DMF decomposes to DMA and CO.

Later, it was discovered that a small amount of dimethylamine was present in the solvent from decomposition of dimethylformamide to dimethylamine and carbon monoxide (Scheme 1.23). It was found that when freshly distilled dimethyl-

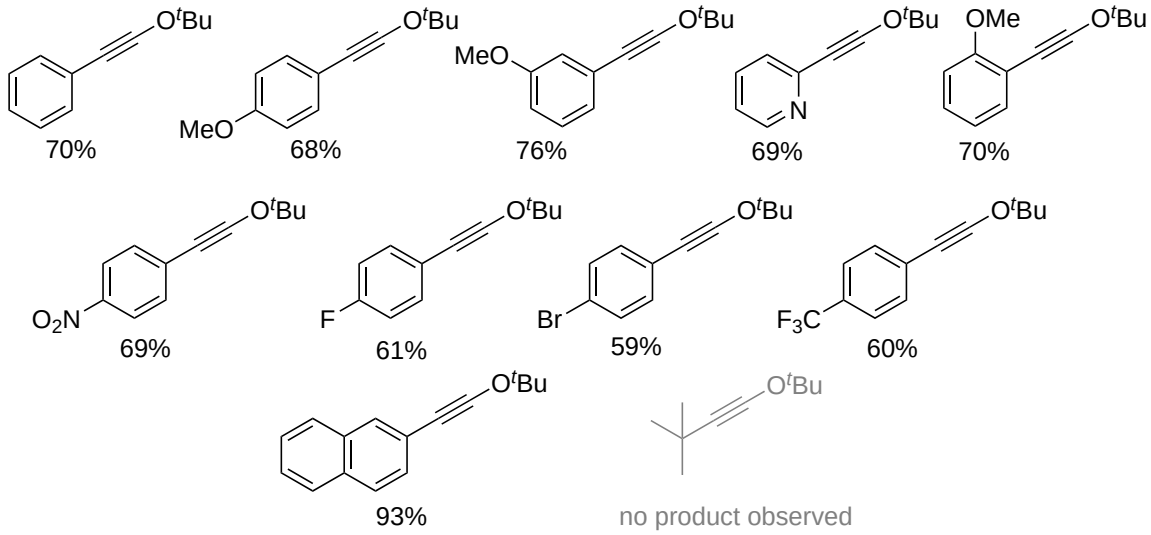


Figure 1.25: A range of alkynyl sulfonamides was transformed into ynol ethers.

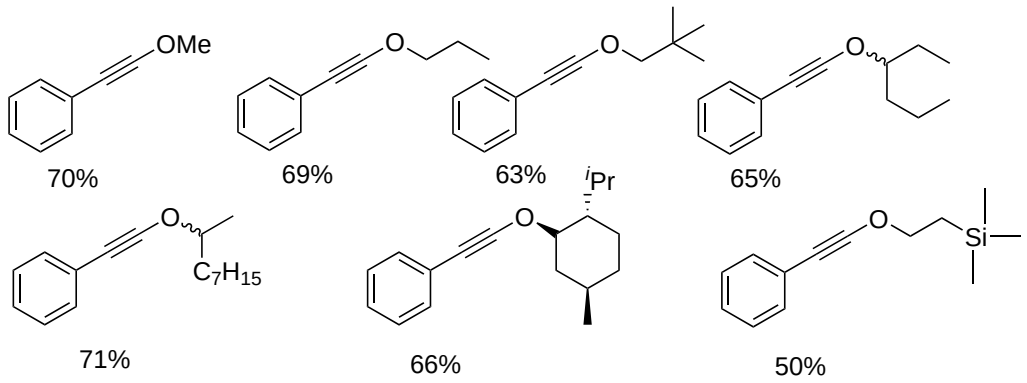


Figure 1.26: A range of ynol ethers was produced by varying the potassium alkoxides.

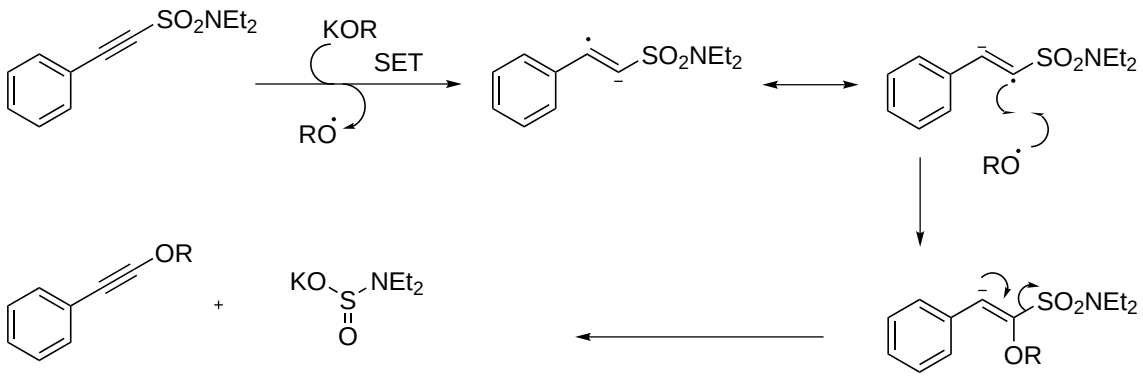
formamide was used, the reaction did not proceed, indicating that dimethylamine played a role in the reaction. This was confirmed when the alkynyl sulfonamide was treated with potassium *tert*-butoxide and dimethylamine in tetrahydrofuran (THF) and the reaction yielded the ynol ether.

The potassium counter-ion is also important in the reaction, since addition of 18-crown-6 ether to trap the potassium ion resulted in complete loss of reactivity. Likewise, no reactivity was observed when other counter-ions were used, including: sodium, lithium and magnesium. In all these cases, the reaction began to proceed as soon as a source of potassium was added to the reaction via KPF_6 as a soluble K^+ source.

These results indicate that both the dimethylamine and potassium are playing key roles in the reaction mechanism. Due to the belief that radicals could also be involved, the group repeated the reaction with several radical inhibitors, but found that they had no effect on the reaction. Undeterred, the group subjected the reaction conditions to electron paramagnetic resonance (EPR) studies and discovered that when potassium *tert*-butoxide and dimethylamine are mixed together, an EPR signal was observed, indicating that there is a free radical present in the solution.[96]

Given what was already known, that potassium and an amine are both integral to the reaction, and using EPR evidence, it was hypothesized that a radical complex is being spontaneously assembled in solution, which generates a free electron that can reduce the organic substrate present in the reaction.[97]

Further experiments conducted within the group suggest that the pathway that now leads to the ynol ether is single electron transfer to the alkynyl sulfonamide followed by an addition-elimination route, as seen in Scheme 1.24.[98]



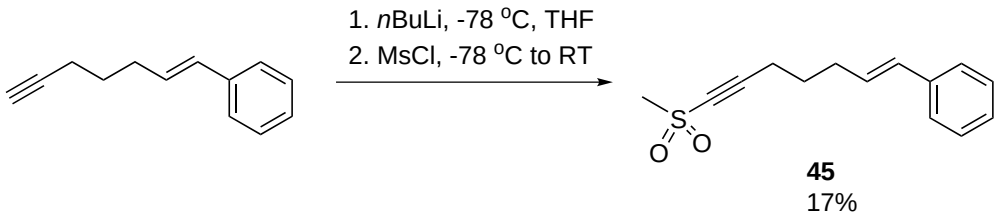
Scheme 1.24: Revised proposed mechanism, adapted from Gray, 2014.[98]

Chapter 2

Results and Discussion

2.1 One Pot Synthesis of Alkynyl Sulfonamides

As can be seen in Section 1.4.2, the two methods used in the Wilden group to make alkynyl sulfonamides are time consuming and generally give overall yields of around 30-35%. Due to the demand for the starting material within the group, an efficient and facile synthesis was highly desirable. An initial consideration was to treat a metal acetylide with sulfonyl chloride, a readily available starting material; however the literature indicated very few successful examples of this type of reaction.



Scheme 2.1: Poor yields were obtained when a lithiated alkyne was treated with methanesulfonyl chloride.

Kocsis *et al.*[99] treated a lithiated alkyne under anhydrous conditions with methanesulfonyl chloride, and was able to obtain product **45** in a yield of 17%. Zhang *et al.*[100] reported a similarly low yield of 20% when 2-methyl-3-butyn-2-ol 1-ethoxyethyl ether was treated with methanesulfonyl chloride. However, Reddy *et al.*[101] obtained

yields of above 80% when reacting deprotonated phenylacetylene with various styrenesulfonyl chlorides.

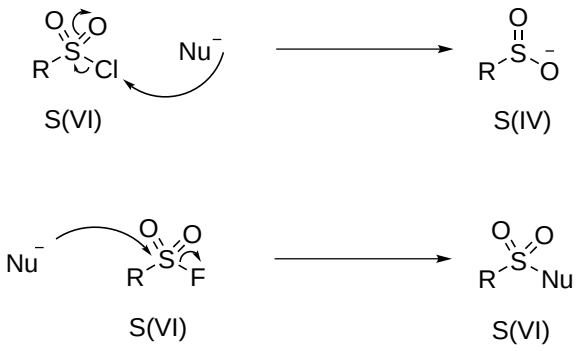
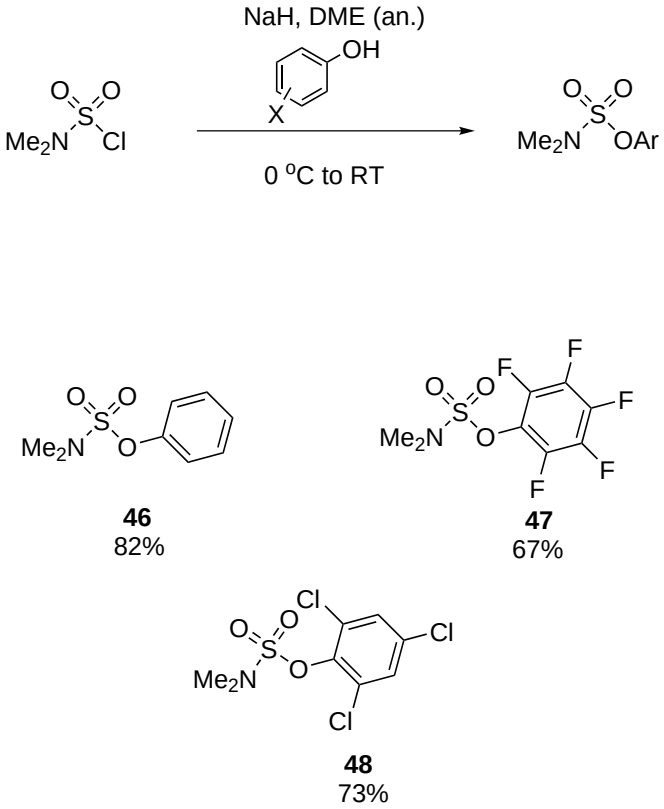


Figure 2.1: As the S-X bond increases in polarity, nucleophilic attack becomes S-philic. Adapted from Alabugin.[102]

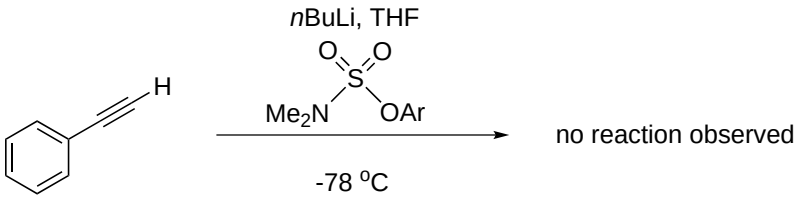
It is known that halophilic attack presents a problem in the chemistry of S(VI) halides.[102] In particular, it limits the utility of sulfonyl chlorides as sulfur electrophiles, because the S-Cl bond is sensitive to reductive collapse,[103] leading to the destruction of the electrophile and generation of a S(IV) species, as shown in Figure 2.1.

The type of reaction that occurs has been dubbed X-philic,[104] and in the case of interest for this work, the lithiated alkyne starting material usually ends up chlorinated with loss of SO_2. This was problematic for forming the C-S bond especially since this type of reaction typically occurs with carbon nucleophiles.

An attempt to circumvent the issue of the X-philic reaction was made by changing the leaving group. Arylsulfamates **46**, **47** and **48** were synthesized in good yields according to standard conditions, as can be seen in Scheme 2.2. However, when lithiated phenylacetylene was treated with these arylsulfamates, no reaction was observed (Scheme 2.3). The literature indicates that no such displacements have been reported and that aryl sulfamates are primarily used in cross coupling reactions,[105–107] so this approach was discarded.

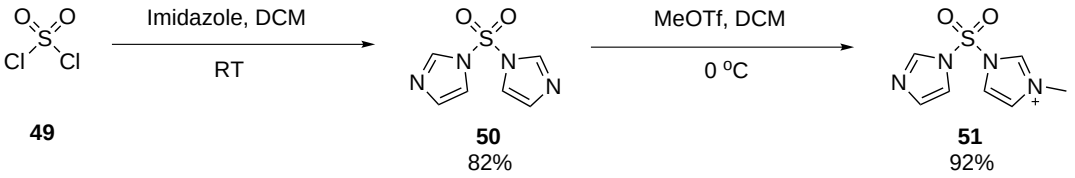


Scheme 2.2: A small range of arylsulfamates was synthesized using standard conditions.[105]



Scheme 2.3: No reaction was observed when a lithiated alkyne was treated with the arylsulfamates.

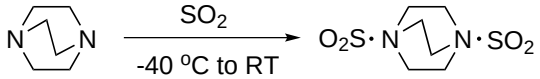
A second attempt was made to use a S(VI) species as an electrophile by activating the leaving group. Sulfuryl chloride **49** was treated with imidazole to form sulfonyl diimidazole **50**, and following this, methyl triflate was used as a methylating agent to activate one of the imidazoles.[108] However, when electrophile **51** was used under the same conditions as in Scheme 2.3, TLC analysis showed that only starting materials were present.



49 **50** 82% **51** 92%

Scheme 2.4: A method by Ye *et al.*[108] was used to prepare the 3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium ion.

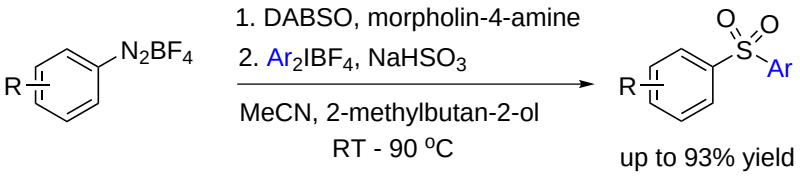
Experimental attempts and an assessment provided by Sharpless[103] confirmed that use of an isolated S(VI) electrophile would not be likely to yield successes. The X-philic problem could potentially be avoided by using sulfur (VI) fluorides, due to the increased polarity of the sulfur halogen bond.[102] As a result, Sharpless makes a strong case for transitioning to sulfur fluorides, however, this is a route that was not explored in this work.



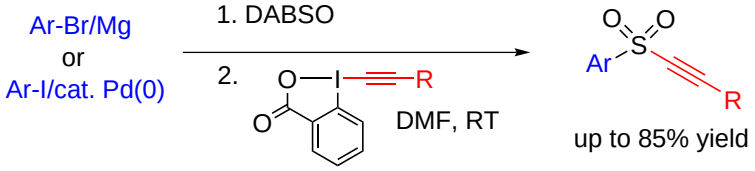
52 94%

Scheme 2.5: DABSO is commercially available but also straightforward to synthesize.

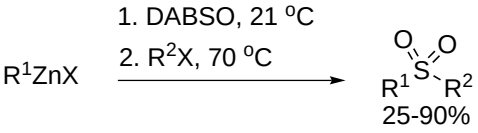
The third consideration was to utilise compound **52**, 1,4-Diazabicyclo[2.2.2]octane-bis(sulfur dioxide), abbreviated as DABSO, which is a commercially available and safer source of SO_2. It is facile to synthesize, and bench stable.[109;110] There are many examples of DABSO mediated reactions in the literature, and a few examples of sulfonylating reactions can be seen in Scheme 2.6, Scheme 2.7 and Scheme 2.8.



Scheme 2.6: Woolven and Willis' one pot synthesis of aryl sulfonamides.[110]



Scheme 2.7: Palladium catalysed three component, one pot synthesis of arylalkynyl sulfones.[111]

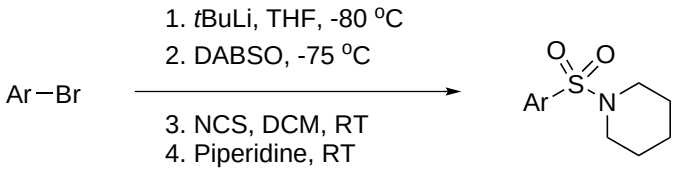


Scheme 2.8: Synthesis of sulfones from organozinc reagents, DABSO, and alkyl halides.[112]

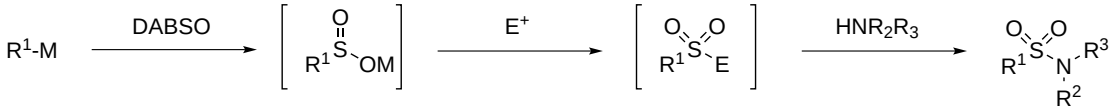
Attention then turned to a recent publication by Waldmann *et al.*, which demonstrated a one-step synthesis of aryl sulfonamides as shown in Scheme 2.9.[113]

These methods suggest one common mechanism: a nucleophilic carbon centre that attacks DABSO to form a S(IV) intermediate, as can be seen in Scheme 2.10. The sulfur centre is oxidised *in situ* with an electrophile, which in the case of a sulfonamide is then displaced by an amine. None of the intermediates are reported to have been isolated so far.

Attempts were made to modify Waldmann's procedure (Scheme 2.9) and apply it to the synthesis of alkynyl sulfonamides in the hopes of improving the yield and diminishing the overall time taken to go from starting material to product. The base, *n*BuLi, was used to deprotonate phenylacetylene instead of *t*BuLi, as it was safer to handle, and previous procedures have indicated that *n*BuLi is sufficiently strong for this purpose. DABSO was made according to a procedure[109] by Willis *et al.*, and added to the mixture in one portion at -78 °C. This was followed by the addition of



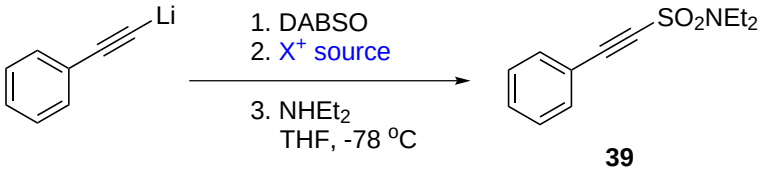
Scheme 2.9: Waldmann's one step synthesis of aryl sulfonamides.[113]



Scheme 2.10: Proposed mechanism of action for DABSO mediated methods of forming sulfonamides.

the chlorinating agent, SO_2Cl_2, and the dropwise addition of diethylamine ($NHEt_2$) and *N,N*-Diisopropylethylamine (DIPEA).

Despite observing a range of different products by TLC, by comparing Rf values with existing samples of alkynyl sulfonamide **39**, the initial result (Entry **1**) showed a trace of product present, so attempts were made to optimise the process to achieve a quantifiable yield of alkynyl sulfonamide. Several halogenating agents were used, and different timings were tested between adding each reagent. The initial screening results are found in Table 2.1 and the reaction is summarised in Scheme 2.11.



Scheme 2.11: Reagents used in the development for the one pot synthesis of alkynyl sulfonamides.

The progress of the reaction was very difficult to monitor by TLC, as the sulfonyl halide intermediate was too unstable to isolate. Entry **2** looked at shortening the times of each step, but this had no effect on the isolated yield. It was hypothesized that diethylamine alone may be sufficient as both a base and a nucleophile, and indeed, Entry **3** demonstrates that the product was formed without the addition of DIPEA. Another halogenating agent, N-bromosuccinimide (NBS), was used in

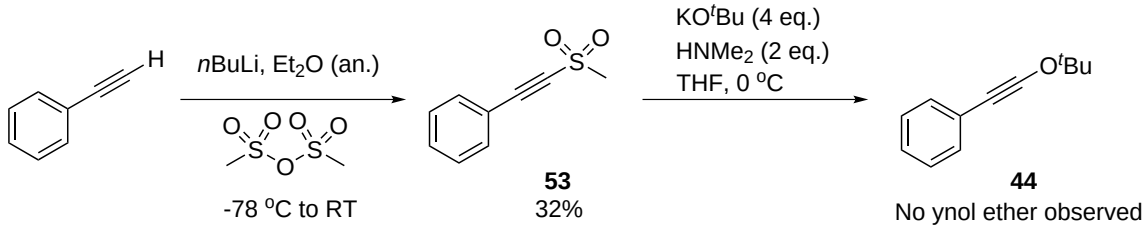
Entry **4** to give the same yields as before; recrystallising the NBS did not appear to affect the yield significantly. When the halogenating agent was switched to Br_2 in Entry **6**, a slightly higher yield of 6% was isolated. Entry **7** was warmed to room temperature prior to the addition of diethylamine, but no product was detected by TLC after 50 minutes, indicating that this reaction requires low temperatures to proceed. Entries **8**, **9** and **10**, looked at expanding the scope of halogenating agents. Whilst $Ca(OCl)_2$ did not give any product at all, overall, yields appeared to be similar regardless of the halogenating agent used.

Table 2.1: Table of results for the optimisation of the one pot synthesis of alkynyl sulfonamide.

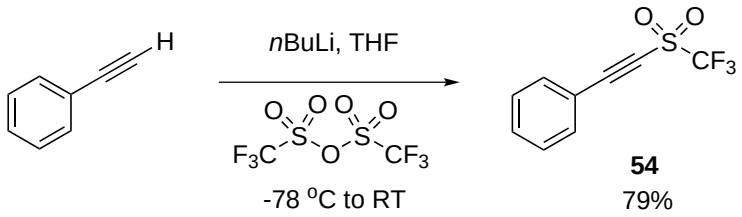
	Stage 1 (min)	Halogenating Agent	Stage 2 (min)	Base	Stage 3 (min)	Yield (%)
1	90	SO_2Cl_2	60	$NHEt_2$, DIPEA*	90	4
2	30	SO_2Cl_2	15	$NHEt_2$, DIPEA*	30	4
3	90	SO_2Cl_2	60	$NHEt_2$	90	4
4	90	NBS	60	$NHEt_2$	90	4
5	60	NBS**	60	$NHEt_2$	60	3
6	90	Br_2	60	$NHEt_2$	90	6
7	135	Br_2	140	$NHEt_2$***	50	-
8	60	$Ca(OCl)_2$	60	$NHEt_2$	30	-
9	60	Na(OCl)	60	$NHEt_2$	30	5
10	60	NCS	60	$NHEt_2$	30	5

Attempts at increasing the yield of the one pot synthesis of alkynyl sulfonamide. Reactions were carried out at -78 ^{o}C and the Stage 1-3 columns indicate the amount of time between the addition of the next reagent; *Dissolved in 20 ml THF, added over 30 min; **NBS recrystallised from water; ***Dissolved in 20 ml THF, added over 15 min.

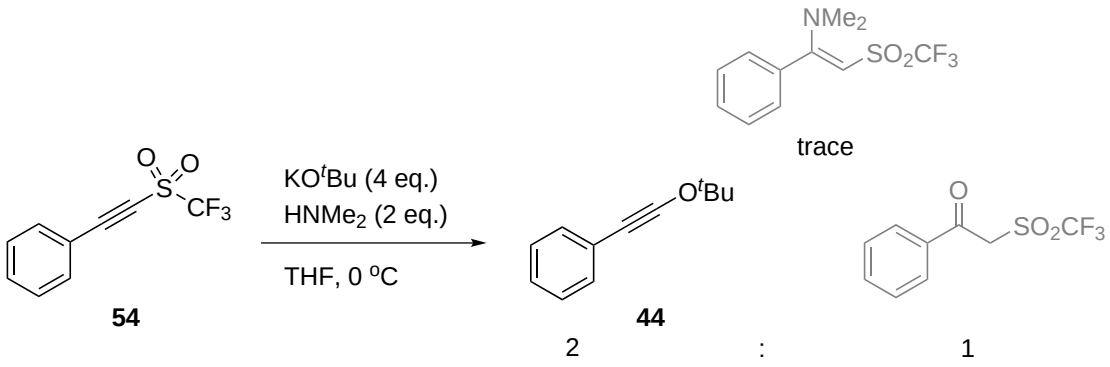
Disappointed by the failure so far in this work, the question was raised as to whether the alkynyl sulfonamide was necessary for the formation of ynol ether **44**. Two other precursors were synthesised: methylsulfonylalkyne **53** in Scheme 2.12 and trifluoromethylsulfonylalkyne **54** in Scheme 2.13. The low yield for **53** was surprising, and could have been attributed to the potential incorrect storage of the



Scheme 2.12: Synthesis of methylsulfonylalkyne was successful with methanesulfonic anhydride, but no ynol ether was observed when this was treated with potassium *tert*-butoxide and dimethylamine.

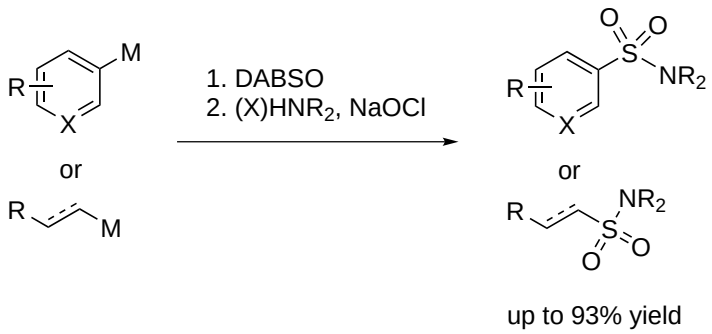


Scheme 2.13: Synthesis of trifluoromethylsulfonylalkyne was facile and complete within three hours.



Scheme 2.14: Trifluoromethylsulfonylalkyne displays the same mode of reactivity as alkynyl sulfonamides for the purpose of the group's research in transition metal free reactions.

methanesulfonic anhydride, which is susceptible to hydrolysis. A range of products was observed by TLC when methylsulfonylalkyne **53** was treated under standard conditions, but more promisingly, **54** was able to undergo the addition-elimination reaction successfully, as summarised in Scheme 2.14. A couple of side products were observed by crude NMR but not isolated. The yield for the ynol ether was 30% but other researchers in the group have subsequently improved it to 50% (Dr. Cuthbertson, unpublished results). Yields of up to 50% have also since been successfully achieved for Scheme 2.12 (Dr. Gray, unpublished results). These alternative methods have since been adopted as standard practice for further investigations of the transition metal free reaction.



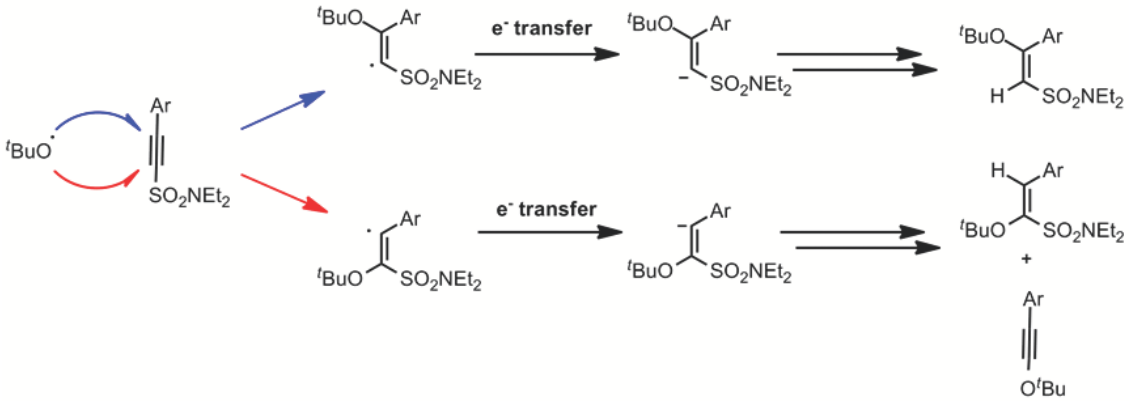
Scheme 2.15: The conditions employed by Willis *et al.*[114] in their one pot synthesis of sulfonamides.

Over the course of this work, a paper by Willis *et al.*[114] was published showing a one pot procedure for alkyl, alkenyl and aryl sulfonamides. Alkynyl sulfonamides are noticeably absent (Scheme 2.15). They favoured the addition of Grignard reagents to a degassed stirring solution of DABSO and THF at -40 °C to form a metal sulfinate *in situ*. After 30 minutes, the solvent was removed under nitrogen and replaced at 0 °C with water, an amine and with the dropwise addition of NaOCl to generate *N*-chloroamine *in situ* that could then react to form the desired product.

At the time, there was no scope to investigate this method with alkynyl Grignards, however it has been noted for future work, should this be resumed.

2.2 Development of a Radical Trap for Mechanistic Studies

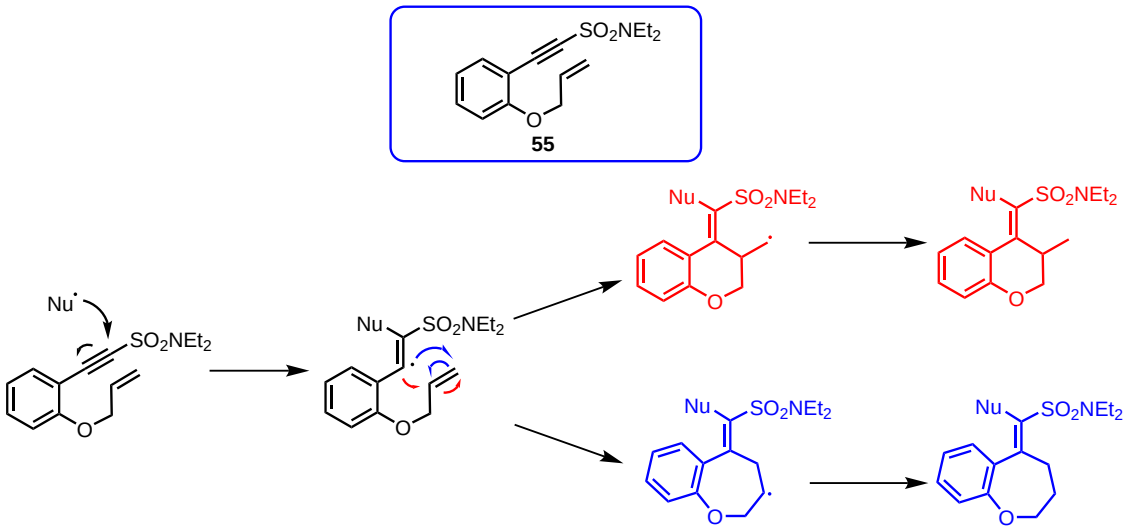
In Section 1.4.3, whilst the mechanism of the addition-elimination reaction was still unclear, work was undertaken to develop a radical trap for mechanistic studies. It was known that when an alkynyl sulfonamide was treated with potassium *tert*-butoxide in DMF at -40 °C, the α and β addition products were observed in a 1:3 ratio with a trace of ynol ether. Initially, the mechanism was thought to be ionic,[34] but other experiments since suggest a radical mechanism.



Scheme 2.16: The initial proposed mechanism of the addition-elimination reaction, before the theory was updated to Scheme 1.24 by Gray.

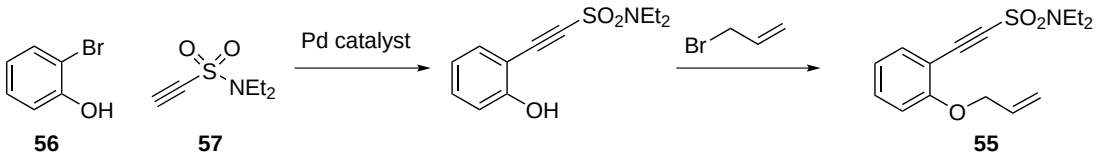
EPR studies showed that when potassium *tert*-butoxide and dimethylamine are mixed together in THF, an EPR signal was observed, indicating the presence of a free radical in the solution.[96] A *tert*-butoxy radical attacks the alkynyl sulfonamide to form a radical intermediate. Electron transfer leads to ionic elimination, as can be seen in Scheme 2.16.

In order to test this mechanism, radical trap **55** was designed in the hope that it would undergo 6-exo trig cyclisation, which was thought to be faster than the elimination step. A 7-endo trig cyclisation is also possible but is expected to be slower than the 6-exo trig cyclisation. This is summarised in Scheme 2.17.



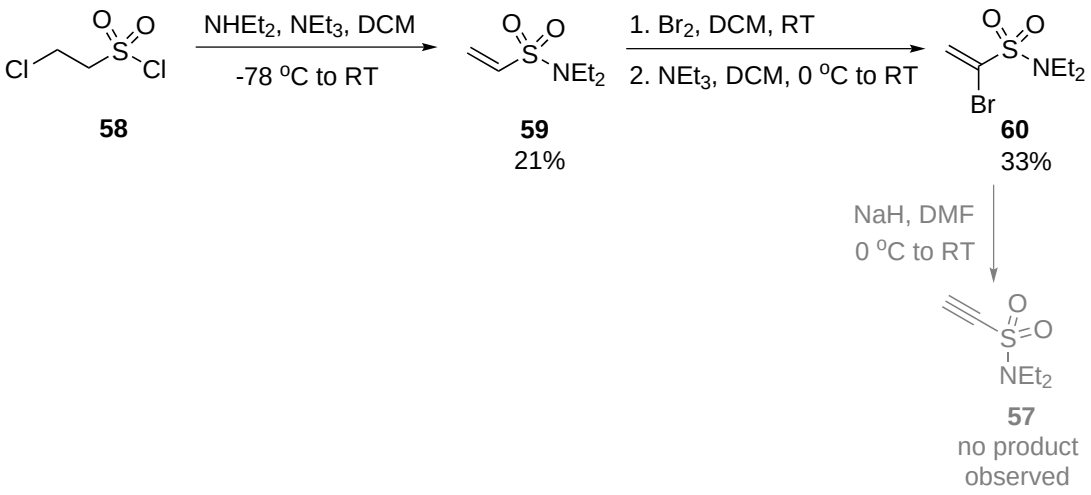
Scheme 2.17: The radical trap and proposed mechanisms of 6-exo trig and 7-endo trig cyclisations.

Initially, disconnections were made for the route as follows in Scheme 2.18, with the palladium coupling of bromophenol **56** and alkynyl sulfonamide **57** envisaged as the key step.

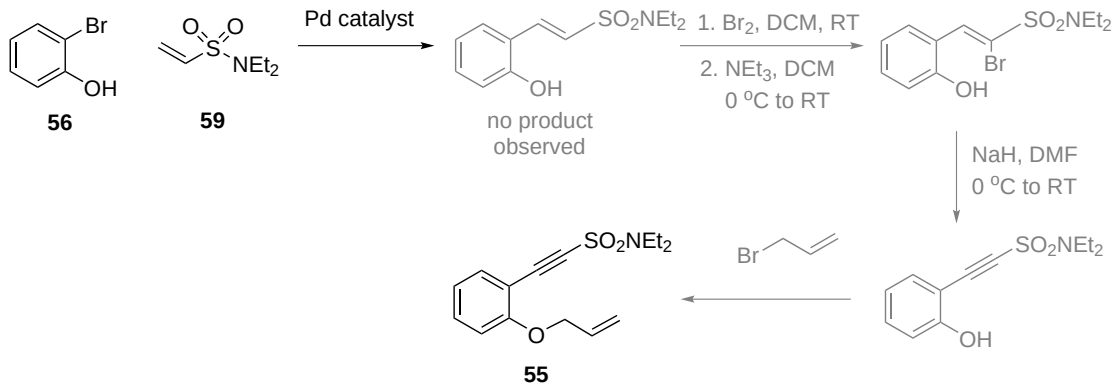


Scheme 2.18: The scheme for the first attempt at synthesising the radical trap.

In Scheme 2.19, **59** was synthesized in a yield of 21% from a protocol adapted from Lee,[115] by treating the starting material **58** with diethylamine and triethylamine in DCM. Disappointingly, scaling the reaction up reduced the yield. **59** was then treated with bromine in DCM at room temperature to form a dibromo intermediate, which, upon treatment with triethylamine eliminated HBr to give the α bromo product **60** in 33%. Unfortunately, in the attempt to convert **60** into the alkynyl sulfonamide, the reaction mixture turned into a black polymeric tar with the starting materials fully consumed. It was rationalised that the high propensity of the product to be a good Michael acceptor would lead it to polymerise rapidly.

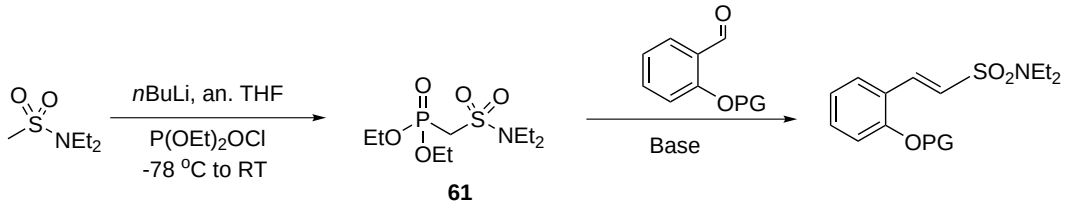


Scheme 2.19: The synthesis of the alkynyl sulfonamide final product was unsuccessful, however, vinyl sulfonamide **59** is facile to access and so provides an alternate coupling pathway.



Scheme 2.20: Another synthetic pathway that ultimately proved unsuccessful.

A second attempt was made to couple vinyl sulfonamide **59** to bromophenol **56** as shown in Scheme 2.20, but unfortunately no products were observed. In anticipation of potential problems with the alcohol group, another attempt was made on this route but with the alcohol protected prior to the Heck coupling. This time, the reaction looked more promising but after 10 hours, both starting materials were still present, with only a trace of a new product observed by TLC. Sadly, this was unable to be isolated. Discouraged with the results, the reaction was terminated. The literature indicates that yields for Heck couplings with vinyl sulfonamides are low.[116–119]

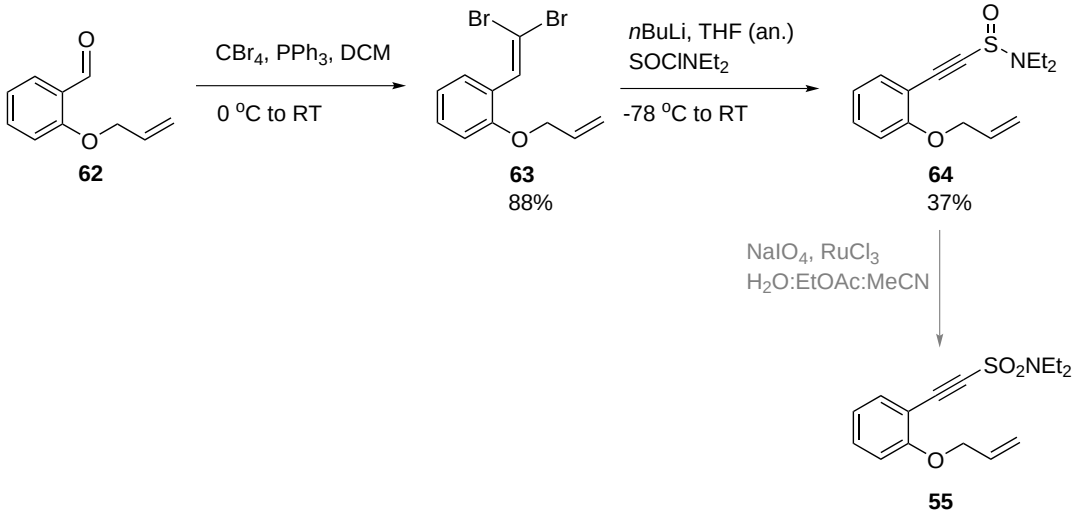


Scheme 2.21: The Horner-Wadsworth-Emmons coupling reaction.

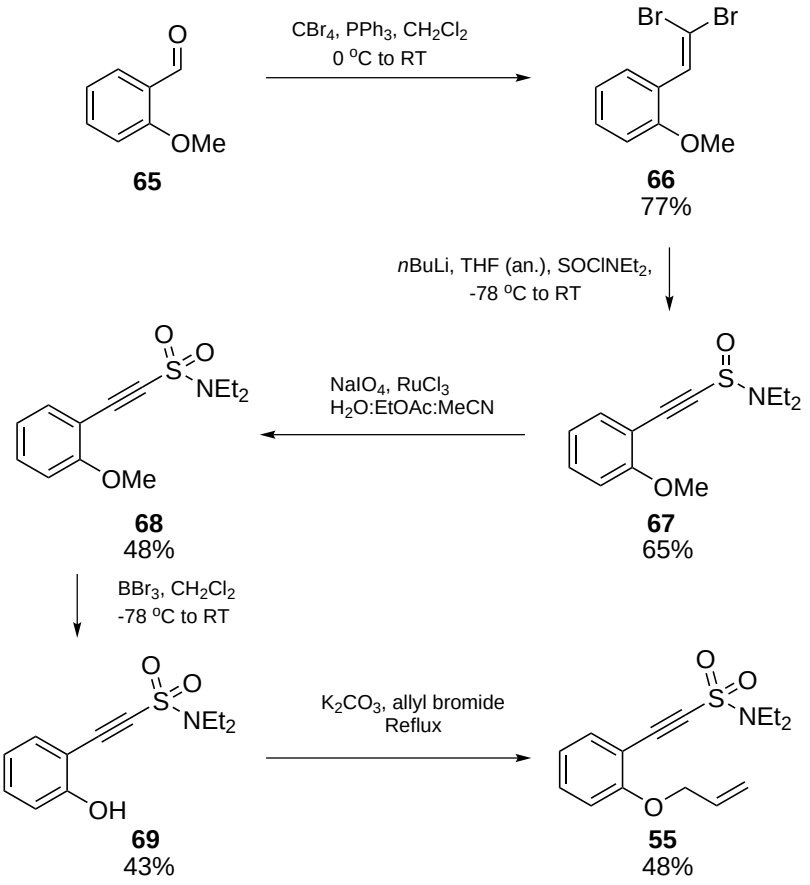
Another potential route involves a Horner–Wadsworth–Emmons coupling, as can be seen in Scheme 2.21. A preparation by Bartlett *et al.*[120] was found to create phosphonate **61**, however, isolating this compound proved to be difficult even after a couple of attempts so this protocol was discarded for a more promising one (Scheme 2.22), which involved the readily available starting material **62**.

62 was treated with carbon tetrabromide in the Corey-Fuchs reaction to make the intermediate **63** in 88% yield. Sulfinamide **64** was then obtained in 37%. Unfortunately, when the sulfinamide was subjected to oxidising conditions, over-oxidation occurred to produce a range of inseparable products.

The final method that proved to be successful was to take methoxybenzaldehyde **65**, with the methyl acting as a protecting group for the alcohol, and repeat the Corey-Fuchs step to form sulfonamide **68**. Deprotection of the alcohol through

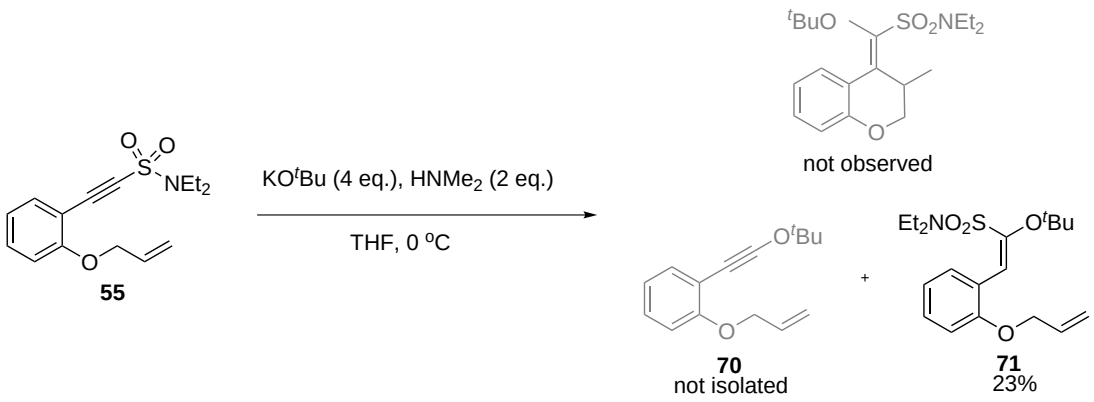


Scheme 2.22: The oxidation step proved to be the downfall of this route.



Scheme 2.23: The successful route for the synthesis of the radical trap.

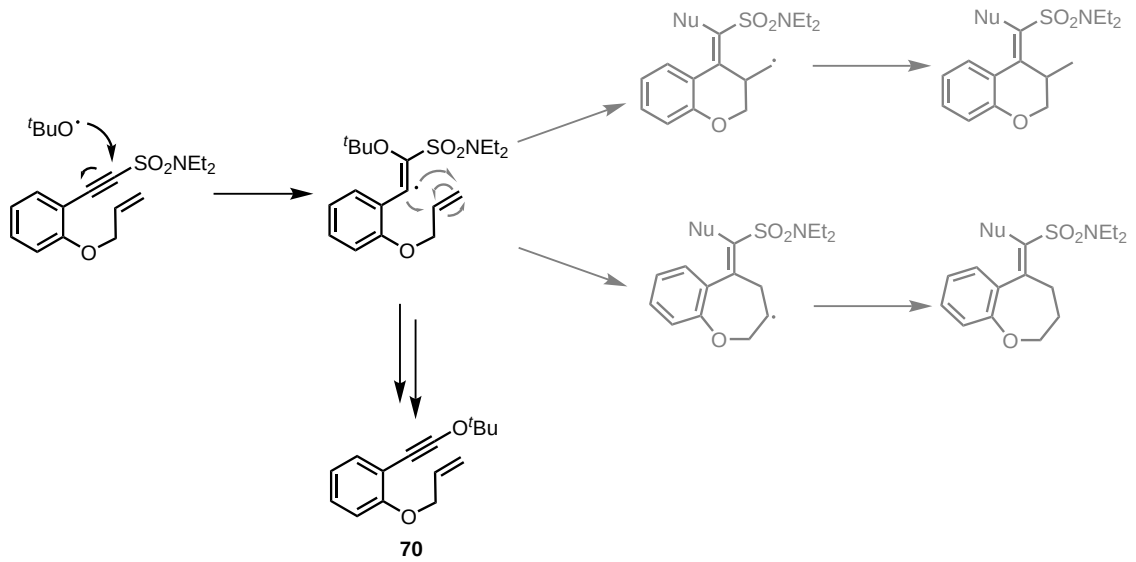
demethylation gave **69**, and addition of the allyl group led to the synthesis of **55**, as can be seen in Scheme 2.23. Whilst the route was more convoluted than initially envisaged, this ultimately yielded the radical trap.



Scheme 2.24: Subjecting the radical trap to these reaction conditions did not give rise to any cyclisation products.

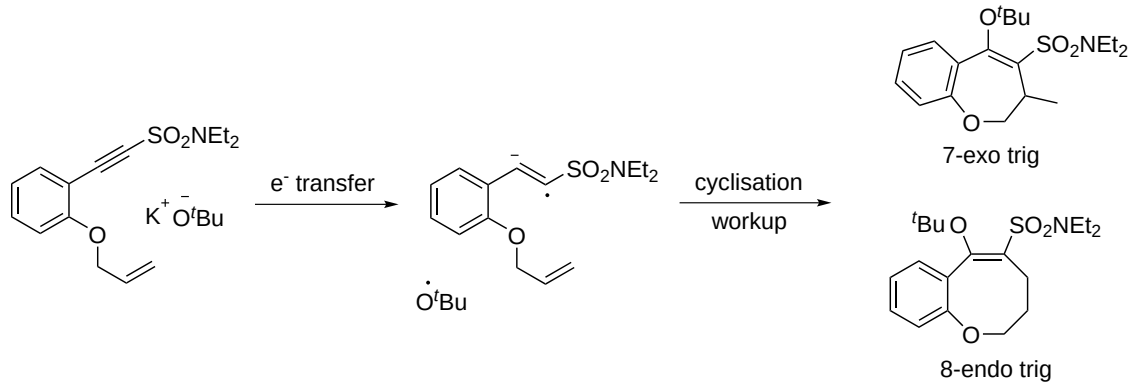
In Scheme 2.24, when radical trap **55** was treated with potassium *tert*-butoxide and dimethylamine in THF, no cyclisation products were observed, only the α addition product **71** which was isolated in 23% yield. Ynol ether **70** was speculatively observed by TLC with a distinctively high Rf, but this was unable to be isolated by column chromatography. It was thought that the product was unstable so had degraded during purification, with the expectation that this would react with the alkene of the starting material.

The result of this experiment indicated that the addition-elimination step is much faster than cyclisation (Scheme 2.25), and was consistent with the results from other radical trap experiments within the group. Later experiments carried out by other group members gave cause to amend the initial hypothesis to the proposed mechanism shown in Scheme 1.24. It is now believed that there is a single electron transfer from the *tert*-butoxide to form a radical anion, with the radical residing preferentially in the α position, as shown by computational studies (Dr. Slater, unpublished results). Provided this is the case, for the radical trap designed, the



Scheme 2.25: The formation of the ynol ether was much quicker than cyclisation.

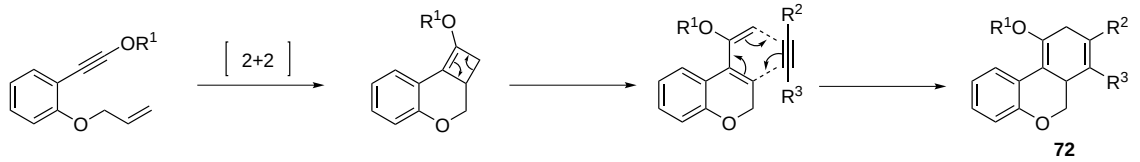
potential cyclisation options would be 7-exo trig and 8-endo trig in Scheme 2.26, as opposed to the 6-exo trig and 7-endo trig cyclisations hypothesized in Scheme 2.17 if the radical was formed at the β position.



Scheme 2.26: An update on proposed products if cyclisation were to occur.

One application of the work that has come out of this is that in theory it is possible to take the ynol ether, heat it to undergo a [2+2] cyclisation to form a diene via electrostatic ring opening. This diene could then undergo a Diels-Alder to yield **72**, the tricyclic core framework in Scheme 2.27, which, upon further modification could lead to cannabinol scaffold **73** in Figure 2.2. Cuthbertson[121] attempted the ene-yne metathesis, but was ultimately unable to induce a [2+2] cyclisation with neither prolonged heating nor irradiation with UV light ($\lambda = 365$ nm). The failure

of ene-yne metathesis reactions was also noted by Kozmin *et al.*[122] with ynol ether substrates.



Scheme 2.27: Hypothesized route towards the cannabinol-like scaffold, a common framework in natural products.

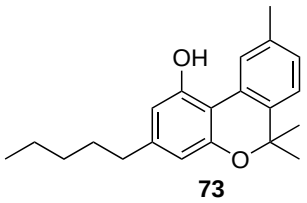
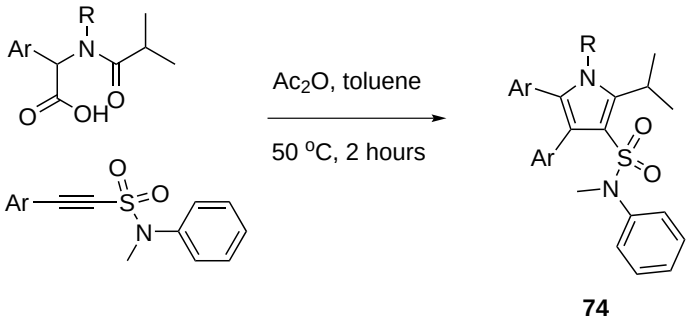


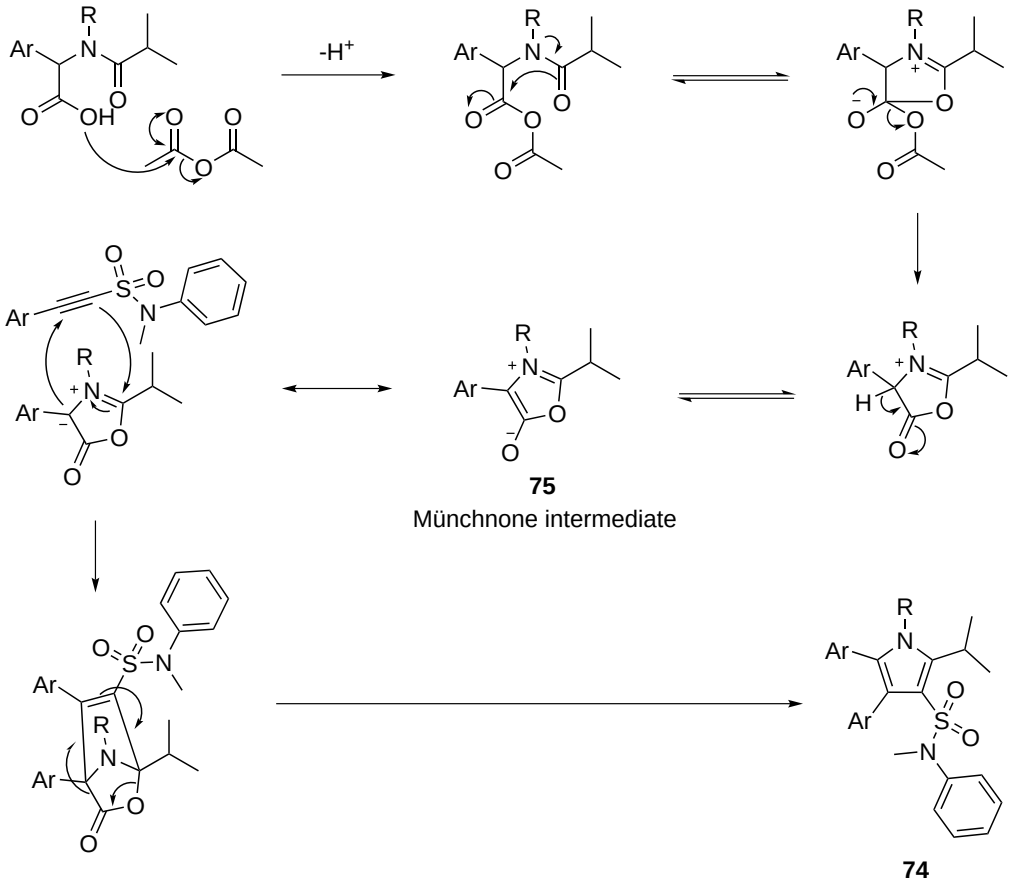
Figure 2.2: The biphenyl cannabinol framework.

2.3 Cycloaddition Reactions of Alkynyl Sulfonamides

There have only been a few reports of alkynyl sulfonamide cyclisations in the literature. One example is the synthesis of **74**, a class of pyrrole-based HMG-CoA reductase inhibitors,[89;90] as shown in Scheme 2.28.



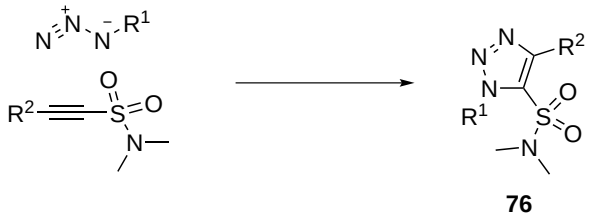
Scheme 2.28: Utilising the Münchnone reaction to form a pyrrole-based HMG-CoA reductase inhibitor.[89]



Scheme 2.29: Mechanism of the Münchnone reaction.[89]

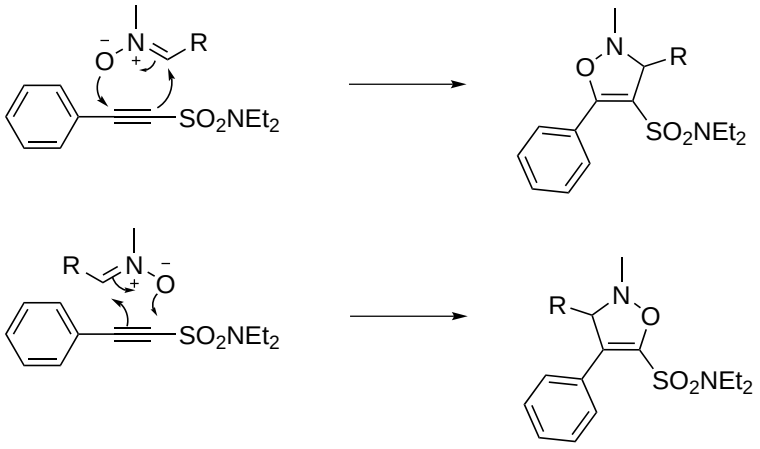
In the reaction, Münchnone intermediate **75** is generated *in situ*, followed by a [3+2] cycloaddition with an alkynyl sulfonamide and retro [4+2] reaction to give the pyrrole. The mechanism of the reaction is shown in Scheme 2.29.

The second example depicted in Scheme 2.30 is an azide-alkyne chemistry cycloaddition, which was used to form **76**, a series of 1,2,3-triazoles that could act as human leukocyte elastase inhibitors.[91]



Scheme 2.30: The Click chemistry synthesis of 1,2,3-triazoles.[91]

As there have been no other reported incidences of cyclisations involving alkynyl sulfonamides, there was interest to investigate the propensity of alkynyl sulfonamides to undergo cycloaddition reactions with compounds such as nitrones in order to generate new drug-like molecules with the motifs shown in Scheme 2.31. These could then be explored for their potential medicinal properties.



Scheme 2.31: Possible cycloaddition mechanisms of the alkynyl sulfonamide with nitrones.

When a search was repeated by making the motif more general in Figure 2.3, a result was found where R^3 is a phenyl group.[123;124] No other wider examples were

found, and no reports have been made yet of the potential medicinal properties that this motif could exhibit, indicating that this is a relatively unexplored area. With this is mind, there was interest in the group to explore the synthesis of these drug-like compounds and observe how they could behave in a cellular environment.

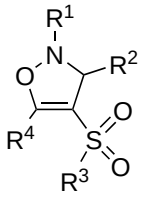
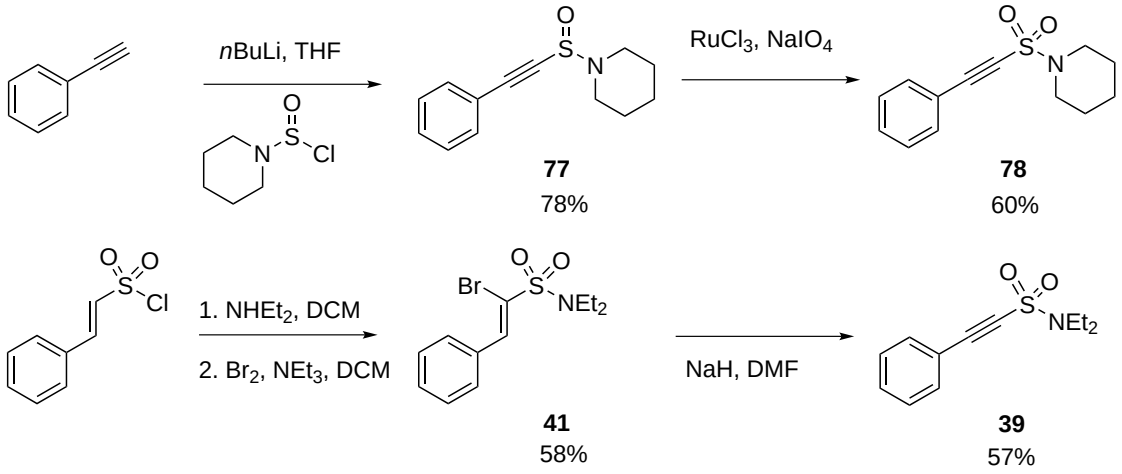


Figure 2.3: The backbone motif of the dihydroisoxazole was one of the focal points of this work, where R^3 is an amine group.

2.3.1 Synthesis of Starting Materials

Synthesis of Alkynyl Sulfonamides

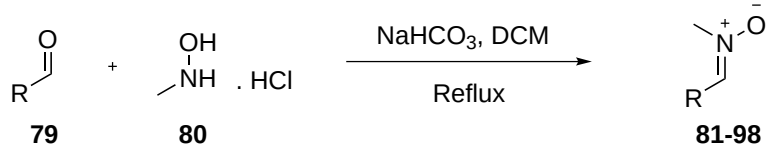


Scheme 2.32: The two routes used to synthesise the sulfonamide starting materials.

The alkynyl sulfonamides were synthesised according to standard methods developed previously within the group, as detailed in Section 1.4.2. **39** was made using the trans-β-styrene sulfonamide route in Scheme 1.21, shown again in Scheme 2.32, whilst **78** involved treating piperidine with thionyl chloride to form the electrophile. This was used to make alkynyl sulfinamide **77** before it was then oxidised to alkynyl sulfonamide **78**.

Synthesis of Nitrones

Several solvent-free methods[125;126] were attempted to synthesize nitrones on the basis that they were reported to be quicker and more environmentally benign than traditional methods. They generally involved grinding the reactants neat in a pestle and mortar with crushed molecular sieves to remove the water side product and thus drive the equilibrium towards nitrone formation in the condensation reaction. Whilst they were found to work on a small scale, the disadvantage of product loss when transferring between various pieces of equipment prompted us to turn to a more traditional method. The general procedure that was employed in Scheme 2.33 was based on a procedure by Torssell,[127] where various aldehydes **79** were condensed with N-methylhydroxylamine hydrochloride **80** under reflux in DCM with a suspension of $NaHCO_3$ for 24 hours.



79 **80** **81-98**

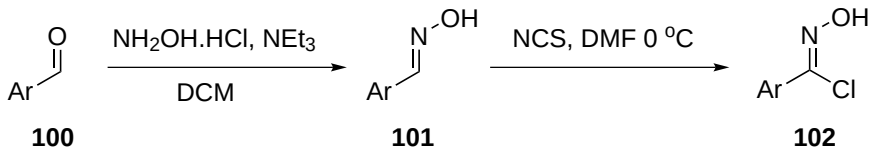
Scheme 2.33: Standard conditions were used to synthesize the nitrones.

The yields obtained were variable but generally good to excellent. No product was obtained with 3,4-dihydroxybenzaldehyde (Entry **99**) in Table 2.2. This is possibly due to the base deprotonating both hydroxy groups, which could react with the starting material and product to form unwanted polymers or the catechol acetal.

Table 2.2: Table of results for the synthesis of functionalised nitrones.[128–131]

	R	Yield (%)
81	phenyl	36
82	4-bromophenyl	95
83	4-chlorophenyl	81
84	4-fluorophenyl	66
85	4-nitrophenyl	63
86	2,5-dimethylphenyl	56
87	4-isopropylphenyl	88
88	n-heptyl	97
89	n-propyl	93
90	ethyl	89
91	naphthalen-2-yl	84
92	2,3-dichlorophenyl	84
93	2-bromophenyl	58
94	2-methoxyphenyl	85
95	1-mesityl	99
96	4-(trifluoromethyl)phenyl	79
97	4-(tert-butyl)phenyl	66
98	[1,1'-biphenyl]-4-yl	74
99	3,4-dihydroxyphenyl	-

Synthesis of Chloroximes



100 **101** **102**

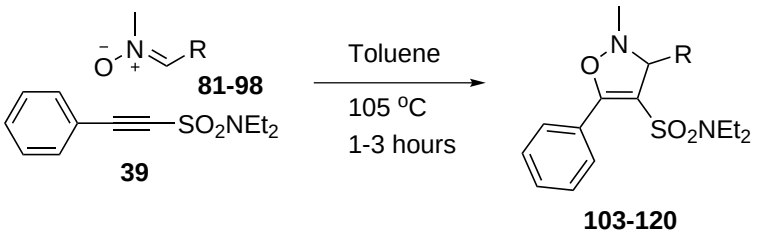
Scheme 2.34: Route towards accessing chloroximes.

Oximes **101** were synthesized according to a preparation by Zheng *et al.*[132] whereby hydroxylamine hydrochloride and triethylamine were added to a solution of aldehyde **100** in DCM and stirred overnight. Saturated sodium hydrogen carbonate was added at 0 °C to quench the reaction, and upon purification, the product was converted straight into chloroxime **102** where Ar = Ph.

The second step for the synthesis of chloroximes was adapted from a method by Liu,[133] as shown in Scheme 2.34. Attempts to purify the products by columnn chromatography led to degradation in all cases, however, literature methods indicated that after workup, the products were sufficiently pure for further use. Only

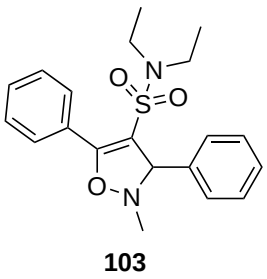
chloroxime **102**, where Ar = Ph, was successfully isolated, so it was stored in the freezer in order to minimise degradation. Other chloroximes were made and used straight away in one pot reactions without being isolated.

2.3.2 Synthesis of Dihydroisoxazoles



Scheme 2.35: Dihydroisoxazole synthesis scheme using alkynyl sulfonamide **39**.

Sulfonamide **39** was heated with two equivalents of the nitrone in toluene at 105 ^{o}C to induce the 1,3-dipolar cycloaddition reaction. This was monitored by TLC until the starting material appeared to be consumed, which usually took 1-2 hours. The reaction was monitored by LC-MS during the first time it was carried out with aryl nitrone **81** in Entry **103** of Table 2.3, which enabled the observation to be made that even after 3 hours, there was still a small amount of sulfonamide starting material left over.



103

Figure 2.4: The structure of *N*,*N*-diethyl-2-methyl-3,5-diphenyl-2,3-dihydroisoxazole-4-sulfonamide **103**.

Nevertheless, a single product was isolated, and the structure was determined by NMR analysis to match that shown in Figure 2.4. NOESY data in Figure 2.5 indicated that the H peak at δ_H5.04 showed an interaction with ortho hydrogens on

one phenyl ring at δ_H7.43-46, but not the other at δ_H7.78. HMBC showed through-bond coupling to five carbons, as can be seen in Figure 2.6. In contrast, six couplings would be expected to show up for the other regioisomer due to an additional carbon being available for three bond HMBC coupling. This is illustrated in Figure 2.7.

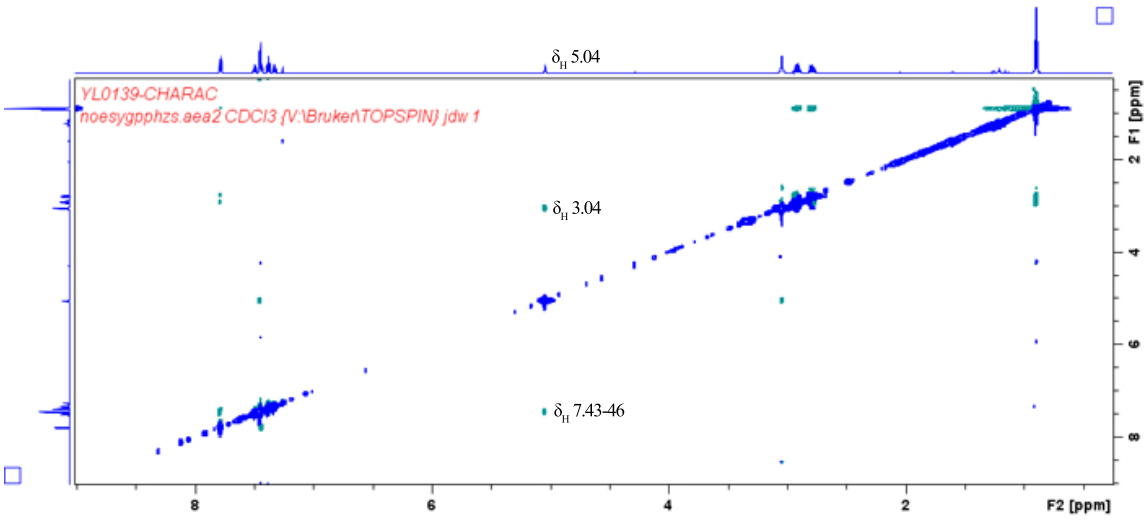


Figure 2.5: NOESY spectra for compound **103**.

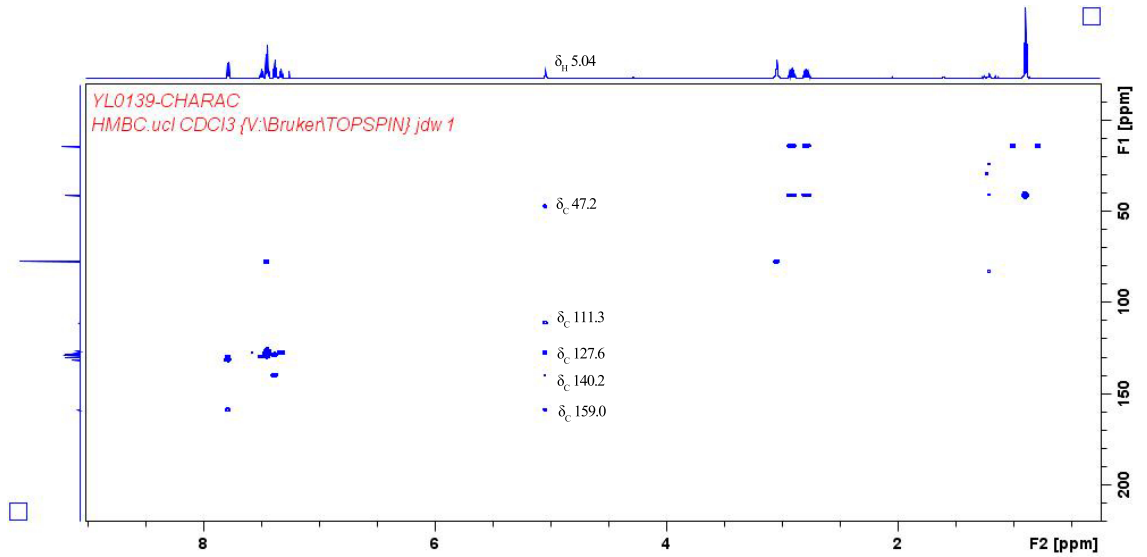


Figure 2.6: HMBC spectra for compound **103**.

The other nitrones were also reacted in a similar manner to generate a range of 2,3-dihydroisoxazoles, as can be seen in Table 2.3. The yields obtained were generally good, with exceptions being compounds **106**, **110**, **111**, and **112**.

Only one product was observed in all cases by crude NMR, which led the group to believe that one mechanism must be favoured, as indicated in Scheme 2.36. This

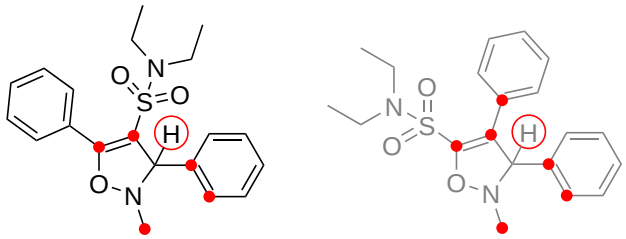
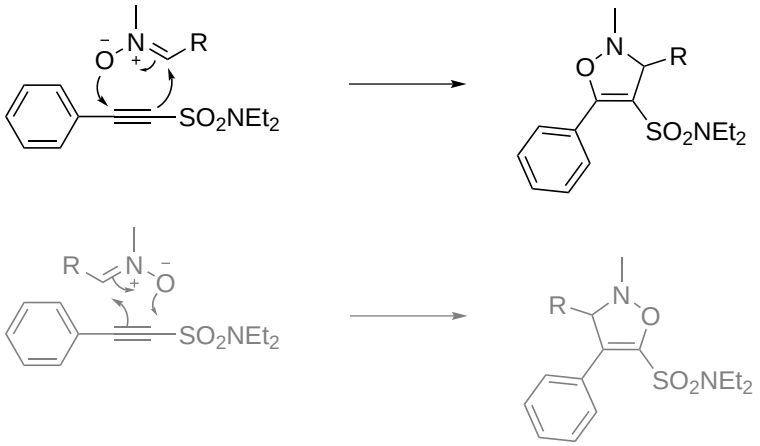


Figure 2.7: HMBC couplings that would occur for regioisomers of compound **103**.

was presumably due to steric clashing between the phenyl ring on the sulfonamide and the aryl group on the nitrone, and electronic repulsion between the oxygen lone pairs on the sulfonamide and the nitrone. In addition, the largest HOMO co-efficient of the nitrone would lie on the oxygen atom, which would interact favourably with the largest LUMO co-efficient of the electron-poor sulfonamide. This lies on the carbon atom adjacent to the phenyl ring.

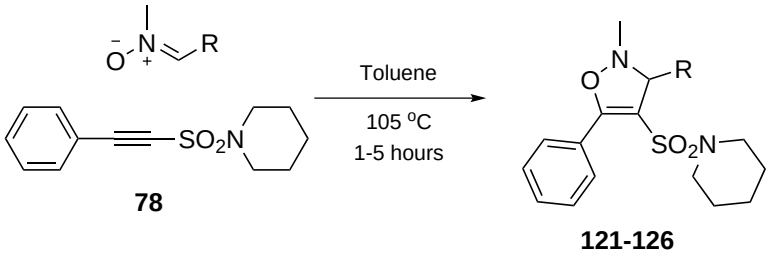


Scheme 2.36: The favoured cycloaddition mechanism of the alkynyl sulfonamide with a nitrone.

Table 2.3: Table of results for the synthesis of 2,3-dihydroisoxazoles by reacting alkynyl sulfonamide **39** with a selection of nitrones.

	R	Yield (%)
103	phenyl	60
104	4-bromophenyl	67
105	4-chlorophenyl	70
106	4-fluorophenyl	25
107	4-nitrophenyl	70
108	2,5-dimethylphenyl	57
109	4-isopropylphenyl	63
110	n-heptyl	48
111	n-propyl	20
112	ethyl	11
113	naphthalen-2-yl	70
114	2,3-dichlorophenyl	62
115	2-bromophenyl	67
116	2-methoxyphenyl	50
117	1-mesityl	65
118	4-(trifluoromethyl)phenyl	88
119	4-(tert-butyl)phenyl	80
120	[1,1'-biphenyl]-4-yl	88

Alkynyl sulfonamide **78** was also used to synthesise a small array of novel 2,3-dihydroisoxazoles, as shown in Table 2.4 and Scheme 2.37. Preliminary biological screening results in Section 2.3.4 indicated that larger compounds seemed to be better at inhibiting ATG4B activity, so nitrones with large R groups were selected when considering further dihydroisoxazoles to synthesise.



Scheme 2.37: Dihydroisoxazole synthesis scheme using alkynyl sulfonamide **78**.

Table 2.4: Table of results for the synthesis of 2,3-dihydroisoxazoles by reacting alkynyl sulfonamide **78** with a selection of bulky nitrones.

	R	Yield (%)
121	phenyl	66
122	4-isopropylphenyl	84
123	naphthalen-2-yl	83
124	4-(tert-butyl)phenyl	68
125	[1,1'-biphenyl]-4-yl	80
126	1-mesityl	53

2.3.3 Synthesis of Isoxazoles

Isoxazoles are five-membered aromatic heterocycles with the nitrogen and oxygen atoms adjacent to each other. First synthesized in 1884 by Ceresole, the chemistry of isoxazoles was popularised by Claisen shortly after.[134] Since then, the isoxazole motif has gained importance over the years, and is now found in many drugs as well as products for everyday use. A few select examples can be seen in Figure 2.8. As well as having medicinal applications, isoxazoles are also used as a tool in synthetic chemistry as they function as masked 1,3-dicarbonyl equivalents, which can be revealed under mild conditions.

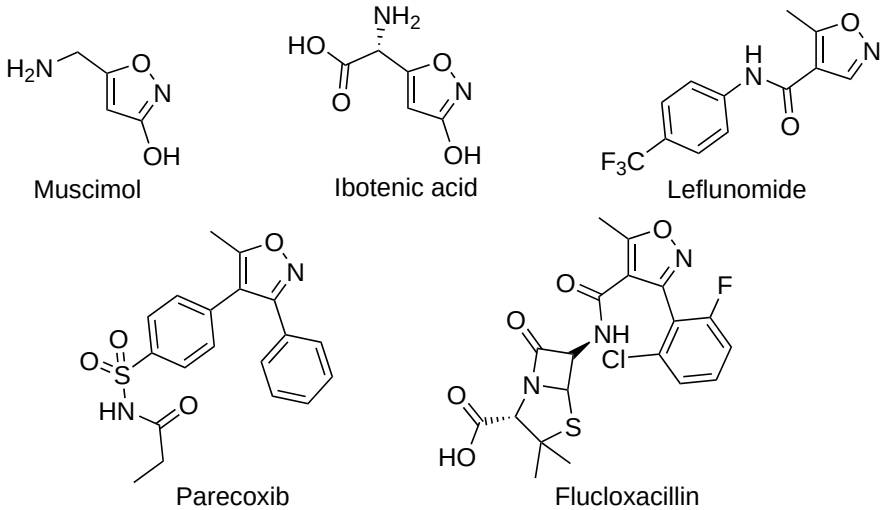


Figure 2.8: Select examples of biologically active isoxazoles, with uses ranging from immunosuppressants, to antibiotics, to neurotoxins amongst others.

There are several different routes towards the synthesis of isoxazoles. The main methods are through cycloadditions, cycloisomerizations, and condensations, as

summarized in Figure 2.9. These methods, along with other routes such as rearrangements and radical intermediates, can be explored in more detail through specialist reviews.[135–137]

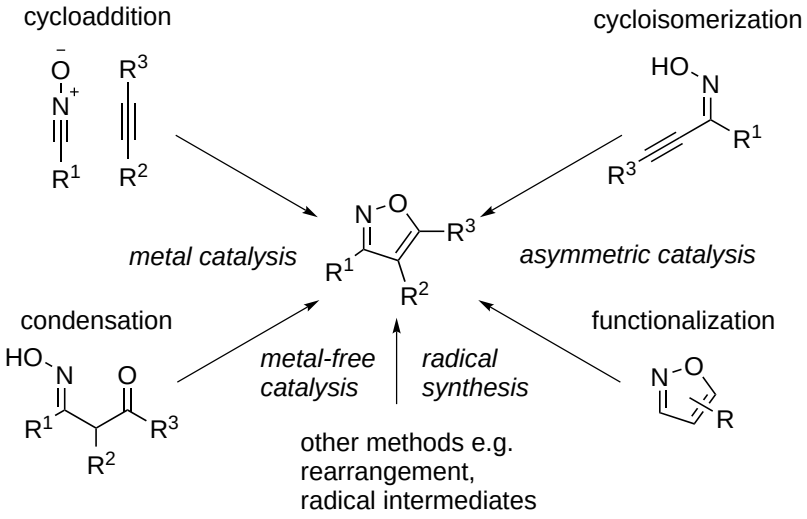
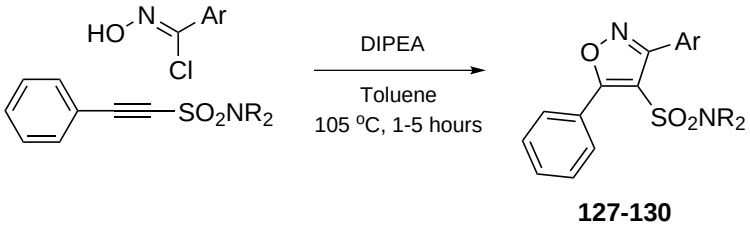


Figure 2.9: Summary of the main methods for the synthesis of isoxazoles.[135]

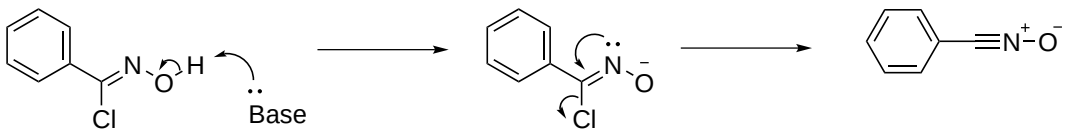
Following on from the synthesis of dihydroisoxazoles, the group wondered about the propensity of alkynyl sulfonamides to form isoxazoles. Synthesis of isoxazoles turned out to be not as straightforward as for dihydroisoxazoles.



Scheme 2.38: Conditions for the formation of isoxazoles.

Initially, a solution of 1.2 equivalents of chloroxime (Ar = Ph), 1 equivalent of alkynyl sulfonamide (R = Et) and 5 equivalents of triethylamine in DMF were stirred under argon. It was thought that the polar solvent would stabilise the nitrile oxide, which was formed *in situ*. The mechanism for this is depicted in Scheme 2.39.

In this instance, no products were observed and the reaction was terminated after 60 hours. Switching the solvent to toluene but maintaining the same conditions led to the formation of the desired product (Scheme 2.38), however TLC analysis



Scheme 2.39: Mechanism for the synthesis of the nitrile oxide.

indicated that whilst the chloroxime had been fully consumed, some alkynyl sulfonamide starting material was still present. Upon purification, the isoxazole product was isolated in 60%, and it was found that the ratio of isolated product to isolated starting material was 2.7:1. Heating the reaction to 60 °C for 4 hours led to a ratio of product to starting material of 1:3.5, but if the reaction was left to stir for 3 hours at 80 °C and left overnight at room temperature, then a yield of 51% was obtained. When the temperature was increased to 110 °C for 1 hour, the yield decreased to 45%. Moving forwards, it was decided that the best conditions to balance the yield versus reaction time would be to heat the reaction under reflux for 1-2 hours. It wasn't possible to fully eliminate dimersation of the nitrile oxide, which would explain why the yields were lower than for the synthesis of 2,3-dihydroisoxazoles.

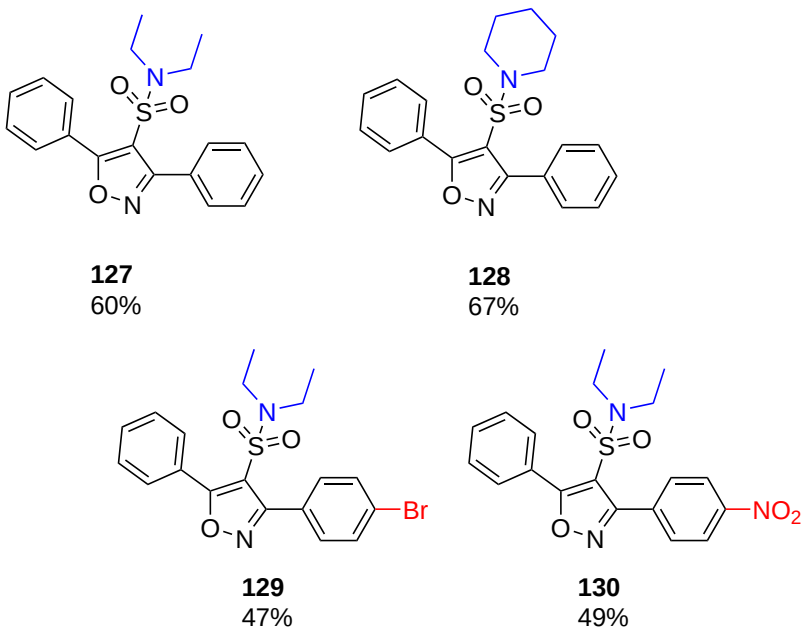
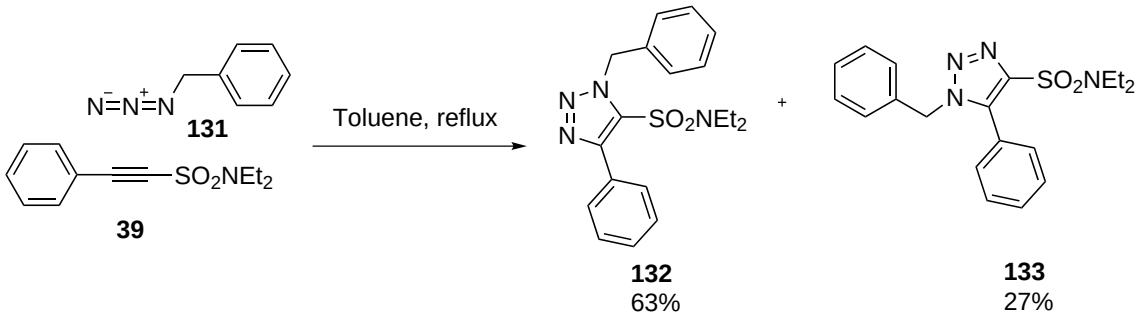


Figure 2.10: A small range of isoxazole products was synthesised through the cycloaddition of alkynyl sulfonamides with nitrile oxides.

Figure 2.10 shows the range of isoxazoles that were synthesized. Here, progress was limited by the difficulty in forming and isolating chloroximes, so for isoxazoles **129** and **130**, the chloroximes were made and used straight away in one pot reactions. Once again, it was surprising to find that only one regioisomer was observed in all cases. This was in contrast to a scoping reaction carried out earlier when benzyl azide **131** was reacted with alkynyl sulfonamide **39** in the absence of any catalysts, to obtain both regioisomers as shown in Scheme 2.40.



Scheme 2.40: Both regioisomers were observed in a ratio of 2:1, with the favoured regioisomer forming in a higher yield presumably due to minimal steric clashing of phenyl groups.

The presence of only one regioisomer in the synthesis of isoxazoles is presumably due to similar reasons as discussed for the dihydroisoxazoles. For example, for compound **130**, the NOESY spectra in Figure 2.11 shows interactions between the hydrogens on the sulfonamide and each ortho hydrogen on both phenyl rings. In the other regioisomer, one would only expect the sulfonamide hydrogens to interact with one phenyl ring due to proximity.

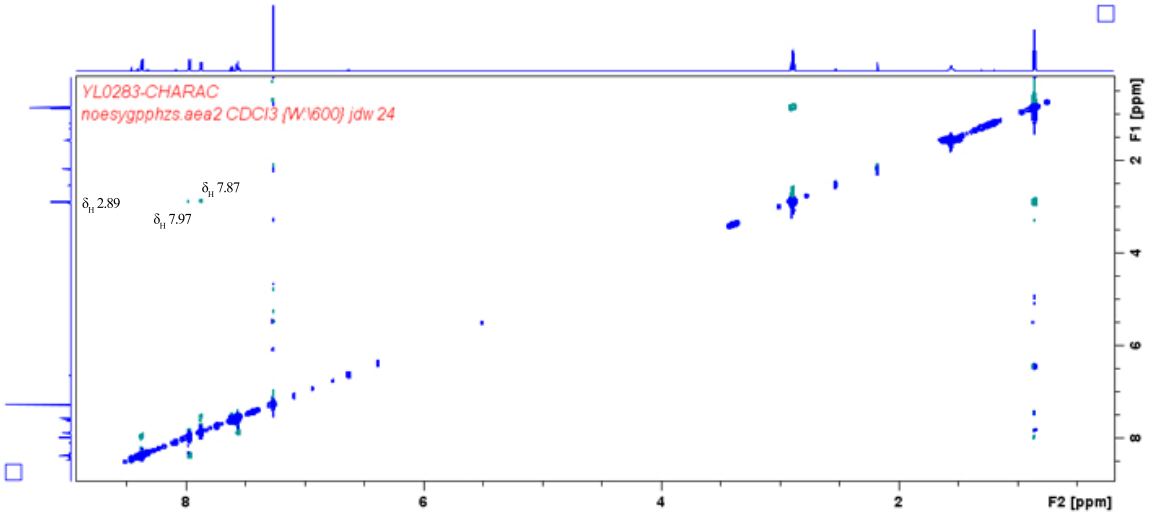
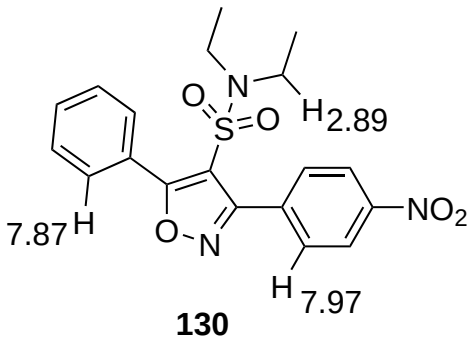


Figure 2.11: NOESY spectra for compound **130**.



130

Figure 2.12: Hydrogen shifts of interest for compound **130** in relation to NOESY spectra in Figure 2.11.

2.3.4 Biological Screening of Sulfonamides

During this work, the group began a collaboration with Pengo and Ketteler in the field of autophagy (Section 1.3.1), as they expressed interest in these drug-like compounds. Using Ketteler's assay, which was previously devised in his group,[138] work was carried out to screen an array of these compounds. Pleasingly, initial screens of the dihydroisoxazoles indicated that several compounds displayed positive activity *in vitro*.

Ketteler's assay takes advantage of gaussia luciferase, a luminescent reporter enzyme from the marine copepod *Gaussia princeps*, which is secreted from cells through signal peptide mediated methods. By deleting the N-terminus of this enzyme (dNGLUC), the protein can be appended to LC3. When ATG4B cleaves the LC3 chain, the gaussia luciferase is released, exits the cell, and any liberated luminescence can be measured in the supernatant. This is illustrated in Figure 2.13.

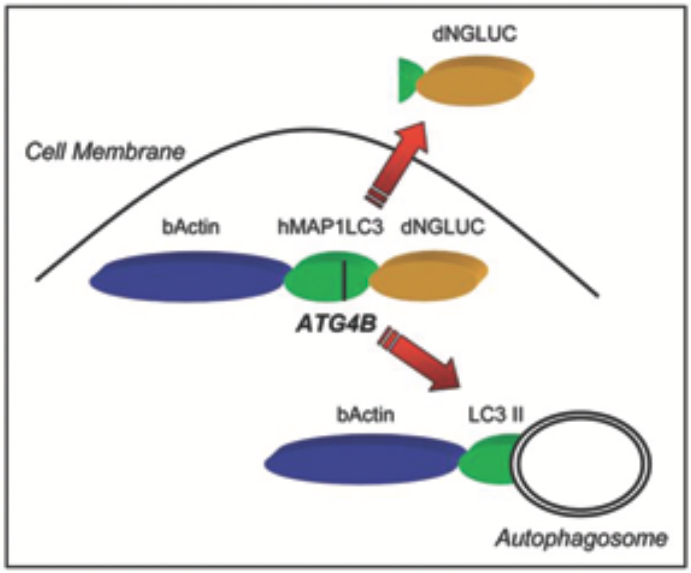


Figure 2.13: The N-terminus of gaussia luciferase is deleted and fused to LC3. Upon proteolytic cleavage of LC3 by ATG4B, the dNGLUC fragment is released and transported across the cellular membrane. Image from Ketteler.[138]

As the amount of luciferase released in the supernatant correlates directly with cellular ATG4B activity, this method is a very simple quantitative assay. In addition, this method allows for non-invasive measurement of protein activity, and for measurements to be taken at different time points.

HeLa cells with gaussia luciferase fused to LC3 were grown in advance in petri dishes, before they were washed with a trypsin and EDTA medium to cleave them from the surfaces. After counting a sample of the cells, the trypsin and EDTA medium was removed and replaced with fresh medium. These cells were then transferred by pipette into wells. With DMSO as a control, one 2,3-dihydroisoxazole was added per well, exposing the HeLa cells to these compounds at 10μM for 48 hours at 37 ^{o}C. Each sample was tested three times. After 48 hours, a sample of the supernatant was harvested and mixed with coelenterazine, which is a light-emitting molecule and also the substrate of gaussia luciferase, prior to reading for luminescence.

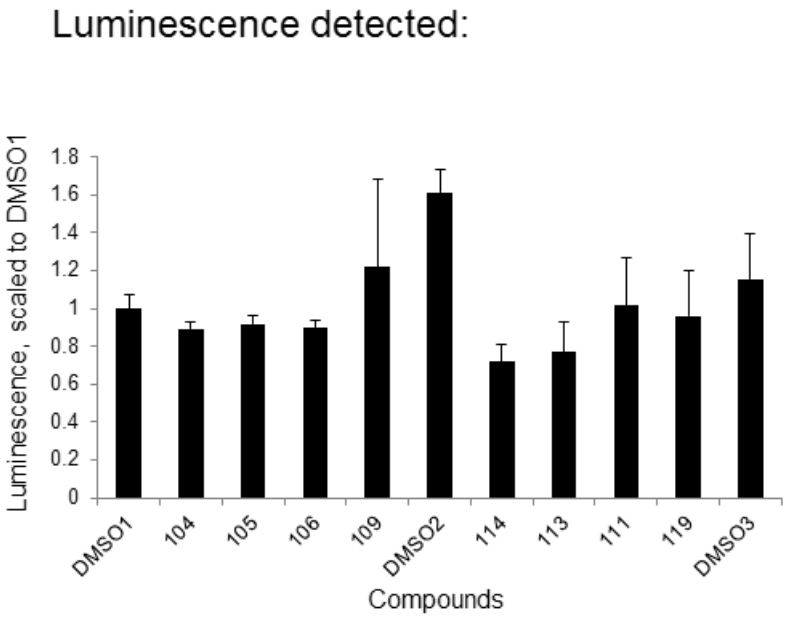


Figure 2.14: First set of results after HeLa cells were subject to 10μM concentrations of 2,3-dihydroisoxazoles for 48 hours. Assay was run on 09-May-14, by Pengo and Luo, results unpublished.

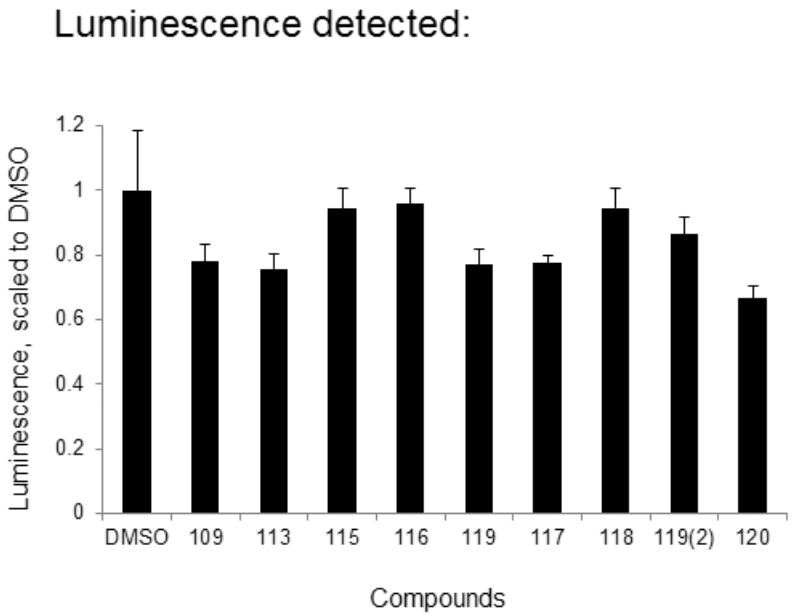


Figure 2.15: Second set of results after HeLa cells were subject to 10μM concentrations of 2,3-dihydroisoxazoles for 48 hours. Assay was run on 25-Jun-14, by Pengo and Luo, results unpublished.

Figure 2.14 shows the amount of luminescence detected after a small subset of samples were tested. The luminescence detected directly correlates with the activity of ATG4B. Unfortunately these results were inconclusive as variation can be seen across the plate at each of the three DMSO controls. This could have been due to temperature fluctuations within the apparatus used to incubate the cells. In order to accommodate for this, compounds were then placed left to right across the plate and then vice versa for the bottom half of the plate. The results appeared to be more promising (Figure 2.15), so the experiment was repeated and a cell counting kit was applied to test for how viable the cells were after being exposed to the 2,3-dihydroisoxazoles. These results can be observed in Figure 2.16 and Figure 2.17.

A number of compounds showed inhibition of ATG4B activity, with lower amounts of luminescence detected than for the control (**119**, **120**, **126**, **122**, **109** and **113**). When the cell counting kit was applied, however, **109** and **113** showed lower cell viability so conclusions could not be made on whether the lower luminescence was due to ATG4B inhibition or the cells themselves dying. With this in mind, **119** and

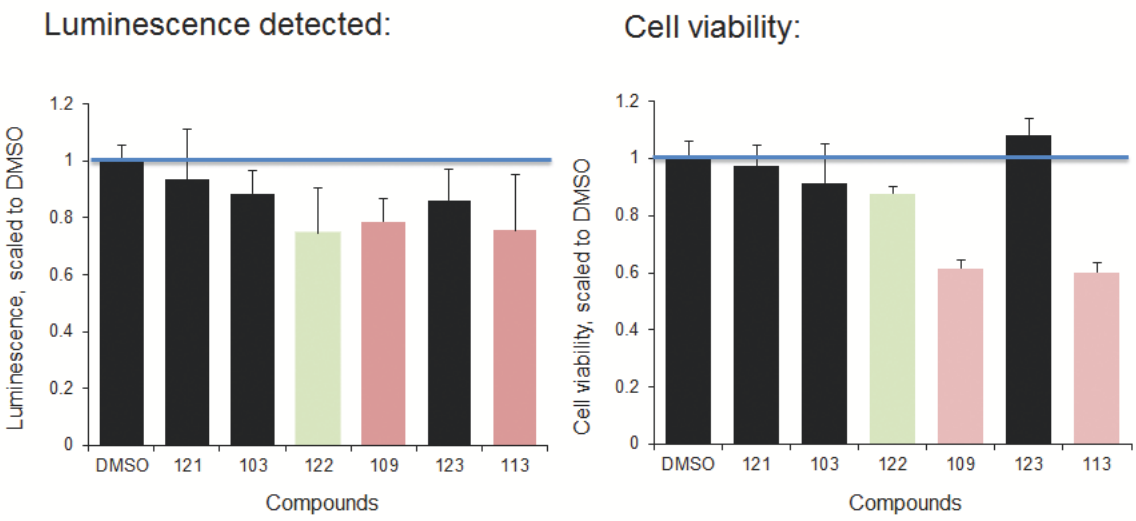


Figure 2.16: Plate 1 of the third set of results after HeLa cells were subject to 10μM concentrations of 2,3-dihydroisoxazoles for 48 hours. Assay was run on 06-Aug-14, by Pengo and Luo, results unpublished.

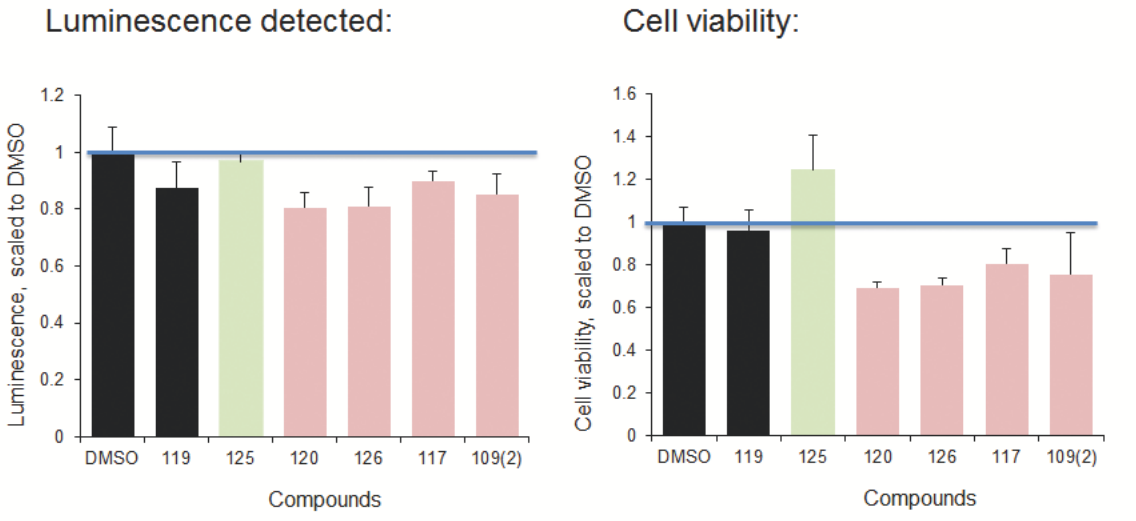


Figure 2.17: Plate 2 of the third set of results after HeLa cells were subject to 10μM concentrations of 2,3-dihydroisoxazoles for 48 hours. Assay was run on 06-Aug-14, by Pengo and Luo, results unpublished.

122 are very interesting as they do not seem to affect cell viability but decrease the reporter cleavage whilst the cell viability of **125** was strikingly high compared to DMSO.

All of these compounds are lipophilic and have large side groups, which suggest that steric factors could play a factor in inhibition or promiscuous binding.

The collaborator proposed increasing the sensitivity of the assay by transfecting the HeLa cells with an ATG4B construct, so that the enzyme would be over expressed in the cell. This would increase the baseline cleavage of the reporter, and thus increase the range of inhibition that could be observed. Previous experiments indicated that this method would work well, and he hypothesized that viable readings would be available after 24 hours.

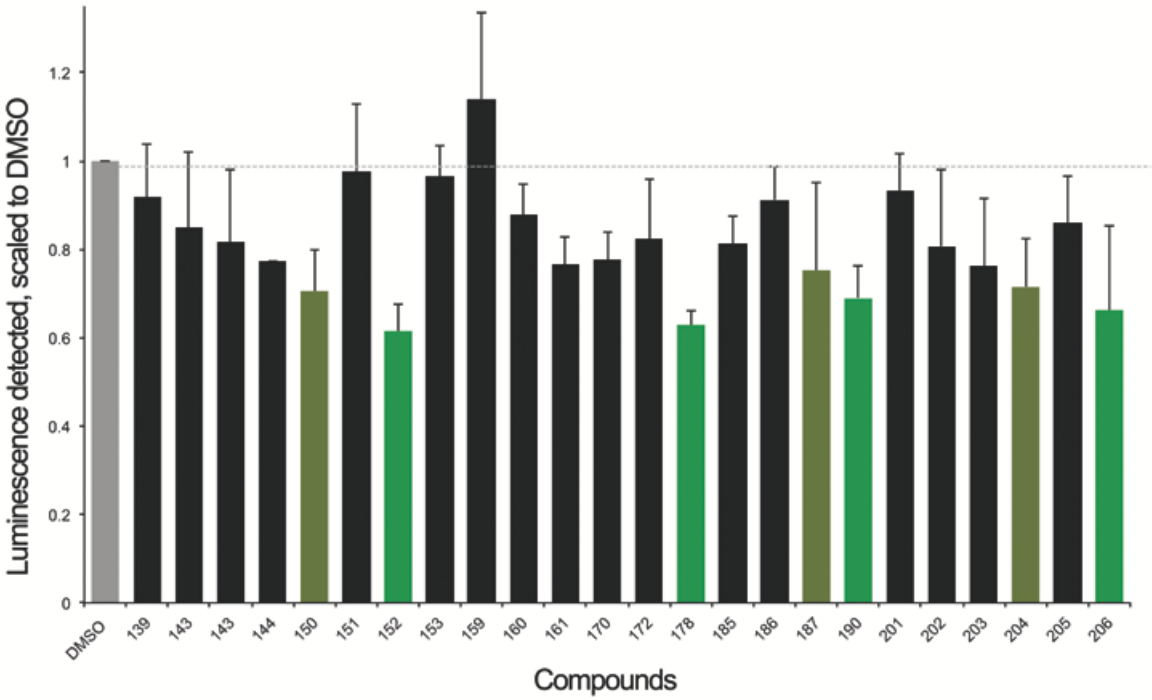


Figure 2.18: New results from the improved assay. Pengo 2014, results unpublished.

Figure 2.18 shows the results from this modified assay. Having viable results at 24 hours was beneficial as this decreases the any non-specific effects due to cell death or proliferation. The media was also changed when treating the cells so to better appreciate the extent of inhibition.

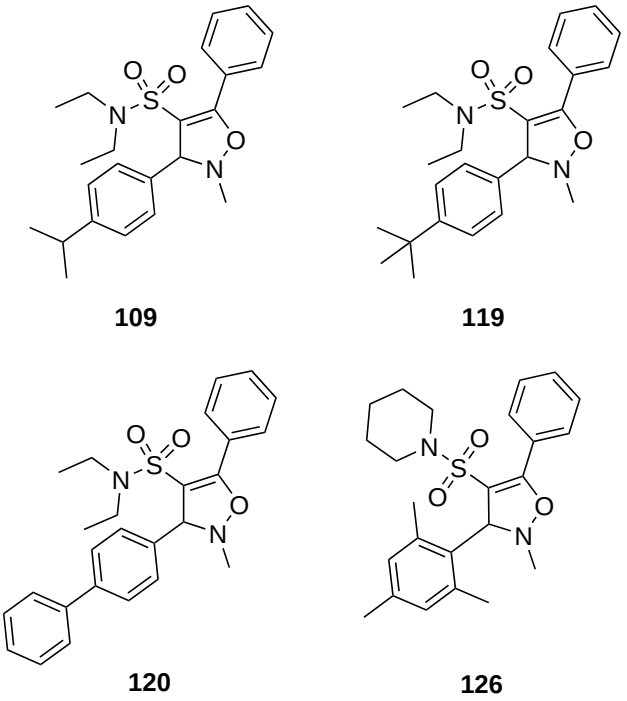


Figure 2.19: The compounds that showed good propensity for further investigation from the improved assay.

Some of the compounds still showed high variability but in any case, combining all of the results so far indicate that **109** (152/178 in Figure 2.8), **119** (187), **120** (190) and **126** (206) seem to be the best at inhibiting ATG4B at 10μM. The structures of the compounds are shown in Figure 2.19. Structure-activity relationships were beyond the scope of this work but should be investigated to build upon these initial findings.

2.3.5 An Application of Dihydroisoxazoles

Previous work in the group on oxazole synthesis[33] (see Scheme 1.8) and isoxazole synthesis (for a brief summary of current synthetic routes see Section 2.3.3) inspired the development of an alternative route to isoxazole synthesis via a 4,5-dihydroisoxazole. This route can be seen in Figure 2.20.

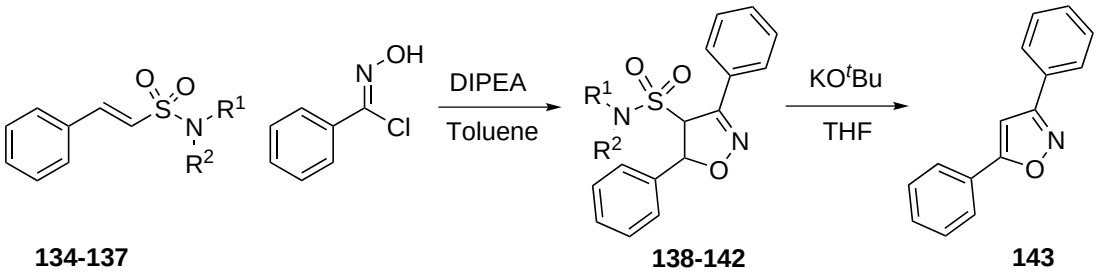


Figure 2.20: The alternate route towards isoxazole synthesis.

Synthesis of Alkenyl Sulfonamides

A small range of alkenyl sulfonamides were synthesized by reacting trans-β-styrene sulfonyl chloride with various amines to displace the chloride. These products were obtained in good yields and are illustrated in Figure 2.21.

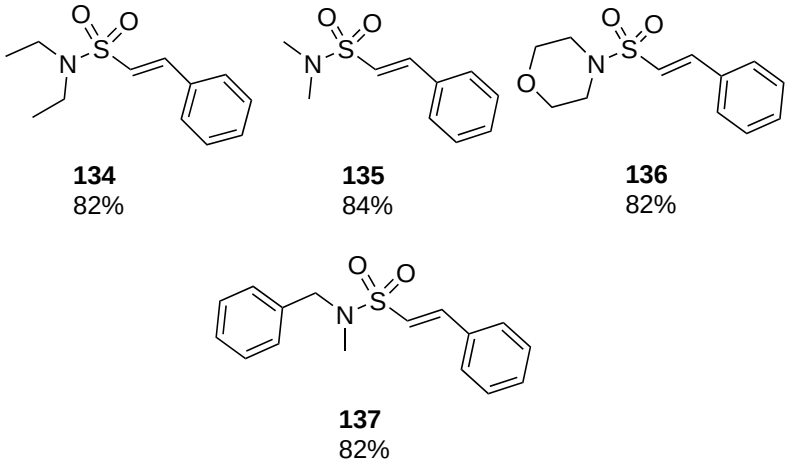


Figure 2.21: The alkenyl sulfonamides used in this work.

Synthesis of Dihydroisoxazoles

For the synthesis of 4,5-dihydroisoxazole **138**, ($R_1 = R_2 = Et$), initial screening results indicated that toluene was the best solvent, and that the reaction was favoured by longer times and greater equivalents of base.

Table 2.5: Table of results for the optimisation of 4,5-dihydroisoxazole synthesis.

	Chloroxime	Base	Solvent	Temperature (°C)	Time (hours)	Yield (%)
1	1.5 eq.	1.5 eq.	Toluene	110	22	23
2	3.0 eq.	6.0 eq.	Toluene	110	48	37
3	1.5 eq.	3.0 eq.	THF	80	24	6
4	5.0 eq.	10.0 eq.	Toluene	110	48	60*
5	5.0 eq.	10.0 eq.	Toluene	180	5	30

*The solvent was heated for 4 hours at 180 °C.

A small range of 4,5-dihydroisoxazoles were synthesised, as can be seen in Figure 2.22. Due to time constraints and the difficulty in chloroxime synthesis, only the amine groups on the alkenyl sulfomanide were able to be varied. Future work could look at expanding the scope of this reaction by exploring the possibility of varying other groups on the starting materials.

Elimination Reaction

Pleasingly, when compound **138** was treated with potassium *tert*-butoxide in DMF at room temperature, a small amount of isoxazole **143** (19%) was observed after 6 days. It was found that switching the solvent to THF, applying heat and increasing the amount of base gave improved results, and that a yield of 74% was obtained with 3.5 equivalents of potassium *tert*-butoxide in anhydrous THF at 60 °C for 1 hour. **139**, **140** and **141** gave the isoxazoles in 41%, 54%, and 32% respectively.

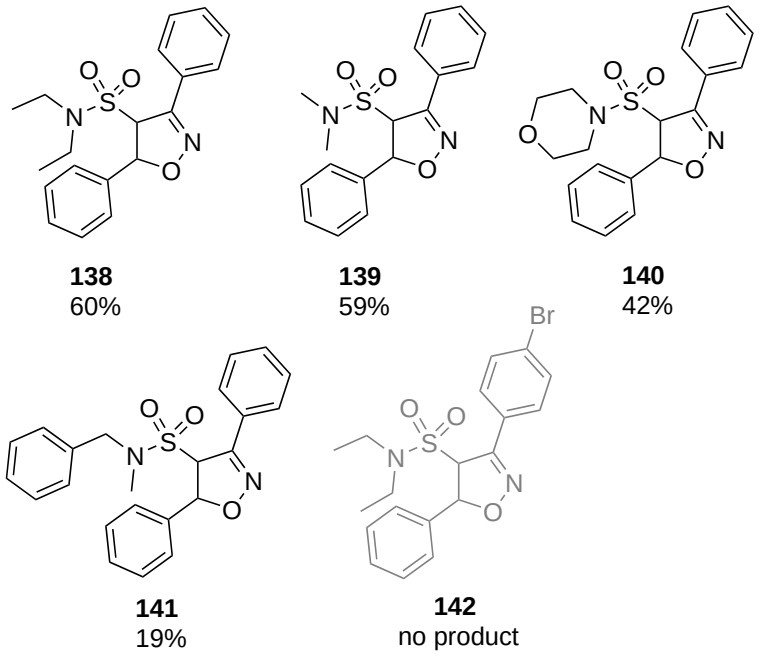


Figure 2.22: A range of dihydroisoxazoles was synthesized in preparation to undergo the elimination reaction to form isoxazole **143**.

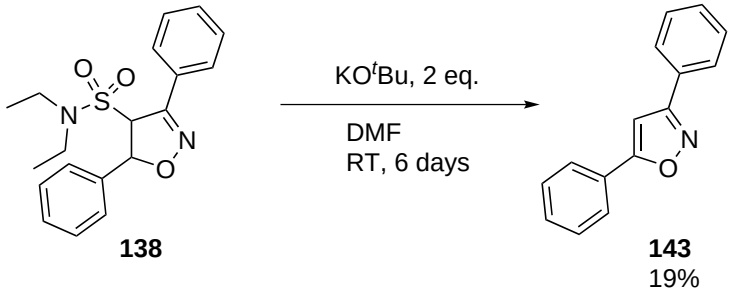


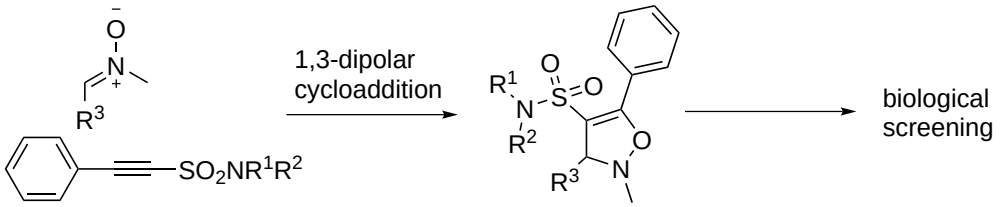
Figure 2.23: Initial conditions for the elimination of sulfonamide from a dihydroisoxazole before the reaction was optimised.

Chapter 3

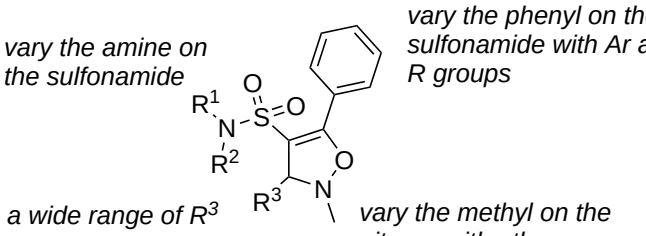
Conclusions and Further Work

In conclusion, the main focus of this work was to investigate the scope of alkynyl sulfonamides in the synthesis of heterocycles. A substantial number of novel "drug-like" 2,3- and 4,5-dihydroisoxazoles were synthesized by reacting alkynyl sulfonamides with nitrones and alkenyl sulfonamides with nitrile oxides respectively in a 1,3-dipolar cycloaddition to form one regioisomer in good yields (Figure 3.1 and Figure 3.3).

Some of the 2,3-dihydroisoxazoles displayed mild biological activity *in vitro* on the ATG4B enzyme. To build on the work carried out in the biological screening of 2,3-dihydroisoxazoles, it would be useful to synthesize a sulfonamide peptidomimetic to mirror the amino acids (threonine-phenylalanine-glycine) surrounding the cleaved glycine. This is the region where the LC3 substrate is cleaved by ATG4B, and as it is very conserved, a peptidomimetic could increase the specificity/potency of the substrate, which should allow it to be administered at lower doses. Computational modelling of the enzyme active site and synthesized substrate would also contribute towards further understanding of structure-activity relationships which could direct synthetic efforts towards a particular pathway.



Increase scope of reaction and measure reaction rates:

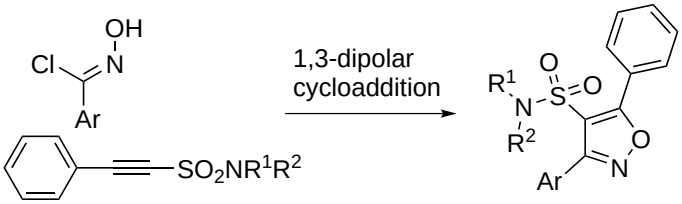


Carry out computational modelling of the reaction mechanism

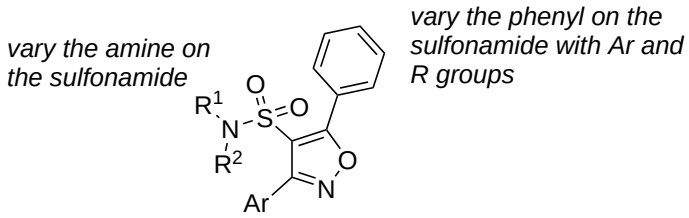
Assess whether the sulfonamide group can assist in cross-coupling

Explore further biological modelling and peptidomimetic investigations

Figure 3.1: Further work required to investigate the full scope for 2,3-dihydroisoxazole synthesis. It would be useful to look at how different electron donating and electron withdrawing substituents could affect the reaction rates.



Increase scope of reaction and measure reaction rates:



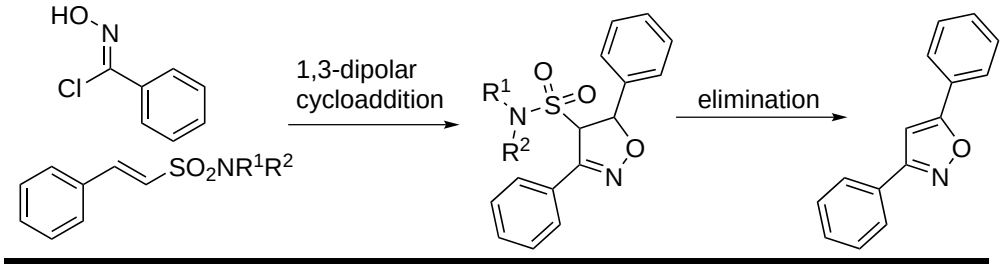
Carry out computational modelling of the reaction mechanism

Carry out biological screening of isoxazoles

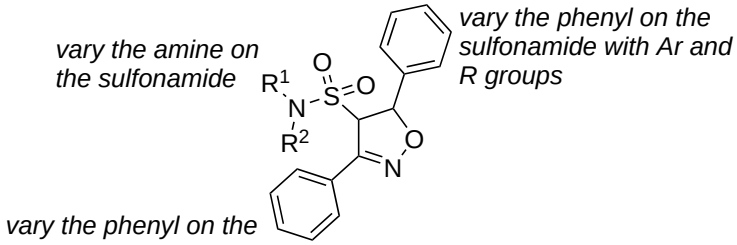
Assess whether the sulfonamide group can assist in cross-coupling

Figure 3.2: Diagram showing the work that was carried out on isoxazole synthesis and further work required to investigate the full scope of the reaction.

It was shown that isoxazoles can be synthesized from 1,3-dipolar reactions between nitrile oxides and alknyl sulfonamides, as can be seen in Figure 3.2. Further investigations on 4,5-dihydroisoxazoles led to the development of an alternate route for isoxazole synthesis. This is highlighted in Figure 3.3.



Increase scope of reaction and measure reaction rates:



Carry out computational modelling of the reaction mechanism for 4,5-dihydroisoxazole synthesis

Assess whether the sulfonamide group in the 4,5-dihydroisoxazole can assist in cross-coupling

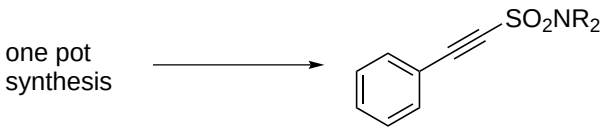
Measure rate of elimination for different sulfonamides

Change the leaving group and assess feasibility of synthetic route

Figure 3.3: Diagram showing the route to 4,5-dihydroisoxazole synthesis and elimination to form isoxazoles. It would be useful to look at how different electron donating and electron withdrawing substituents could affect the reaction rates.

It would be desirable to expand on the range of both 2,3- and 4,5-dihydroisoxazoles by varying the sulfonamide and R groups, and look at alternate methods of generating the nitrile oxide. An expansion on the range of 4,5-dihydroisoxazoles would enable reactivity trends to be made in the elimination reaction to isoxazole formation.

Finally, this project also contributed towards the understanding of the addition-elimination reaction of alkynyl sulfonamides to form ynol ethers, and explored routes towards a one pot synthesis of alkynyl sulfonamides, which was achieved but un-



Further optimisation required to reduce side product formation and increase yields
Explore scaling up of this reaction
Explore expanding the scope of this reaction

Figure 3.4: Whilst success was achieved with the one pot synthesis of alkynyl sulfonamides, yields were low and the reaction turned out to be too difficult to scale up.

fortunately proved to be largely unscalable. However, the results from this line of work led to the development of other analogues that were also able to undergo the same transformation into ynol ethers.

Chapter 4

Experimental

4.1 General Remarks

All reactions were carried out at atmospheric pressure, in flame-dried glassware under an atmosphere of argon unless otherwise stated. All chemicals, reagents and solvents for the synthesis of the compounds in this work were analytical grade, purchased from commercial sources and used without further purification unless otherwise specified. Solvents were purified and dried by literature methods where necessary. Flash column chromatography was performed on normal phase silica gel (Merck Kieselgel 60, 0.040-0.063 mm) and sand. Thin layer chromatography (TLC) was carried out on aluminium plates pre-coated with silica gel (Silica gel 60 F_{254}). Compounds were visualised by UV light (254 nm) and chemical stain (potassium permanganate, $KMnO_4$) followed by heating. Solvent removal *in vacuo* refers to Büchi rotary evaporation between 17 ^{o}C and 60 ^{o}C, at approximately 10 mmHg unless otherwise stated. Room temperature is defined as 19–23 ^{o}C.

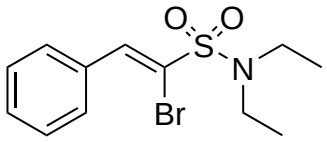
^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker AMX600 MHz spectrometer, operating at ambient temperature. TMS and $CDCl_3$ were used as internal standards and all chemical shift values are given in parts per million (δ), referenced to the residual proton impurity of the deuterated solvent. Values of the coupling constant J are given in Hertz (Hz) to one decimal place. The following abbreviations in brackets are used for the description of ^{1}H NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint.), sextet (sext.), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), doublet of doublet of doublets (ddd) and multiplet (m) where overlap or complex coupling of signals makes definitive descriptions of peaks difficult. The symbol * is used to denote apparent descrip-

tions, where finer splitting has not been fully resolved. Attempts have been made to assign ^{13}C NMR spectra as accurately as possible, but in instances where carbons have not been assigned, (q) denotes a quaternary carbon. Mass spectra were measured on either a VG70-SE or a Thermo Finnigan MAT 900 XP spectrometer operating in EI and CI mode. ESI spectra were measured on a Waters LCT premier XE LC-TOF mass spectrometer. Infrared spectra were measured on a FT-IR Perkin Elmer Spectrum 100, operating in ATR mode. Melting points were measured using Gallenkamp apparatus and are uncorrected.

4.2 Experimental Procedures

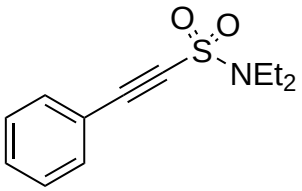
Method A for the synthesis of
***N*,*N*-Diethyl-2-phenylethyne-1-sulfonamide 39**

1-Bromo-*N*,*N*-diethyl-2-phenylethenesulfonamide 41



Trans-β-styrenesulfonyl chloride (2.00 g, 9.9 mmol, 1.0 eq) was dissolved in DCM (50 ml) and stirred to form a brown solution. Diethylamine (2.1 ml, 19.8 mmol, 2.0 eq) in DCM (50 ml) was added slowly over 2 minutes at 0 ^{o}C, before the mixture was warmed to room temperature and stirred for 30 minutes, becoming a pale yellow colour. The reaction was monitored by TLC and upon consumption of the starting material, was washed with 2M HCl (2x 50 ml) and brine (50 ml). Br_2 (5 ml, 84.6 mmol) was added as droplets to the organic phase at room temperature, and the reaction was left to stir overnight. Once TLC indicated that the sulfonamide intermediate had been fully consumed, $Na_2S_2O_3$ (50 ml) was added slowly until the mixture became a pale yellow colour. This biphasic mixture was dissolved in DCM, separated and washed with brine, dried with $MgSO_4$, and reduced to give the dibromo-intermediate as a yellow solid, which was dissolved in DCM (100 ml). The solution was cooled in an ice bath, charged with triethylamine (2 ml) and allowed to warm to room temperature before the reaction was washed with 1M HCl (50 ml) and brine (50 ml). The organic layer was separated, dried with $MgSO_4$ and reduced to give a golden solid that was purified by column chromatography (0-10 % ether in petroleum ether), to afford the title compound as a colourless oil, (1.35 g, 58 %); ν_{max} (film)/cm^{-1} 3059, 2935, 2870, 1695, 1496, 1435, 1389, 1258; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.04 (1H, s, C*H*=C), 7.77-7.75 (2H, m, Ar-H), 7.45-7.43 (3H, m, Ar-H), 3.42 (4H, q, J = 7.2 Hz, N(CH_2CH$_3$)$_2$), 1.24 (6H, t, J = 7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 137.7 (*C*-C=C), 132.5 (Ar-C), 130.5 (Ar-C), 129.9 (Ar-C), 128.7 (*C*=CBr), 119.9 (*C*-Br), 43.1 (N(*C*H$_2$CH$_3$)$_2$), 14.5 (N(CH$_2$*C*H$_3$)$_2$); HRMS (CI) calc'd for $C_{12}H_{18}NO_2S$ (M+H$^+$) 240.1058, found 240.1052. Data in agreement with literature values.[139]

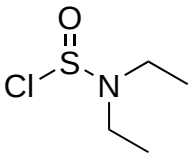
***N*,*N*-Diethyl-2-phenylethyne-1-sulfonamide 39**



A flame-dried flask was charged with compound **41** (1.27 g, 3.98 mmol, 1.0 eq) in dry DMF (6 ml) under argon before it was cooled to 0 ^{o}C. Sodium hydride (0.23 g, 5.75 mmol, 1.4 eq) was added slowly, and the mixture was left to stir for 1 hour, whilst it was gradually allowed to warm to room temperature. Upon full consumption of the starting material, the mixture was dissolved in DCM (100 ml), washed with saturated LiCl (2 x 20 ml) before the organic layer was dried in $MgSO_4$, reduced and purified by column chromatography (0-20 % diethyl ether in petroleum ether) to give **39** as a yellow oil, (0.94 g, 57 %); ν_{max} (film)/cm^{-1} 2978, 2181, 1356, 1151, 1016; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.54 (2H, d, J=7.2 Hz, H_{ortho}), 7.47 (1H, t, J=7.6 Hz, H_{para}), 7.39 (2H, t, J=7.7 Hz, H_{meta}), 3.39 (4H, q, J=7.2 Hz, CH_2CH_3), 1.30 (6H, t, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 132.6 (C_{ortho}), 131.1 (C_{para}), 128.8 (C_{meta}), 118.7 (*C*CCS), 88.3 (CC*C*S), 83.9 (C*C*CS), 43.0 (*C*H_2CH$_3$), 13.5 (CH$_2$*C*H$_3$); HRMS (CI) calc'd for $C_{12}H_{15}NO_2S$ (M+H$^+$) 238.0896, found 238.0890. Data in agreement with literature values.[34]

Method B for the synthesis of alkynyl sulfonamides 39 and 78

***N*,*N*-Diethylsulfurous chloride**



A flame-dried flask was placed under argon and charged with a stirring bar and thionyl chloride (5.9 ml, 81.4 mmol, 1.0 eq.). Anhydrous Et_2O (150 ml) was then added and the solution was cooled to -78 ^{o}C. Diethylamine (17.0 ml, 162.7 mmol, 2.0 eq.) was dissolved in anhydrous Et_2O (100 ml) and added dropwise over 2 hours to the cooled solution of thionyl chloride. Upon complete addition, the reaction mixture became a milky brown colour, and was gradually warmed to room

temperature as it was stirred for a further 1 hour and quickly filtered though a pad of Celite. The contents were then carefully concentrated *in vacuo* and immediately stored under argon at -20 ^{o}C between use as a brown oil, (7.6 g, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.44 (4H, m, N(CH_2CH_3)$_2$), 1.31 (6H, t, J=7.6 Hz, N(CH_2CH_3)$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 38.2 (N(CH_2CH_3)$_2$), 12.2 N(CH_2CH_3)$_2$); LRMS (EI) mass ion not detected. Data in agreement with literature values.[34]

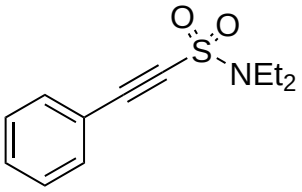
General method for the synthesis of alkynyl sulfinamides

A flame-dried flask was charged with a stirring bar and aromatic acetylene (1.0 mmol, 1.0 eq), followed by anhydrous THF under argon. The flask was then cooled to -78 ^{o}C and *n*BuLi (1.6 M in THF, 1.0-2.0 mmol, 1.0-2.0 eq) was added dropwise to the reaction mixture which was allowed to stir for 10 minutes. *N*,*N*-diethyl sulfurous chloride (1.6 mmol, 1.6 eq.) was then added dropwise via syringe, and the solution stirred at -78 ^{o}C for 20 minutes. The reaction was allowed to warm to room temperature, dissolved in DCM, washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product which was purified via column chromatography (0-5 % ethyl acetate in petroleum ether) to yield the alkynyl sulfinamides.

General method for the oxidation of alkynyl sulfinamides to alkynyl sulfonamides

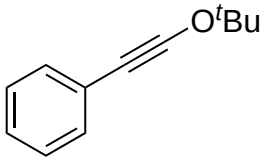
A flask was charged with $NaIO_4$ (2.0 mmol, 1.3 eq.) in H_2O (4 ml) with rapid stirring. MeCN (5 ml) was then added and the flask was cooled to 0 ^{o}C. After the solid had fully dissolved, EtOAc (5 ml) was added and the reaction was stirred for 5 minutes at 0 ^{o}C. $RuCl_3.3H_2O$ (0.015 mmol, 0.01 eq.) was added in one portion and the mixture stirred for a further 2 minutes. Alkynyl sulfinamide (1.54 mmol, 1.0 eq.) dissolved in EtOAc (5 ml) was then added to the reaction flask in one portion and the reaction stirred vigorously at 0 ^{o}C until complete consumption of the starting material was observed via TLC (5-6 hours). The crude reaction mixture was then dissolved in DCM and washed with H_2O, brine, dried over $MgSO_4$ and reduced to yield the crude sulfonamide which was purified via column chromatography using ethyl acetate or diethyl ether in petroleum ether.

General method for the one pot synthesis of *N*,*N*-diethyl-2-phenylethyne-1-sulfonamide 39



A flame-dried flask was placed under argon and charged with aromatic acetylene (1-11.7 mmol, 1.0 eq) in dry THF (10-100 ml) at -78 ^{o}C, before *n*BuLi (1.2-12 mmol, 1.2 eq) was added dropwise with stirring. DABSO (1.0 mmol, 1.0 eq) was added, and the mixture was left to stir for 30-135 minutes. The halogenating agent (1.2 mmol, 1.2 eq) was added and likewise, the mixture was left to stir for a variable amount of time before the amine (1.0 mmol, 1.0 eq) was added dropwise. The mixture was monitored by TLC and worked up by evaporating the THF, dissolving the mixture in DCM and washing with H_2O, and brine. The organic layer was dried with $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (0-20 % ethyl acetate in petroleum ether) to give **39** as a yellow oil, (3-6 %).

(*tert*-Butoxyethynyl)benzene 44

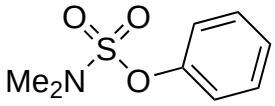


A flame-dried flask was placed under argon and charged with dimethylamine (0.3 ml, 0.6 mmol, 2.0 eq) and KO*t*Bu (0.135 g, 1.2 mmol, 4.0 eq) in dry THF (1 ml) and cooled to 0 ^{o}C. The reaction mixture was stirred rapidly for 1 minute and then **54** (0.07 g, 0.3 mmol, 1.0 eq) was added in one burst. The reaction was quenched after 10 minutes with H_2O, dried in DCM with $MgSO_4$ and reduced to a yellowy brown oil which was purified by column chromatography (0-30 % ethyl acetate in petroleum ether) to give a colourless oil, (30 mg, 34 %); ν_{max} (film)/cm^{-1} 2975, 2231, 1390, 1352; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.34 (2H, J=7.2 Hz, H_{ortho}), 7.25 (2H, J=7.2 Hz, H_{meta}), 7.19 (1H, J=7.4 Hz, H_{para}), 1.48 (9H, s, $OC(CH_3)_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 131.5 (C_{ortho}), 128.1 (C_{para}), 126.4 (C_{meta}), 124.8 (OCC*C*), 95.7 (O*C*C), 87.0 (OC*C*), 42.9 ($C(CH_3)_3$), 27.3 ($C(CH_3)_3$). Data in agreement with literature values.[34]

General procedure for synthesis of arylsulfamates 46-48

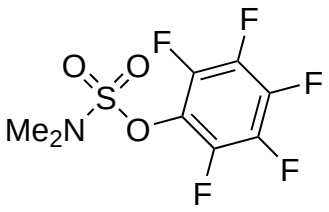
A flame dried flask was placed under argon, cooled to 0 ^{o}C and charged with phenol (8.5-10.0 mmol, 1.0 eq) dissolved in DME (10 ml). Sodium hydride (10.2-12.0 mmol, 1.2 eq) was added slowly whilst the solution was stirred. The mixture was warmed to room temperature, stirred for 10 minutes, then cooled back to 0 ^{o}C. Dimethylsulfamoyl chloride (10.2-12.0 mmol, 1.2 eq) in DME (5 ml), was added slowly and the mixture was stirred overnight before the solvent was removed under reduced pressure and the crude product used without any further purification.

Phenyl dimethylsulfamate 46



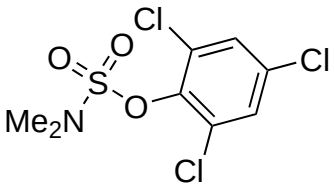
(Pale orange viscous liquid, 1.40 g, 82 %); ν_{max} (film)/cm^{-1} 2922, 2854, 1487, 1368, 1194, 1146; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.39 (2H, t, J=7.9 Hz, H_{meta}), 7.29 (3H, d*, J=7.9 Hz, H_{ortho}, H_{para}), 2.97 (6H, s, N(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 150.3 (CO), 129.9 (C_{meta}), 126.9 (C_{para}), 121.9 (C_{ortho}), 38.9 (CH$_3$)$_2$); LRMS (ES+) 391.28 (28 %), 224.04 (30 %), 202.05 (M$^+$, 100 %); HRMS (ES+) calc'd for $C_8H_{12}NO_3S$ (M$^+$) 202.0538, found 202.0540.

Perfluorophenyl dimethylsulfamate 47



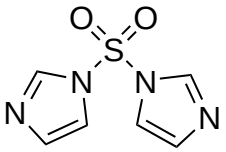
(Light yellow viscous liquid, 1.95 g, 67 %); ν_{max} (film)/cm^{-1} 2953, 2920, 2852, 1515, 1467, 1423, 1387, 1182; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 3.08 (6H, s, N(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 142.3 (d*, J=254.1 Hz, C_{meta}), 140.1 (d*, J=255.5 Hz, C_{para}), 138.1 (d*, J=254.5 Hz, C_{ortho}), 125.4 (OC), 38.3 (CH$_3$); LRMS (EI) 290.9 (M$^+$, 10 %), 183.0 (14 %), 155.5 (32 %), 107.7 (100 %).

2,4,6-Trichlorophenyl dimethylsulfamate 48



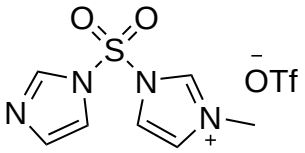
(Pale yellow liquid, 1.99 g, 73 %); ν_{max} (film)/cm^{-1} 3076, 1559, 1369, 1177; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.38 (2H, s, Ar-H), 3.11 (6H, s, N(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 142.6 (CO), 132.6 (C_{ortho}), 130.6 (C_{para}), 129.4 (C_{meta}), 38.9 ((CH_3)$_2$); LRMS (ES+) 803.53 (100 %), 413.25 (48 %), 391.28 (97 %), 303.94 (10 %); HRMS (ES+) calc'd for $C_8H_9Cl_3NO_3S$ (M^+) 303.9369, found 303.9373.

***N*,*N*'-Sulfuryldiimidazole 50**



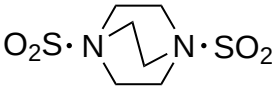
A solution of imidazole (20 g, 294 mmol, 4.8 eq) in DCM (200 ml) was cooled to 0 ^{o}C, and sulfuryl chloride (5.0 ml, 61.6 mmol, 1.0 eq) in DCM (30 ml) was added dropwise. The mixture was stirred at room temperature overnight, then filtered, and the filtrate was evaporated under reduced pressure. The crude product was recrystallized in isopropanol to give the title compound as a colourless solid (10.0 g, 81 %); m.p. 141-144 ^{o}C; ν_{max} (film)/cm^{-1} 3121, 1527, 1431, 1197, 1151, 1086, 1046; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.04 (2H, s, Ar-H), 7.32 (2H, t, J=1.5 Hz, Ar-H), 7.17 (2H, s, Ar-H); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 136.7 (C-H), 132.6 (Ar-C), 117.5 (Ar-C); LRMS (EI) 198.02 (30 %), 107.06 (100 %), 68.04 (30 %); HRMS (EI) calc'd for $C_6H_6SO_2N_4$ (M^+) 198.0206, found 198.0209. Data in agreement with literature values.[108;140]

1-((1*H*-Imidazol-1-yl)sulfonyl)-3-methyl-1*H*-imidazol-3-ium triflate 51



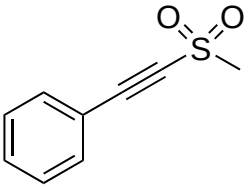
Compound **50** (9.8 g, 49.5 mmol, 1.0 eq) was dissolved in DCM (200 ml) at 0 ^{o}C, and methyl triflate (6.6 ml, 45 mmol, 1.1 eq) was added dropwise over 10 min. The mixture was stirred for 3 hours at 0 ^{o}C, before it was filtered and dried under high vacuum to give the product as a white solid (16.6 g, 92 %); m.p. 121-124 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 3150, 3119, 3066, 1459, 1250, 1150, 1030; ^{1}H NMR (600 MHz, D_2O) δ_H 8.59 (1H, s, Ar-H), 8.25 (1H, d, J=2.3 Hz, Ar-H), 7.88 (1H, s, Ar-H), 7.80 (1H, d, J=2.2 Hz, Ar-H), 7.36 (1H, s, Ar-H), 4.09 (3H, s, CH_3); ^{13}C NMR (600 MHz, D_2O) δ_C 139.2 (Ar-C), 132.6 (Ar-C), 126.7 (Ar-C), 121.3 (Ar-C), 119.5 (Ar-C), 37.8 (CH$_3$). Data in agreement with literature values.[108;140]

Bis(sulphur dioxide) 1,4-diazabicyclo[2.2.2]octane, (DABSO) 52



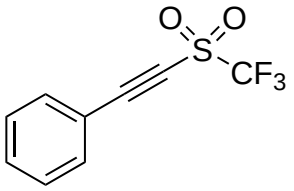
A two-necked 250 ml RBF was fitted with a cold trap condenser, and flushed with argon before it was charged with 1,4-Diazabicyclo[2.2.2]octane (DABCO) (2.00 g, 16.4 mmol) and flushed again. The cold trap condenser was filled with acetone and dry ice, and SO_2 gas was pumped into the RBF whilst the DABCO was stirred, condensing until the DABCO was completely submerged in liquid SO_2. At that point, the flask was allowed to warm to room temperature and the contents were stirred for a further 2 hours. Any excess SO_2 was evaporated to leave a white powder, (4.04 g, 94 %); m.p. 179-184 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 1474, 1223, 1098, 1052; ^{1}H NMR (600 MHz, CD_3OD) δ_H 3.22 (12H, s, CH_2); ^{13}C NMR (600 MHz, CD_3OD) δ_C 45.4; LRMS (CI) mass ion not detected. Data in agreement with literature values.[109]

((Methylsulfonyl)ethynyl)benzene 53



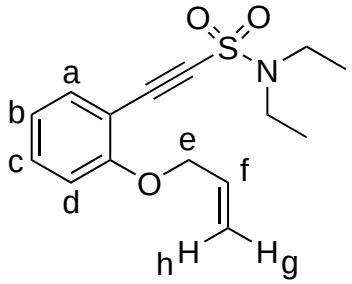
A flame-dried RBF was charged with phenylacetylene (1.02 ml, 10 mmol, 1.0 eq) in anhydrous ether (50 ml) under argon, and cooled to -78 ^{o}C. *n*BuLi (6.88 ml, 11 mmol, 1.1 eq) was added dropwise over 1 minute and the mixture was left to stir for 1 hour. Methanesulfonic anhydride (1.8 g, 10 mmol, 1.0 eq) in anhydrous ether (40 ml) was added dropwise over 1 hour and the mixture was left to stir for a further 30 minutes before being warmed to room temperature. The reaction was quenched with H_2O, and the organic layer was dried with $MgSO_4$ before it was reduced and purified by column chromatography (0 - 5 % ethyl acetate in petroleum ether) to give a colourless oil, (0.57 g, 32 %); ν_{max} (film)/cm^{-1} 3060, 2928, 2183, 1723, 1315, 1138, 962; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.60 (2H, d, J=6.9 Hz, H_{ortho}), 7.53 (1H, t, J=7.4 Hz, H_{para}), 7.42 (2H, t, J=7.8 Hz, H_{meta}); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 133.0 (C_{ortho}), 131.9 (C_{para}), 128.9 (C_{meta}), 117.6 (*C*CCS), 91.7 (CC*C*S), 84.5 (C*C*CS), 46.9 (S*C*H$_3$); LRMS (CI) 181.03 (100 %, M+H$^+$), 105.00 (22 %), 88.97 (24 %). Data in agreement with literature values.[141]

Phenylethynyl trifluoromethyl sulfone 54



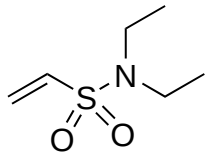
A flame-dried flask was placed under argon and charged with phenylacetylene (0.50 ml, 4.5 mmol, 1.0 eq) in dry ether (50 ml) at -78 ^{o}C, before *n*BuLi (3.0 ml, 4.8 mmol, 1.1 eq) was added dropwise with stirring. After 1 hour, the lithium acetylide was added by syringe to a stirring solution of triflic anhydride (0.74 ml, 4.5 mmol, 1.1 eq) in dry ether (20 ml) over a period of 1 hour and the reaction was monitored at room temperature by TLC until complete. The reaction was quenched with H_2O, dried with $MgSO_4$ and reduced to a yellowy brown oil which was purified by column chromatography (0-5 % ethyl acetate in petroleum ether) to give a yellow oil, (0.82 g, 79 %); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.70 (2H, d, J=8.0 Hz, H_{ortho}), 7.63 (1H, t, J=7.8 Hz, H_{para}), 7.49 (2H, t, J=8.0 Hz, H_{meta}); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 133.9 (C_{ortho}), 133.5 (C_{para}), 129.2 (C_{meta}), 119.1 (q, J_{CF}=323 Hz, CF_3), 115.9 (*C*CCS), 100.9 (CC*C*S), 77.3 (C*C*CS); LRMS (CI) 234.95 (M^+, 100 %). Data in agreement with literature values.[142]

2-(2-(Allyloxy)phenyl)-*N*,*N*-diethylethyne-1-sulfonamide 55



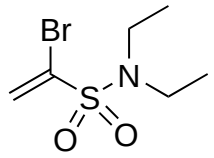
A flame-dried RBF was charged with sulfonamide **68** (1.1 g, 3.9 mmol, 2.4 eq) in DCM (100 ml) under argon and cooled to -78 ^{o}C. BBr_3 (1M in DCM, 9.0 ml, 9.0 mmol, 5.6 eq) was added dropwise rapidly whilst the mixture was being stirred. The reaction was allowed to warm to room temperature and left overnight. Once the reaction was complete, H_2O (100 ml) was added to quench the reaction, which was stirred vigorously for 30 minutes before it was transferred into a large separating funnel and extracted 3 times with ethyl acetate. This was dried with $MgSO_4$ and reduced to give the crude intermediate **69** as an oil (43 %, 0.4 g, 1.6 mmol, 1.0 eq) that was transferred to a 3-necked flask, to which was also added potassium carbonate (0.33 g, 2.4 mmol, 1.0 eq) and acetone (10 ml). The contents were stirred for a few minutes, after which vinyl bromide (0.21 ml, 2.4 mmol, 1.5 eq) was added and the mixture was refluxed until the intermediate had been fully consumed. The mixture was filtered before the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with H_2O, dried with $MgSO_4$ and reduced to an oil which was purified by column chromatography (0-20 % ether in petroleum ether) to give a yellow oil, (0.23 g, 48 %); $\nu_{\max}$ (film)/cm^{-1} 2977, 2935, 2873, 2360, 2178, 1595, 1487, 1447, 1355, 1152, 1015, 937; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.47 (1H, dd, J=7.7, 1.5 Hz, H^d), 7.39 (1H, t, J=8.0 Hz, H^b), 6.95 (1H, t, J=7.5 Hz, H^c), 6.89 (1H, d, J=8.5 Hz, H^a), 5.99-6.06 (1H, m, H^f), 5.46 (1H, d, J=17.5 Hz, H^h), 5.31 (1H, d, J=10.6 Hz, H^g), 4.59 (2H, d, J=5.3 Hz, H^e), 3.38 (4H, q, J=7.3 Hz, N(CH_2CH$_3$)$_2$), 1.29 (6H, t, J=7.3 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 160.6 (*C*O), 134.4 (C^d), 132.5 (C^b), 132.5 (C^f), 120.8 (C^c), 118.2 (C=*C*H$_2$), 112.2 (C^a), 108.4 (*C*CCS), 87.5 (CC*C*S), 85.9 (C*C*CS), 69.3 (C^e), 43.0 (N(*C*H$_2$CH$_3$)$_2$), 13.4 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 294.08 (M+H$^+$, 51%), 230.04 (59%), 189.12 (100%); HRMS (CI) calc'd for $C_{15}H_{20}NO_3S$ (M+H$^+$) 294.1158, found 294.1161.

***N*,*N*-Diethyl vinylsulfonamide 59**



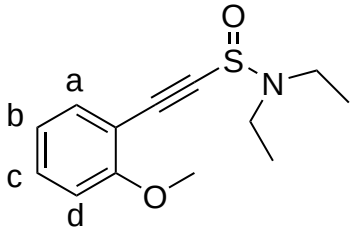
A flame-dried flask was charged with 2-chloroethanesulfonyl chloride (3.0 ml, 28.8 mmol, 1.0 eq) in DCM (20 ml) and cooled to -78 ^{o}C under argon. Triethylamine (7.9 ml, 57.5 mmol, 2.0 eq) and diethylamine (2.0 g, 27.6 mmol, 1.0 eq) in DCM (20 ml) was added via syringe pump over 2 hours. The mixture was then warmed to room temperature, washed with HCl, dried with $MgSO_4$ and reduced to give the product that was purified by column chromatography (0-20 % ethyl acetate in petroleum ether) as a yellow oil, (2.03 g, 45 %); $\nu_{\max}$ (film)/cm^{-1} 2976, 2938, 2879, 1465, 1322, 1200, 1135, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.44 (1H, dd, J=16.5, 10.2 Hz, SC*H*), 6.22 (1H, d, J=16.5 Hz, SCHCH_{trans}) 5.91 (1H, d, J=9.8 Hz, SCHCH_{cis}), 3.25 (4H, q, J=7.0 Hz, N(CH_2CH$_3$)$_2$), 1.22 (6H, t, J=7.3 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 135.6 (S*C*H), 125.9 (SCH*C*H$_2$), 41.7 (N(*C*H$_2$CH$_3$)$_2$), 14.4 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 181.1 (54 %), 164.1 (M+H$^+$, 100 %), 148.1 (%); HRMS (CI) calc'd for $C_6H_{14}NO_2S$ (M+H$^+$) 164.0740, found 164.0738. Data in agreement with literature values.[143]

1-Bromo-*N*,*N*-diethyl vinylsulfonamide 60



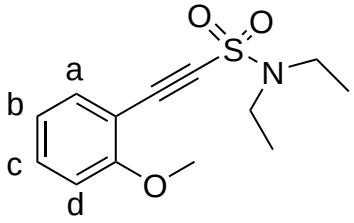
Compound **59** (3.51 g, 21.5 mmol, 1.0 eq) in DCM (100 ml) was charged with excess bromine (14.6 ml, 247.3 mmol, 11.5 eq) and stirred for an hour until it was fully consumed. The mixture was diluted with DCM (100 ml) before $Na_2S_2O_3$ (150 ml) was slowly added to quench the reaction. The organic phase was washed with H_2O, dried with $MgSO_4$, and reduced to give a brown viscous intermediate. This was dissolved in DCM (100 ml) at 0 ^oC, before triethylamine (3.3 ml, 23.65 mmol, 1.1 eq) was added slowly whilst stirred. The mixture was warmed to room temperature and a further portion of triethylamine (1.5 ml, 10.75 mmol, 0.5 eq) was added. The reaction was monitored by TLC, and after 3 hours, the reaction was diluted with DCM (300 ml), washed with both HCl and brine, dried with $MgSO_4$ and concentrated *in vacuo* to give a crude brown oil that was purified by column chromatography (0-10 % ether in petroleum ether) to give a light brown oil, (1.7 g, 33 %); ν_{max} (film)/cm^{-1} 3111, 2977, 2938, 2877, 1601, 1467, 1334, 1154; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 6.80 (1H, d, J=2.7 Hz, C*H*), 6.13 (1H, d, J=2.7 Hz, C*H*) 3.37 (4H, q, J=7.2 Hz, N(CH_2CH$_3$)$_2$), 1.23 (6H, t, J=7.1 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 128.1 (*C*CH$_2$), 127.7 (C*C*H$_2$), 43.1 (N(*C*H$_2$CH$_3$)$_2$), 14.5 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 261.0 (96 %), 259.0 (100 %), 242.0 (10 %), 227.9 (56 %); HRMS (CI) calc'd for $C_6H_{13}NO_2SBr$ (M+H$^+$) 241.9845, found 241.9846. Data in agreement with literature values.[33]

***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethyne-1-sulfinamide 67**



Using Method B for the synthesis of alkynyl sulfinamides with compound **66** (3.42 g, 11.7 mmol, 1.0 eq) derived from methoxybenzaldehyde, to give the title compound as a colourless oil, (2.0 g, 65 %); ν_{max} (film)/cm^{-1} 2972, 2934, 2163, 1595, 1489, 1459, 1255, 1019; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.45 (1H, dd, J=7.6, 1.7 Hz, H^d), 7.38 (1H, td, J=8.0, 1.6 Hz, H^b), 6.93 (1H, td, J=7.6, 0.7 Hz, H^c), 6.89 (1H, d, J=8.5 Hz, H^a), 3.87 (3H, s, OCH_3), 3.45 (2H, dq, J=14.2, 7.1 Hz, NCH_2CH$_3$), 3.36 (2H, dq, J=14.2, 7.0 Hz, NCH_2CH$_3$), 1.29 (6H, t, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 160.9 (*C*O), 134.1 (C^d), 131.9 (C^b), 120.6 (C^c), 110.8 (C^a), 109.5 (*C*CCS), 93.3 (CC*C*S), 90.2 (C*C*CS), 55.8 (O*C*H$_3$), 42.6 (N(*C*H$_2$CH$_3$)$_2$), 14.3 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 262.08 (24 %), 252.09 (M+H$^+$, 64 %), 235.15 (61 %), 203.13 (100 %), 120.3 (55 %). Data in agreement with literature values.[97]

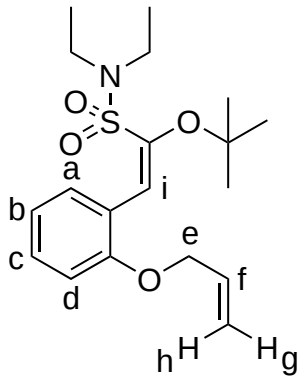
***N*,*N*-Diethyl-2-(2-methoxyphenyl)ethyne-1-sulfonamide 68**



Using Method B for the oxidation of sulfinamides, to give the title compound as a colourless oil, (1.1 g, 48 %); ν_{max} (film)/cm^{-1} 2975, 2937, 2177, 1596, 1490, 1461, 1342, 1285, 1259, 1201, 1151, 1017, 938; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.46 (1H, dd, J=7.6, 1.5 Hz, H^d), 7.42 (1H, td, J=8.6, 1.8 Hz, H^b), 6.94 (1H, t, J=7.6 Hz, H^c), 6.90 (1H, d, J=8.5 Hz, H^a), 3.86 (3H, s, OCH_3), 3.39 (2H, q, J=14.2, 7.2 Hz, N(CH_2CH$_3$)$_2$), 1.30 (6H, t, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 161.6 (*C*O), 134.3 (C^d), 132.7 (C^b), 120.7 (C^c), 110.9 (C^a), 108.0 (*C*CCS), 87.5 (CC*C*S), 85.8 (C*C*CS), 55.8 (O*C*H$_3$), 42.9 (N(*C*H$_2$CH$_3$)$_2$), 13.3 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 268.06 (M+H$^+$, 100%); HRMS (CI) calc'd for $C_{13}H_{18}NO_3S$ (M+H$^+$) 268.1002, found 268.1000. Data in agreement with literature values.[97]

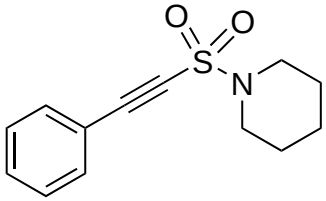
(*Z*)-2-(2-(Allyloxy)phenyl)-1-(*tert*-butoxy)-*N*,*N*-diethylethene-1-sulfonamide

71



A flame-dried RBF was placed under argon and charged with sulfonamide **55** (0.67 ml, 0.23 mmol, 1.0 eq) in THF (5 ml). The mixture was stirred and cooled to -78 ^{o}C. In a separate flask, DMA (0.23 ml, 0.45 mmol, 2.0 eq) and potassium *tert*-butoxide (0.10 g, 0.90 mmol, 4.0 eq) were mixed together and THF was added until the potassium *tert*-butoxide was fully dissolved. This mixture was transferred via syringe to the sulfonamide, allowed to stir for 10 minutes and then warmed to room temperature. TLC indicated that the starting material was consumed, so the reaction was quenched with H_2O, dissolved in DCM and washed with both brine and water, before being dried with $MgSO_4$ and reduced *in vacuo*. The crude mixture was purified by column chromatography (0-5 % ether in petroleum ether) to give a yellow oil, (19 mg, 23 %); ν_{max} (film)/cm^{-1} 2976, 2928, 2873, 1712, 1597, 1451, 1245, 1151, 1060, 1016, 912; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.75 (1H, dd, J=7.7, 1.3 Hz, H^{d}), 7.36 (1H, s, H^{i}), 7.23-7.24 (1H, m, H^{b}), 6.91 (1H, t, J=7.4 Hz, H^{c}), 6.86 (1H, d, J=8.2 Hz, H^{a}), 6.00-6.06 (1H, m, H^{f}), 5.40 (1H, dd, J=17.3, 1.5 Hz, H^{h}), 5.27 (1H, dd, J=10.6, 1.3 Hz, H^{g}), 4.57 (2H, dt, J=5.1, 1.5 Hz, H^{e}), 3.35 (4H, q, J=7.2 Hz, N(CH_2CH$_3$)$_2$), 1.30 (9H, s, C(CH_3)$_3$), 1.22 (6H, q, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 156.4 (*C*O), 149.0 (S*C*O), 133.1 (C^{f}), 130.9 (C^{d}), 130.0 (C^{b}), 122.7 (*C*CHCS), 120.2 (C^{c}), 119.9 (C^{i}), 117.6 (C=*C*H$_2$), 112.0 (C^{a}), 86.5 (*C*(CH$_3$)$_3$), 69.1 (C^{e}), 42.0 (N(*C*H$_2$CH$_3$)$_2$), 29.3 (C(*C*H$_3$)$_3$), 14.4 (N(CH$_2$*C*H$_3$)$_2$); LRMS (CI) 368.14 (M+H^{+}, 6 %), 312.10 (51 %), 247.13 (40 %), 174.05 (96 %), 120.03 (100 %); HRMS (CI) calc'd for $C_{19}H_{30}NO_4S$ (M+H^{+}) 368.1890, found 368.1906.

1-((Phenylethynyl)sulfonyl)piperidine 78

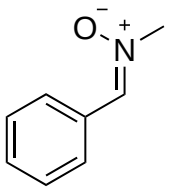


As per the two-step synthesis of the sulfonamide in Method B, using piperidine-1-sulfinic chloride instead of diethyl sulfurous chloride, to give product **78** as a pale yellow oil, (0.78 g, 60 %); ν_{max} (film)/cm^{-1} 2953, 2851, 2168, 1361, 1344, 1164, 1052; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.58 (2H, dd*, J=8.4, 1.3 Hz, H_{ortho}), 7.49 (1H, tt, J=7.5, 1.5 Hz, H_{para}), 7.41 (2H, t, J=7.7 Hz, H_{meta}), 3.23 (4H, t, J=5.5 Hz, $N(CH_2CH_2CH)_2$), 1.75 (4H, quin, J=5.6 Hz, $N(CH_2CH_2CH)_2$), 1.55-1.59 (2H, m, $N(CH_2CH_2CH)_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 132.9 (C_{ortho}), 131.3 (C_{para}), 128.8 (C_{meta}), 118.4 ($CCCS$), 90.4 ($CCCS$), 80.4 ($CCCS$), 47.5 $N(CH_2CH_2CH)_2$), 24.9 $N(CH_2CH_2CH)_2$), 23.5 ($N(CH_2CH_2CH)_2$)); LRMS (CI) 250.07 (M+H$^+$, 100%), 185.11 (11%); HRMS (CI) calc'd for $C_{13}H_{16}NO_2S$ (M+H$^+$) 250.0902, found 250.0904.

General synthesis of Nitrones 81-98

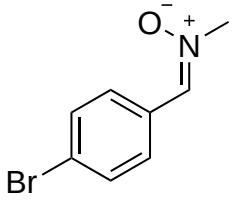
To *N*-methylhydroxylamine hydrochloride (4-9 mmol, 1.2 eq) in DCM (20 ml) was added the aldehyde (4-9 mmol, 1 eq) and $NaHCO_3$ (12-27 mmol, 3 eq). The mixture was refluxed for 24 hours and the resulting suspension was filtered. The residue was washed with cold DCM, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the nitrone which was used without further purification.

(*Z*)-*N*-Methyl-1-phenylmethanimine oxide 81



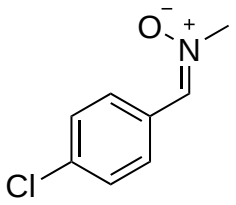
(White powder, 0.26 g, 78 %); m.p. 83-84 ^{o}C; ν_{max} (film)/cm^{-1} 3056, 1593, 1400, 1163, 941; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.21-8.22 (2H, m, H_{ortho}), 7.42-7.43 (3H, m, H_{meta}, H_{para}), 7.37 (1H, s, C*H*N), 3.89 (3H, s, CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 135.48 (C*C*HN), 130.63 (C_{para}), 130.52 (*C*CHN), 128.64 (C_{meta}), 128.58 (C_{ortho}), 54.54 (*C*H$_3$); LRMS (CI) 136.08 (M+H$^+$, 100 %), 120.07 (9 %). Data in agreement with literature values.[128]

(*Z*)-1-(4-Bromophenyl)-*N*-methylmethanimine oxide 82



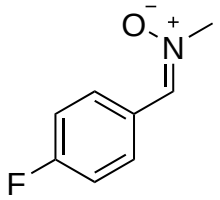
(White flaky crystals, 1.10 g, 95 %); m.p. 129-131 ^{o}C; ν_{max} (film)/cm^{-1} 3079, 1582, 1396, 1164, 945; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.10 (2H, d, J=8.7 Hz, H_{ortho*}), 7.55 (2H, d, J=8.6 Hz, H_{meta}), 7.34 (1H, s, C*H*N), 3.88 (3H, s, CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 134.3 (C*C*HN), 131.9 (C_{meta}), 129.8 (C_{ortho}), 129.4 (*C*CHN), 124.4 (*C*Br), 54.7 (*C*H$_3$); LRMS (EI) 213.99 (M$^+$, ^{81}Br, 100 %), 211.99 (M$^+$, ^{79}Br, 98 %), 196.01 (37 %), 184.98 (28 %), 119.04 (59 %), 68.89 (81 %). Data in agreement with literature values.[128] *ortho to Br

(*Z*)-1-(4-Chlorophenyl)-*N*-methylmethanimine oxide 83



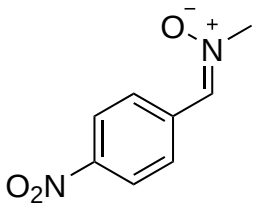
(White flaky solid, 0.98 g, 81 %); m.p. 127-129 ^{o}C; ν_{max} (film)/cm^{-1} 3079, 1590, 1424, 1165, 1082, 947; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.18 (2H, d, J=8.7 Hz, H_{ortho*}), 7.39 (2H, d, J=8.7 Hz, H_{meta}), 7.36 (1H, s, C*H*N), 3.88 (3H, s, CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 136.0 (*C*Cl), 134.3 (C*C*HN), 129.7 (C_{ortho}),129.0 (*C*CHN), 128.9 (C_{meta}), 54.6 (*C*H$_3$); LRMS (EI) 169.05 (M$^+$, 87 %), 168.04 (100 %), 152.04 (31 %), 139.00 (25 %), 119.04 (36 %). Data in agreement with literature values.[128] *ortho to Cl

(*Z*)-1-(4-Fluorophenyl)-*N*-methylmethanimine oxide 84



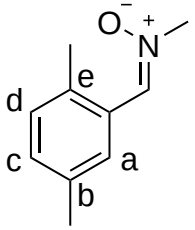
(Creamy amorphous paste, 0.81 g, 66 %); ν_{max} (film)/cm^{-1} 3078, 1698, 1597, 1501, 1401, 1230, 1149, 943; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.22-8.28 (2H, m, H_{ortho*}), 7.36 (1H, s, C*H*N), 7.11 (2H, t, J=8.7 Hz, H_{meta}), 3.89 (3H, s, CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 163.5 (d, J=253.4 Hz, *C*F), 134.5 (*C*HN), 130.9 (d, J=8.3 Hz, C_{ortho}), 126.9 (d, J=3.3 Hz, *C*CHN), 115.6 (d, J=21.9 Hz, C_{meta}), 54.4 (*C*H$_3$); LRMS (ES+) 154.06 (M+H$^+$, 100 %), 136.05 (42 %). *ortho to F

(*Z*)-*N*-Methyl-1-(4-nitrophenyl)methanimine oxide 85



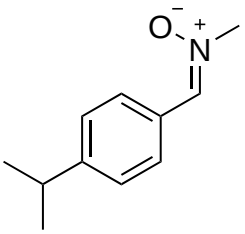
(Yellow crystals, 0.74 g, 63 %); m.p. 210-213 ^{o}C; ν_{max} (film)/cm^{-1} 1597, 1576, 1508, 1332, 1163, 1109, 946; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.38 (2H, d, J=9.1 Hz, H_{ortho*}), 8.27 (2H, d, J=9.1 Hz, H_{meta}), 7.52 (1H, s, C*H*N), 3.96 (3H, s, CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 147.9 (*C*NO_2), 136.1 (*C*CHN), 133.3 (C*C*HN), 128.8 (C_{ortho}), 124.0 (C_{meta}), 55.3 (*C*H_3); LRMS (ES+) 181.05 (M+H$^+$, 100 %), 135.06 (34 %). Data in agreement with literature values.[130] *ortho to N_2O

(*Z*)-1-(2,5-Dimethylphenyl)-*N*-methylmethanimine oxide 86



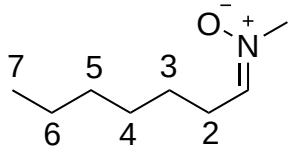
(Off-white crystals, 0.67 g, 56 %); m.p. 112-114 ^{o}C; ν_{max} (film)/cm^{-1} 2919, 1583, 1490, 1412, 1215, 1172, 1123, 1092, 941; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.95 (1H, s, H_a), 7.50 (1H, s, C*H*N), 7.08-7.12 (2H, m, H_c, H_d), 3.92 (3H, s, NCH_3), 2.35 (3H, s, C_bCH_3), 2.34 (3H, s, C_eCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 136.0 (*C*CHN), 133.3 (*C*$_b$CH$_3$), 132.8 (*C*HN), 131.3 (C_c), 130.2 (C_d), 128.6 (*C*$_e$CH$_3$), 128.4 (C_a), 55.1 (N*C*H$_3$), 21.3 (C_b*C*H$_3$), 19.5 (C_e*C*H$_3$); LRMS (EI) 163.09 (M$^+$, 16 %), 148.06 (29 %), 97.05 (44 %), 85.01 (72 %); HRMS (EI) calc'd for $C_{10}H_{13}NO$ (M$^+$) 163.0997, found 163.0999.

(*Z*)-1-(4-Isopropylphenyl)-*N*-methylmethanimine oxide 87



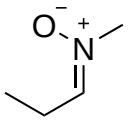
(White crystals, 1.03 g, 88 %); m.p. 61-64 ^{o}C; ν_{max} (film)/cm^{-1} 2955, 1590, 1461, 1415, 1313, 1171, 1051, 945; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.14 (2H, d, J=8.5 Hz, H_{ortho*}), 7.34 (1H, s, CC*H*N), 7.28 (2H, d, J=8.2 Hz, H_{meta}), 3.87 (3H, s, NCH_3), 2.90-2.97 (1H, m, C*H*(CH_3)$_2$), 1.25 (6H, d, J=7.0 Hz, CH(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 151.9 (*C*CHN), 135.5 (C*C*HN), 128.8 (C_{ortho}), 128.2 (*C*CH(CH_3)$_2$), 126.7 (C_{meta}), 54.3 (N*C*H_3), 34.3 (*C*HCH_3), 23.8 (CH(*C*H_3)$_2$); LRMS (EI) 176.10 (M-H$^+$, 77 %), 161.11 (20 %), 149.01 (25 %), 111.08 (32 %), 97.05 (52 %); HRMS (EI) calc'd for $C_{11}H_{15}NO$ (M$^+$) 177.1154, found 177.1551. *ortho to nitrone

(*Z*)-*N*-Methylheptan-1-imine oxide 88



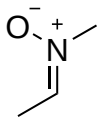
(Colourless oil, 0.83 g, 97 %); ν_{max} (film)/cm^{-1} 3211, 2926, 2856, 1459, 947; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 6.64 (1H, t, J=5.8 Hz, C*H*N), 3.65 (3H, s, NCH_3), 2.43-2.47 (2H, m, H^2), 1.48 (2H, d, J=7.6 Hz, H^3), 1.24-1.35 (6H, m, H^4, H^5, H^6), 0.85 (3H, t, J=7.2 Hz, H^7); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 140.8 (*C*HN), 52.5 (N*C*H_3), 31.6 (C^6), 29.2 (C^4), 27.0 (C^2), 25.6 (C^3), 22.6 (C^5), 14.1 (C^7); LRMS (EI) 143.14 (M$^+$, 18 %), 86.00 (51 %), 72.92 (100 %); LRMS (EI) 143.14 (M$^+$, 18 %), 115.10 (6 %), 86.00 (51 %), 72.92 (100 %); HRMS (EI) calc'd for $C_8H_{17}NO$ (M$^+$) 143.1310, found 143.1309. Data in agreement with literature values.[130]

(*Z*)-*N*-Methylpropan-1-imine oxide 89



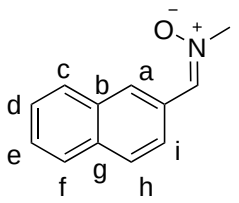
(Pale yellow oil, 0.48 g, 93 %); ν_{max} (film)/cm^{-1}1 3221, 2964, 2877, 1458, 932; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 6.62 (1H, t, J=5.7 Hz, C*H*N), 3.64 (3H, d, J=0.6 Hz, NCH_3), 2.46 (2H, d quin, J=7.6, 1.2 Hz, CH_2CH$_3$), 1.07 (3H, t, J=7.7 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 141.81 (*C*HN), 52.39 (N*C*H$_3$), 20.39 (*C*H$_2$CH$_3$), 9.96 (CH$_2$*C*H$_3$); LRMS (CI) 88.12 (M+H$^+$, 100 %), 72.03 (11 %); HRMS (CI) calc'd for C_4H_9NO (M+H$^+$) 88.0762, found 88.0760. Data in agreement with literature values.[131]

(*Z*)-*N*-Methylethanimine oxide 90



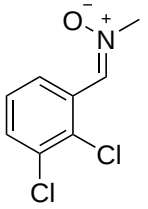
(Pale yellow oil, 0.39 g, 89 %); ν_{max} (film)/cm^{-1} 3185, 2964, 2849, 1618, 1436, 1376; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 6.76 (1H, q, J=5.7 Hz, C*H*N), 3.67 (3H, s, NCH_3), 1.99 (3H, dd, J=5.9, 1.1 Hz, CHCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 135.66 (*C*HN), 52.38 (N*C*H$_3$), 12.96 (CH*C*H$_3$); LRMS (CI) 74.13 (M+H$^+$, 100 %); HRMS (CI) calc'd for C_3H_7NO (M+H$^+$) 74.0606, found 74.0601.

(*Z*)-*N*-(Naphthalen-2-ylmethylene)methanamine oxide 91



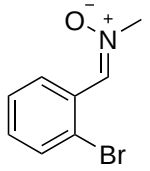
(White crystals, 0.21 g, 84 %); m.p. 117-119 ^{o}C; ν_{max} (film)/cm^{-1} 3059, 1576, 1364, 1170, 1124, 967; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 9.20 (1H, s, H^{a}), 7.94 (1H, d, J=7.5 Hz, H^{c}), 7.88 (1H, dd, J=8.6, 1.6 Hz, H^{i}), 7.84 (1H, d, J=8.7 Hz, H^{h}), 7.82 (1H, d, J=7.8 Hz, H^{f}), 7.49-7.54 (3H, m, H^{d}, H^{e}, NC*H*), 3.95 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 135.5 (C*C*HN), 134.2 (C^{g}), 133.2 (C^{b}), 129.4 (C^{c}), 128.6 (C^{a}), 128.1 (C^{h}), 127.7 (*C*CH), 127.7 (C^{f}), 127.5 (C^{e}), 126.6 (C^{d}), 125.8 (C^{i}), 54.6 (*C*H$_3$); LRMS (EI) 185.10 (M$^+$, 51 %), 139.06 (26 %), 127.05 (31 %), 115.04 (37 %), 83.88 (100 %); HRMS (EI) calc'd for $C_{12}H_{11}NO$ (M$^+$) 185.0841, found 185.0843.

(*Z*)-*N*-(2,3-Dichlorobenzylidene)methanamine oxide 92



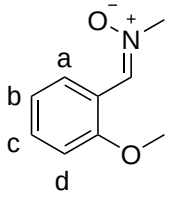
(White crystals, 0.68 g, 84 %); m.p. 121-123 ^{o}C; ν_{max} (film)/cm^{-1} 2947, 1577, 1400, 1169, 1045, 959; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 9.23 (1H, dd, J=8.2, 1.5 Hz, H$_{ortho*}$), 7.92 (1H, s, NC*H*), 7.50 (1H, dd, J=8.0, 1.5 Hz, H$_{para}$), 7.31 (1H, t, J=8.1 Hz, H$_{meta}$), 3.96 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 133.3 (*C*CHN), 131.9 (C$_{para}$), 131.3 (*C*HN), 130.8 (C$_{ortho}$Cl), 130.1 (C$_{meta}$Cl), 127.7 (C$_{meta}$), 127.2 (C$_{ortho}$), 55.6 (*C*H$_3$); LRMS (EI) 168.03 (100 %), 141.02 (61 %), 122.99 (40 %), 98.97 (30 %); HRMS (EI) calc'd for $C_8H_7Cl_2NO$ (M$^+$) 202.9905, found 202.9901. *ortho to nitrone

(*Z*)-1-(2-Bromophenyl)-*N*-methylmethanimine oxide 93



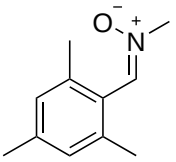
(White crystals, 0.31 g, 58 %); ν_{max} (film)/cm^{-1} 1695, 1585, 1414, 1172; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.47 (1H, t, J=1.8 Hz, H_{ortho*}), 8.05 (1H, d, J=7.9 Hz, H_{meta}), 7.52 (1H, ddd, J=8.0, 2.0, 1.0 Hz, H_{para}), 7.33 (1H, s, C*H*N), 7.27 (1H, t, J=8.0 Hz, H_{meta}CBr), 3.88 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 133.9 (*C*HN), 133.4 (C_{para}), 132.4 (*C*CHN), 130.9 (C_{ortho}), 130.1 (C_{meta}CBr), 126.9 (C_{meta}), 122.7 (*C*Br), 54.8 (N*C*H$_3$); LRMS (CI) 215.97 (90 %, M+H$^+$, Br^{81}) 213.97 (100 %, M+H$^+$, Br^{79}), 134.05 (23 %); HRMS (CI) calc'd for C_8H_8BrNO (M+H$^+$) 213.9868, found 213.9850. *ortho to nitrone

(*Z*)-*N*-(2-Methoxybenzylidene)methanamine oxide 94



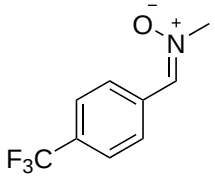
(Pale pink solid, 0.56 g, 85 %); m.p. 84-86 ^{o}C; ν_{max} (film)/cm^{-1} 2937, 2833, 1594, 1242, 1165, 1022, 945; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 9.24 (1H, dd, J=7.9, 1.7, H^a), 7.82 (1H, s, C*H*N), 7.36 (1H, t, J=7.8, H^c), 7.02 (1H, t, J=7.7 Hz, H^b), 6.87 (1H, dd, J=8.3, 0.8 Hz, H^d), 3.88 (3H, s, OCH_3), 3.85 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 156.8 (*C*COCH$_3$), 131.7 (C^c), 130.0 (*C*HN), 128.7 (C^a), 120.9 (C^b), 119.6 (*C*CHN), 109.9 (C^d), 55.6 (N*C*H$_3$), 54.9 (O*C*H$_3$); LRMS (EI) 165.08 (M$^+$, 36 %), 134.05 (100 %), 119.03 (61 %), 91.00 (61 %); HRMS (EI) calc'd for $C_9H_{11}NO_2$ (M$^+$) 165.0790, found 165.0781.

(*Z*)-1-Mesityl-*N*-methylmethanimine oxide 95



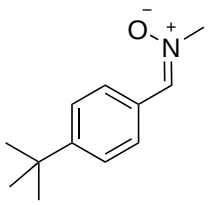
(White crystals, 0.70 g, 99 %); m.p. 166-168 ^{o}C; ν_{max} (film)/cm^{-1} 2915, 1683, 1608, 1445, 1179, 1040, 956; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.54 (1H, s, C*H*N), 6.89 (2H, s, H_{meta*}), 3.90 (3H, s*, NCH_3), 2.27 (3H, s, $C_{para}CH_3$), 2.26 (6H, s, $C_{ortho}CH_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 139.6 (*C*CHN), 137.6 (*C*C_{para}), 135.7 (*C*HN), 128.5 (C_{meta}), 125.8 (*C*C_{ortho}), 53.4 (N*C*H_3), 21.3 (C_{para}*C*H_3), 19.9 (C_{ortho}*C*H_3); LRMS (EI) 117.12 (10 %, M^+), 162.10 (100 %), 147.08 (49 %), 119.06 (15 %); HRMS (EI) calc'd for $C_{11}H_{15}NO$ (M^+) 177.1154, found 117.1151. *meta to nitrone

(*Z*)-*N*-(4-(Trifluoromethyl)benzylidene)methanamine oxide 96



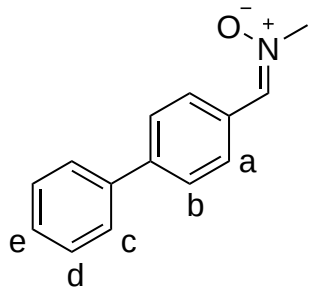
(White crystals, 0.64 g, 79 %); m.p. 110 ^{o}C; ν_{max} (film)/cm^{-1} 3046, 1586, 1414, 1313, 1169, 1108, 1064, 946; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.32 (2H, d, J=8.3 Hz, H_{ortho*}), 7.67 (2H, d, J=8.3 Hz, H_{meta}), 7.45 (1H, s, C*H*N), 3.93 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 134.0 (*C*HN), 133.6 (*C*CHN), 131.7 (q, J=32.8 Hz, *C*CF_3), 128.5 (C_{ortho}), 125.6 (q, J=3.8 Hz, C_{meta}), 123.9 (q, J=272.1 Hz, *C*F_3), 55.0 (*C*H_3); LRMS (EI) 203.05 (M+H^+, 62 %), 201.98 (M^+, 100 %), 145.03 (20 %), 127.03 (14 %); HRMS (EI) calc'd for $C_9H_8F_3NO$ (M^+) 202.0558, found 202.0556. *ortho to nitrone

(*Z*)-*N*-(4-(*tert*-Butyl)benzylidene)methanamine oxide 97



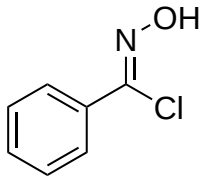
(White crystals, 0.50 g, 66 %); m.p. 97-100 ^{o}C; ν_{max} (film)/cm^{-1} 2957, 1596, 1402, 1360, 1172, 946; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.14 (2H, d, J=8.5 Hz, H_{ortho*}), 7.44 (2H, d, J=8.7 Hz, H_{meta}), 7.34 (1H, s, C*H*N), 3.87 (3H, s, NCH_3), 1.32 (9H, s, C(CH_3)$_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 154.1 (C_{para}), 135.3 (*C*HN), 128.5 (C_{ortho}), 127.9 (*C*CHN), 125.6 (C_{meta}), 54.3 (N*C*H$_3$), 35.1 (*C*(CH$_3$)$_3$), 31.2 (C(*C*H$_3$)$_3$); LRMS (EI) 191.14 (M$^+$, 100 %), 176.12 (95 %), 147.09 (40 %); HRMS (EI) calc'd for $C_{12}H_{17}NO$ (M$^+$) 191.1310, found 191.1313. *ortho to nitrone

(*Z*)-1-([1,1'-Biphenyl]-4-yl)-*N*-methylmethanimine oxide 98



(White crystals, 0.62 g, 74 %); m.p. 125-129 ^{o}C; ν_{max} (film)/cm^{-1} 3320, 1602, 1407, 1153, 938; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.30 (2H, d, J=8.02 Hz, H^a), 7.68 (2H, d, J=8.02 Hz, H^b), 7.64 (2H, d, J= 7.7 Hz, H^c), 7.46 (2H, t, J=7.4 Hz, H^d), 7.42 (1H, s, NC*H*), 7.38 (1H, t, J=7.4 Hz, H^e), 3.92 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 143.1 (*C*C^b), 140.3 (*C*C^c), 135.1 (*C*HN), 129.5 (*C*CHN), 129.0 (C^a), 129.0 (C^d), 128.0 (C^e), 127.2 (C^c), 127.2 (C^b), 54.6 (*C*H$_3$); LRMS (TOFES+) 202.11 (M+H$^+$, 100 %); HRMS (ES+) calc'd for $C_{14}H_{14}NO$ (M+H$^+$) 212.1075, found 212.1066.

(*Z*)-*N*-Hydroxybenzimidoyl chloride 102

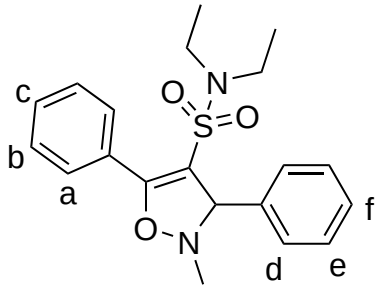


A flame-dried RBF was charged with benzaldehyde (0.92 ml, 9.0 mmol, 1.0 eq) and hydroxylamine hydrochloride (0.94 g, 13.5 mmol, 1.5 eq) in DMF (10 ml) under argon and stirred vigorously. Triethylamine (1.25 ml, 9.0 mmol, 1.0 eq) was added dropwise and the reaction was stirred for 30 minutes at room temperature before it was cooled to -40 ^{o}C. NCS (1.2 g, 9.0 mmol, 1.0 eq) was added in portions and after another 30 minutes, the reaction was allowed to warm to room temperature and quenched with H_2O. The mixture was dissolved in DCM (50 ml) and washed 3 times with lithium chloride (150 ml), before it was reduced *in vacuo* and dissolved in diethyl ether to remove any residual DMF. This was washed with brine, dried with $MgSO_4$, and reduced *in vacuo* to give a pale cream solid, that was stored in the freezer and used without further purification, (1.2 g, 86 %); m.p. 51-53 ^{o}C; ν_{max} (film)/cm^{-1} 3071, 2827, 2545, 1681, 1582, 1453, 1289, 931; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.86 (2H, d, J=7.2 Hz, H_{ortho}), 7.78 (1H, s, O*H*), 7.46 (1H, t, J=7.2 Hz, H_{para}), 7.42 (2H, t, J=7.2 Hz, H_{meta}); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 140.2 (*C*=N), 132.6 (*C*C=N), 130.9 (C_{para}), 128.6 (C_{meta}), 127.3 (C_{ortho}); LRMS (ESI) 155.01 (M^+, 100%), 156.02 (10%). Data in agreement with literature values.[133;144]

General synthesis of 2,3-Dihydroisoxazole-4-sulfonamides 103-126

A mixture of alkynyl sulfonamide (0.21 mmol, 1.0 eq) and nitrone (0.42 mmol, 2.0 eq) in toluene (3 ml) was heated in a sealed tube with stirring at 105 ^{o}C for 1-3 hours until the alkynyl sulfonamide was fully consumed. The mixture was concentrated *in vacuo* and purified with column chromatography (0-30 % ethyl acetate in petroleum ether).

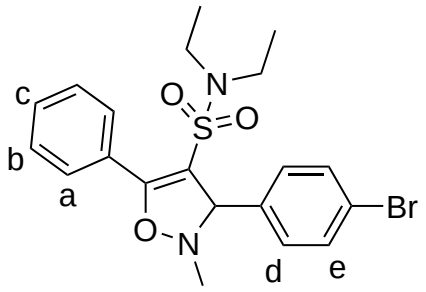
***N*,*N*-Diethyl-2-methyl-3,5-diphenyl-2,3-dihydroisoxazole-4-sulfonamide 103**



(Yellow oil, 48 mg, 60 %); $\nu_{\max}$ (film)/cm^{-1} 3063, 1631, 1449, 1330, 1200, 1149, 1017, 934; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.78 (2H, d, J=7.0 Hz, H^{a}), 7.50 (1H, tt, J= 7.4, 1.5 Hz, H^{c}), 7.43-7.46 (4H, m, H^{d}, H^{b}), 7.38 (2H, t, J=7.7 Hz, H^{e}), 7.32 (1H, t, J=7.3 Hz, H^{f}), 5.04 (1H, s, C=C(SO_2NEt_2)C*H*), 3.04 (3H, s, NCH_3), 2.92 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 2.79 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 0.90 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.0 (*C*=C(SO_2NEt_2)CH), 140.2 (*C*CHN), 131.4 (C^{c}), 129.9 (C^{a}), 128.8 (C^{e}), 128.6 (C^{f}), 128.2 (C^{b}), 127.6 (C^{d}), 126.7 (*C*C=C(SO_2NEt_2)), 111.3 (C=*C*(SO_2NEt_2)CH), 77.8 (C=C(SO_2NEt_2)*C*H), 47.3 (N*C*H$_3$), 41.2 (CH$_2$*C*H$_3$), 14.2 (CH$_2$CH_3); LRMS (CI) 373.10 (M+H^{+}, 52 %), 300.03 (40 %), 295.08 (63 %), 236.09 (58 %), 104.99 (100 %); HRMS (CI) calc'd for $C_{20}H_{24}N_2O_3S$ (M+H^{+}) 373.1586, found 373.1590.

3-(4-Bromophenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

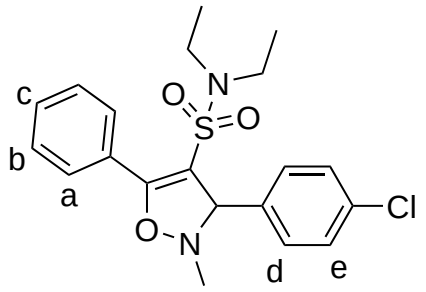
104



(Yellow oil, 64 mg, 67 %); ν_{max} (film)/cm^{-1} 2974, 1631, 1488, 1317, 1147, 1092, 1011, 932; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.77 (2H, d, J= 7.3 Hz, H^a), 7.49-7.52 (3H, m, H^c, H^e), 7.44 (2H, t, J=7.6 Hz, H^b), 7.35 (2H, d, J=8.4 Hz, H^d), 5.02 (1H, s, C=C(SO_2NEt_2)C*H*), 3.03 (3H, s, NCH_3), 2.97 (2H, dq, J= 14.6, 7.2 Hz, CH_2CH$_3$), 2.85 (2H, dq, J= 14.2, 7.2 Hz, CH_2CH$_3$), 0.92 (6H, t, J=7.20 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.0 (*C*=C(SO_2NEt_2)CH), 139.4 (*C*CHN), 131.9 (C^e), 131.7 (C^c), 129.9 (C^a), 129.3 (C^d), 128.3 (C^b), 126.4 (*C*C=C(SO_2NEt_2)), 122.6 (C-Br), 111.0 (C=*C*(SO_2NEt_2)CH), 60.5 (C=C(SO_2NEt_2)*C*H), 47.1 (N*C*H$_3$), 41.2 (*C*H$_2$CH$_3$), 14.0 (CH$_2$*C*H$_3$); LRMS (ESI) 451.07 (M+H$^+$, 100 %), 449.06 (30 %); HRMS (ESI) calc'd for $C_{20}H_{23}BrN_2O_3S$ (M+H$^+$) 451.0691, found 451.0675.

3-(4-Chlorophenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

105

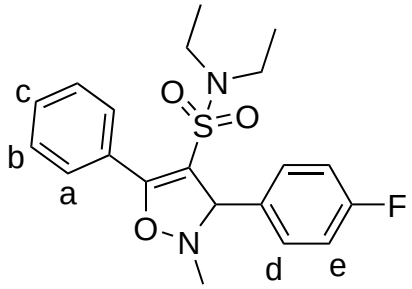


(Yellow crystalline solid, 60 mg, 70 %); m.p. 68-70 ^{o}C; ν_{max} (film)/cm^{-1} 2975, 1723, 1490, 1317, 1148, 1091, 1015, 933; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.77 (2H, d, J=7.1 Hz, H^a), 7.49-7.52 (1H, tt, J=7.4, 1.5 Hz, H^c), 7.44 (2H, t, J=7.6 Hz, H^b), 7.41 (2H, d, J=8.5 Hz, H^d), 7.35 (2H, d, J=8.6 Hz, H^e), 5.03 (1H, s,

C=C(SO_2NEt_2)C*H*), 3.04 (3H, s, NCH_3), 2.97 (2H, dq, J=14.3, 7.3 Hz, C$H_2$$CH_3$), 2.85 (2H, dq, J=14.2, 7.1 Hz, C$H_2$$CH_3$), 0.92 (6H, t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.0 (*C*=C(SO_2NEt_2)CH), 138.8 (*C*CHN), 134.4 (C-Cl), 131.7 (C^c), 129.9 (C^a), 129.0 (C^d), 129.0 (C^e), 128.3 (C^b), 126.4 (*C*C=C(SO_2NEt_2)), 111.0 (C=*C*(SO_2NEt_2)CH), 77.1 (C=C(SO_2NEt_2)*C*H), 47.2 (N*C*H_3), 41.2 (*C*$H_2$$CH_3$), 14.0 ($CH_2$*C*$H_3$); LRMS (ES+) 407.12 (M+H$^+$, 30 %), 334.02 (28 %), 271.07 (50 %), 166.04 (18 %); HRMS (ES+) calc'd for $C_{20}H_{23}ClN_2O_3S$ (M+H$^+$) 407.1196, found 407.1167.

_N_,_N_-Diethyl-3-(4-fluorophenyl)-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

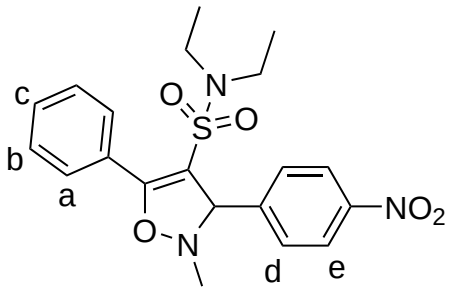
106



(Yellow oil, 20 mg, 25 %); ν_{max} (film)/cm^{-1} 2975, 1599, 1508, 1330, 1223, 1147, 1094, 1015, 932; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.78 (2H, d, J=7.2 Hz, H^b), 7.50 (1H, t, J=7.4 Hz, H^c), 7.43-7.46 (4H, m, H^a, H^d), 7.07 (2H, d, J=8.8 Hz, H^e), 5.04 (1H, s, C=C(SO_2NEt_2)C*H*), 3.04 (3H, s, NCH_3), 2.96 (2H, dq, J=14.3, 7.1 Hz, C$H_2$$CH_3$), 2.84 (2H, dq, J=14.3, 7.1 Hz, C$H_2$$CH_3$), 0.91 (6H, t, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 162.9 (d, J=247.8 Hz, C-F), 158.9 (*C*=C(SO_2NEt_2)CH), 135.9 (*C*CHN), 131.6 (C^c), 129.9 (C^b), 129.4 (d, J=8.0 Hz, C^d), 128.3 (C^a), 126.5 (*C*C=C(SO_2NEt_2)), 115.7 (d, J=21.5 Hz, C^e), 111.2 (C=*C*(SO_2NEt_2)CH), 77.1 (C=C(SO_2NEt_2)*C*H), 47.2 (N*C*H_3), 41.2 (*C*$H_2$$CH_3$), 14.1 ($CH_2$*C*$H_3$); LRMS (ES+) 413.13 (M+Na$^+$, 100 %), 391.16 (75 %), 371.15 (60 %), 350.10 (21 %), 318.07 (82 %); HRMS (ES+) calc'd for $C_{20}H_{23}FN_2O_3S$ (M+Na$^+$) 413.1311, found 413.1323.

***N*,*N*-Diethyl-2-methyl-3-(4-nitrophenyl)-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

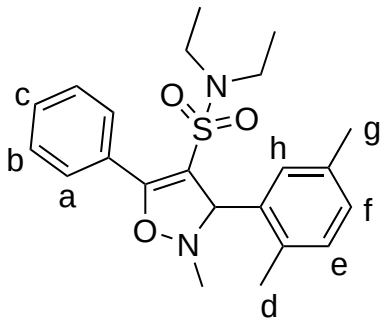
107



(Yellow oil, 61 mg, 70 %); ν_{max} (film)/cm^{-1} 2976, 1597, 1519, 1343, 1314, 1149, 1014, 931; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.25 (2H, d, J=8.9 Hz, H^e), 7.77 (2H, d, J=7.2 Hz, H^b), 7.70 (2H, J=8.7 Hz, H^d), 7.53 (1H, t, J=7.5 Hz, H^c), 7.46 (2H, t, J=7.5 Hz, H^a), 5.16 (1H, s, C=C(SO_2NEt_2)C*H*), 3.08 (3H, s, NCH_3), 3.02 (2H, dq, J=14.4, 7.2 Hz, CH_2CH$_3$), 2.89 (2H, dq, J=14.4, 7.2 Hz, CH_2CH$_3$), 0.91 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.1 (*C*=C(SO_2NEt_2)CH), 147.9 (*C*-NO$_2$), 147.5 (*C*CHN), 132.0 (C^c), 129.9 (C^b), 128.5 (C^d), 128.4 (C^a), 126.0 (*C*C=C(SO_2NEt_2)), 124.0 (C^e), 110.6 (C=*C*(SO_2NEt_2)CH), 76.9 (C=C(SO_2NEt_2)*C*H), 47.2 (N*C*H$_3$), 41.1 (*C*H$_2$CH$_3$), 13.8 (CH$_2$*C*H$_3$); LRMS (ES+) 440.13 (M+Na$^+$, 100 %), 418.15 (33 %), 416.12 (22 %); HRMS (ES+) calc'd for $C_{20}H_{23}N_3O_5S$ (M+Na$^+$) 440.1256, found 440.1277.

3-(2,5-Dimethylphenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

108

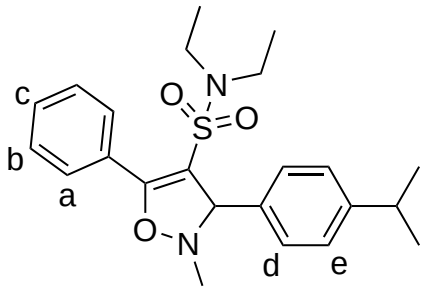


(Yellow oil, 48 mg, 57 %); ν_{max} (film)/cm^{-1} 2973, 1631, 1448, 1318, 1200, 1148, 1016, 933; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.82 (2H, d, J=7.0 Hz, H^b), 7.51 (1H, t,

J=7.4 Hz, H^{c}), 7.46 (2H, t, J=7.4 Hz, H^{a}), 7.24 (1H, s, H^{h}), 7.07 (1H, d, J=7.7 Hz, H^{e}), 7.02 (1H, dd, J=7.7, 0.9 Hz, H^{f}), 5.34 (1H, s, C=C(SO_2NEt_2)C*H*), 3.06 (3H, s, NCH_3), 2.94 (2H, dq, J=14.4, 7.2 Hz, CH_2CH$_3$), 2.80 (2H, dq, J=14.2, 7.0 Hz, CH_2CH$_3$), 2.41 (3H, s, H^{d}), 2.32 (3H, s, H^{g}), 0.92 (6H, t, J=7.2 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.3 (C*C*=C(SO_2NEt_2)), 137.4 (*C*CHN), 136.0 (*C*-Cg), 133.0 (*C*-Cd), 131.4 (C^{c}), 130.8 (C^{e}), 129.9 (C^{b}), 129.2 (C^{f}), 128.3 (2C, C^{a}, C^{h}), 126.8 (*C*C=C(SO_2NEt_2)CH), 110.4 (CC=*C*(SO_2NEt_2)CH), 74.0 (C=C(SO_2NEt_2)*C*H), 47.7 (N*C*H$_3$), 41.2 (*C*H$_2$CH$_3$), 21.3 (C^{g}), 19.2 (C^{d}), 14.2 (CH$_2$*C*H$_3$); LRMS (EI) 400.12 (M$^+$, 36 %), 295.06 (38 %), 248.10 (20 %), 104.99 (100 %); HRMS (EI) calc'd for $C_{22}H_{28}N_2O_3S$ (M$^+$) 400.1821, found 400.1813.

_N_,_N_-Diethyl-3-(4-isopropylphenyl)-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

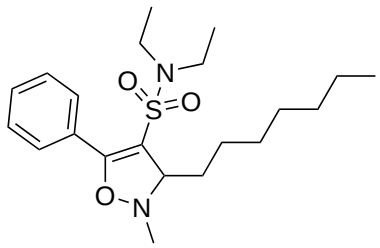
109



(Yellow oil, 55 mg, 63 %); ν_{max} (film)/cm^{-1} 2961, 1630, 1448, 1317, 1147, 1016, 930; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.78 (2H, d, J=7.1 Hz, H^{a}), 7.49 (1H, tt, J=7.4, 1.6 Hz, H^{c}), 7.44 (2H, t, J=7.4 Hz, H^{b}), 7.36 (2H, d, J=8.2 Hz, H^{d}), 7.23 (2H, d, J=8.2 Hz, H^{e}), 5.02 (1H, s, C=C(SO_2NEt_2)C*H*), 3.03 (3H, s, NCH_3), 2.88-2.95 (3H, m, C*H*(CH$_3$)$_2$, CH_2CH$_3$), 2.78 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 1.23 (6H, d, J=6.9 Hz, CH(CH_3)$_2$), 0.89 (6H, t, J=7.2 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 158.9 (*C*=C(SO_2NEt_2)), 149.4 (*C*CH(CH$_3$)$_2$), 137.6 (*C*CHN), 131.4 (C^{c}), 129.9 (C^{a}), 128.2 (C^{b}), 127.6 (C^{d}), 126.9 (C^{e}), 126.8 (*C*C=C(SO_2NEt_2)CH), 111.3 (C=*C*(SO_2NEt_2)CH), 77.6 (C=C(SO_2NEt_2)*C*H), 47.3 (N*C*H$_3$), 41.2 (*C*H$_2$CH$_3$), 34.0 (*C*H(CH$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 24.1 (CH(*C*H$_3$)$_2$), 14.1 (CH$_2$*C*H$_3$); LRMS (EI) 414.11 (M$^+$, 29 %), 262.12 (35 %), 104.99 (100 %); HRMS (EI) calc'd for $C_{23}H_{30}N_2O_3S$ (M$^+$) 414.1977, found 414.1980.

***N*,*N*-Diethyl-3-heptyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

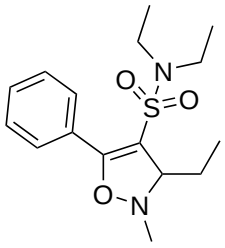
110



(Yellow oil, 40 mg, 48 %); ν_{max} (film)/cm^{-1} 2924, 1631, 1447, 1331, 1148, 928; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.70 (2H, d*, J=7.0 Hz, H_{ortho}), 7.46 (1H, tt, J=7.4, 1.6 Hz, H_{para}), 7.41 (2H, tt, J=7.5 Hz, H_{meta}), 3.92 (1H, dd, J=8.9, 2.8 Hz, C*H*$(CH_2)_6CH_3$), 3.15 (2H, dq, J=14.4, 7.2 Hz, NC*H*$_2CH_3$), 3.07 (2H, dq, J=14.4, 7.2 Hz, NC*H*$_2CH_3$), 2.88 (3H, s, NC*H*$_3$), 1.84-1.89 (1H, m, CHC*H*$_2CH_3$), 1.71-1.77 (1H, m, CHC*H*$_2CH_3$), 1.24-1.38 (10H, m, aliphatic protons), 1.02 (6H, t, J=7.2 Hz, NCH_2CH_3), 0.87 (3H, t, J=7.0 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 158.2 (C*C*=C(SO_2NEt_2)), 131.4 (C_{para}), 130.1 (C_{ortho}), 128.1 (C_{meta}), 126.8 (*C*C=C(SO_2NEt_2)), 110.1 (C=*C*(SO_2NEt_2)), 74.7 (*C*H$(CH_2)_6CH_3$), 47.1 (N*C*H$_3$), 41.3 (N*C*H$_2CH_3$), 35.1 ($CH_2CH_2CH_3$), 32.0 (*C*H$_2$), 29.6 (*C*H$_2$), 29.4 (*C*H$_2$), 25.5 (*C*H$_2$), 22.8 (*C*H$_2$), 14.2 ($CH_2CH_2CH_3$), 14.1 (NCH_2CH_3); LRMS (ES+) 395.24 (M+H$^+$, 100 %), 371.12 (30 %); HRMS (ES+) calc'd for $C_{21}H_{35}N_2O_3S$ (M+H$^+$) 395.2368, found 395.2374.

***N*,*N*-3-Triethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

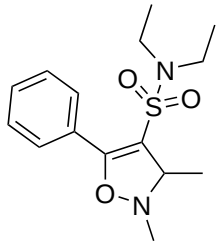
111



(Yellow oil, 14 mg, 20 %); ν_{max} (film)/cm^{-1} 2969, 1633, 1448, 1329, 1149, 931; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.71 (2H, dd, J=8.2, 1.2 Hz, H_{ortho}), 7.46 (1H, tt, J=7.5, 1.6 Hz, H_{para}), 7.41 (2H, tt, J=7.5, 1.4 Hz, H_{meta}), 3.90 (1H, dd, J=8.1,

3.2 Hz, C*H*CH_2CH_3), 3.15 (2H, dq, J=14.3, 7.2 Hz, NC*H*$_2CH_3$), 3.07 (2H, dq, J=14.2, 7.2 Hz, NC*H*$_2CH_3$), 2.89 (3H, s, NC*H*$_3$), 1.91 (1H, dqd, J=14.7, 7.5, 3.1 Hz, C*H*CH_2CH_3), 1.78 (1H, dqd, J=14.7, 7.5, 3.1 Hz, C*H*CH_2CH_3), 1.04 (3H, t, J=7.4 Hz, $CHCH_2$C*H*$_3$), 1.02 (6H, t, J=7.1 Hz, NCH_2C*H*$_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 158.4 (C*C*=C(SO_2NEt_2)), 131.4 (C_{para}), 130.0 (C_{ortho}), 128.1 (C_{meta}), 126.8 (*C*C=C(SO_2NEt_2)), 109.7 (C=*C*(SO_2NEt_2)), 75.8 (*C*HCH_2CH_3), 47.2 (N*C*H$_3$), 41.3 (N*C*H_2CH_3), 28.1 (CH*C*H_2CH_3), 14.1 (NCH_2*C*H$_3$), 9.6 ($CHCH_2$*C*H$_3$); LRMS (CI) 325.12 (M+H$^+$, 34 %), 295.08 (82 %), 222.00 (24 %), 188.10 (73 %), 105.00 (100 %); HRMS (CI) calc'd for $C_{16}H_{25}N_2O_3S$ (M+H$^+$) 325.1586, found 325.1590.

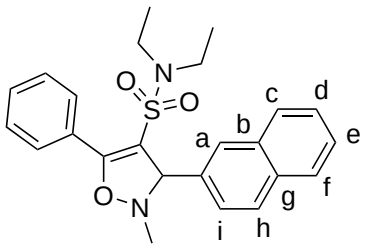
***N*,*N*-Diethyl-2,3-dimethyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide 112**



(Yellow oil, 7 mg, 11 %); ν_{max} (film)/cm^{-1} 2974, 1632, 1330, 1150, 1016, 931; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.71 (2H, d*, J=7.0 Hz, H_{ortho}), 7.47 (1H, tt, J=7.4, 1.6 Hz, H_{para}), 7.41 (2H, t*, J=7.4 Hz, H_{meta}), 4.06 (1H, s*, C*H*CH_3), 3.15 (2H, dq, J=14.3, 7.2 Hz, C*H*$_2CH_3$), 3.10 (2H, dq, J=14.2, 7.2 Hz, C*H*$_2CH_3$), 2.88 (3H, s, NC*H*$_3$), 1.52 (3H, d, J=6.5 Hz, CHC*H*$_3$), 1.04 (6H, t, J=7.2 Hz, CH_2C*H*$_3$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 158.1 (C*C*=C(SO_2NEt_2)), 131.4 (C_{para}), 130.0 (C_{ortho}), 128.1 (C_{meta}), 126.8 (*C*C=C(SO_2NEt_2)), 111.7 (C=*C*(SO_2NEt_2)), 70.2 (*C*HCH_3), 46.4 (N*C*H$_3$), 41.3 (*C*H_2CH_3), 21.6 (CH*C*H$_3$), 14.1 (CH_2*C*H$_3$); LRMS (EI) 310.07 (M$^+$, 5 %), 295.05 (100 %), 222.00 (24 %), 105.00 (35 %); HRMS (EI) calc'd for $C_{15}H_{22}N_2O_3S$ (M$^+$) 310.1351, found 310.1353.

***N*,*N*-Diethyl-2-methyl-3-(naphthalen-2-yl)-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

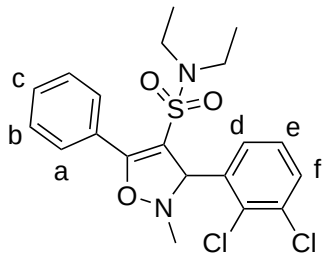
113



(Yellow oil, 63 mg, 70 %); ν_{max} (film)/cm^{-1} 2973, 1628, 1317, 1145, 1015, 932; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.81-7.89 (6H, m, aromatic H), 7.60 (1H, dd, J=8.6, 1.5 Hz, H^i), 7.45-7.53 (5H, m, aromatic H), 5.24 (1H, s, C*H*N), 3.01 (3H, s, NC*H*^{3}), 2.91 (2H, dq, J=14.3, 7.3 Hz, CH_2CH$_3$), 2.77 (2H, dq, J=14.3, 7.3 Hz, CH_2CH$_3$), 0.85 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.1 (C*C*=C(SO$_2$NEt$_2$)), 137.4 (q), 133.5 (C^g), 133.3 (q), 131.5 (Ar-C), 129.9 (Ar-C), 128.9 (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 127.8 (Ar-C), 126.8 (Ar-C), 126.7 (*C*C=C(SO$_2$NEt$_2$), 126.4 (Ar-C), 126.4 (Ar-C), 125.2 (C^i), 111.2 (C=*C*(SO$_2$NEt$_2$)), 78.0 (C=C(SO$_2$NEt$_2$)*C*H), 47.3 (N*C*H$_3$), 41.2 (*C*H2CH$_3$), 14.1 (CH$_2$*C*H$_3$); LRMS (EI) 422.11 (M$^+$, 17 %), 295.08 (38 %), 222.00 (24 %), 105.00 (41 %), 68.95 (100 %); HRMS (EI) calc'd for $C_{24}H_{26}N_2O_3S$ (M$^+$) 422.1664, found 422.1662.

3-(2,3-Dichlorophenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

114

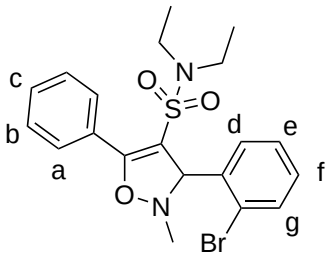


(White solid, 58 mg, 62 %); m.p. 116-119 ^{o}C; ν_{max} (film)/cm^{-1} 2972, 1624, 1302, 1144, 1073, 1009, 933; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.86 (2H, d, J=7.2 Hz, H^a), 7.54 (1H, tt, J=7.5, 1.4 Hz, H^c), 7.45-7.50 (4H, m, H^b, H^d, H^f), 7.29 (1H, t, J=8.0 Hz, H^e), 5.62 (1H, s, C=C(SO$_2$NEt$_2$)C*H*), 3.13 (3H, s*, NC*H*$_3$), 3.13 (2H, dq, J=14.4,

7.2 Hz, CH_2CH$_3$), 3.03 (2H, dq, J=14.1, 6.9 Hz, CH_2CH$_3$), 1.02 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, CDCl$_3$) δ_C 160.8 (CC=C(SO$_2$NEt$_2$)), 139.1 (CCHN), 133.7 (C^f C-Cl), 132.4 (CC-Cl), 132.0 (C^c), 130.7 (C^f), 130.2 (C^a), 128.4 (C^b), 127.9 (C^e), 127.3 (C^d), 126.1 (CC=C(SO$_2$NEt$_2$)), 108.0 (C=C(SO$_2$NEt$_2$)CH), 74.5 (C=C(SO$_2$NEt$_2$)CH), 47.4 (NCH$_3$), 41.6 (CH$_2$CH$_3$), 14.3 (CH$_2$$CH_3$); LRMS (EI) 440.01 (M+, 6 %), 295.08 (16 %), 105.0 (100 %); HRMS (EI) calc'd for C$_{20}$H$_{22}$Cl$_2$N$_2$O$_3$S (M$^+$) 440.0728, found 440.0723.

3-(2-Bromophenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

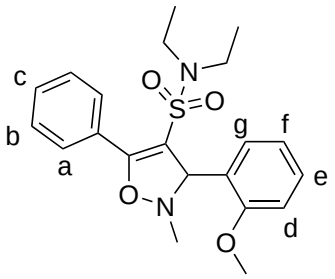
115



(Golden oil, 64 mg, 67 %); ν_{max} (film)/cm^{-1} 2973, 1628, 1318, 1148, 1071, 933; ^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.77 (1H, d*, J=6.9 Hz, H^a), 7.61 (1H, t, J=1.7 Hz, H^e), 7.51 (1H, tt, J=7.4, 1.6 Hz, H^c), 7.45 (3H, t*, J=7.5 Hz, H^b, H^f), 7.41 (1H, d, J=7.7 Hz, H^d), 7.25 (1H, t, J=7.8 Hz, H^g), 5.02 (1H, s, C=C(SO$_2$NEt$_2$)CH), 3.04 (3H, s, NCH_3), 2.96 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 2.83 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 0.91 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, CDCl$_3$) δ_C 159.2 (CC=C(SO$_2$NEt$_2$)), 142.5 (CCHN), 131.6 (C^c), 130.7 (C^e), 130.4 (C^g), 129.9 (C^a), 128.3 (C^b), 126.4 (CC=C(SO$_2$NEt$_2$)), 126.3 (C^d), 122.8 (C-Br), 110.9 (C=C(SO$_2$NEt$_2$)), 77.2 (C=C(SO$_2$NEt$_2$)CH), 47.2 (NCH$_3$), 41.1 (CH$_2$CH$_3$), 14.0 (CH$_2$$CH_3$); LRMS (ES) 451.07 (100 %), 317.03 (80 %); HRMS (ES) calc'd for C$_{20}$H$_{24}$BrN$_2$O$_3$S (M$^+$) 451.0691, found 451.0717.

***N*,*N*-Diethyl-3-(2-methoxyphenyl)-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

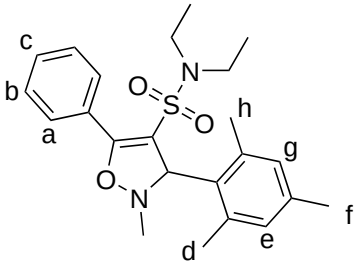
116



(Yellow oil, 42 mg, 50 %); ν_{max} (film)/cm^{-1} 2973, 1599, 1490, 1330, 1242, 1148, 1019, 930; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.83 (2H, d*, J=7.8 Hz, H^a), 7.50 (1H, tt, J=7.4, 1.7 Hz, H^c), 7.43-7.49 (3H, m, H^b, H^g), 7.30 (1H, td, J=7.8, 1.6 Hz, H^e), 7.00 (1H, t, J=7.5 Hz, H^f), 6.91 (1H, d, J=7.6 Hz, H^d), 5.57 (1H, br s, C=C(SO_2NEt_2)C*H*), 3.87 (3H, s, OCH_3), 3.04 (2H, dq, J=14.4, 7.2 Hz, CH_2CH$_3$, 3H, br s, NCH_3), 2.94 (2H, dq, J=14.2, 7.0 Hz, CH_2CH$_3$), 0.98 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 160.0 (*C*=C(SO_2NEt_2)CH), 157.1 ($COCH_3$), 131.5 (C^c), 130.1 (C^a), 129.8 (C^e), 128.3 (C^g), 128.2 (C^b), 127.8 (*C*CHN), 126.8 (*C*C=C(SO_2NEt_2)), 121.0 (C^f), 110.9 (C^d), 108.6 (C=*C*(SO_2NEt_2)CH), 70.8 (C=C(SO_2NEt_2)*C*H), 55.7 (O*C*H$_3$), 47.5 (N*C*H$_3$), 41.7 (*C*H$_2$CH$_3$), 14.5 (CH$_2$*C*H$_3$); LRMS (CI) 403.09 (M+H$^+$, 82 %), 330.02 (46 %), 295.06 (62 %), 266.08 (75 %), 226.03 (100 %); HRMS (CI) calc'd for $C_{21}H_{27}N_2O_4S$ (M+H)$^+$ 403.1692, found 403.1695.

***N*,*N*-Diethyl-3-mesityl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide**

117

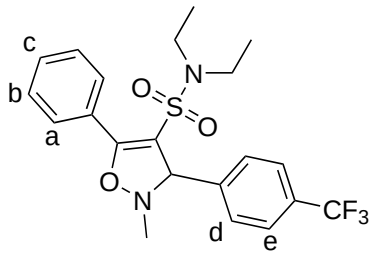


(Yellow oil, 57 mg, 65 %); ν_{max} (film)/cm^{-1} 2973, 1634, 1447, 1314, 1146, 1015; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.68 (2H, d*, J=7.0 Hz, H^a), 7.47 (1H,

tt, J=7.4, 1.7 Hz, H^{c}), 7.43 (2H, t*, J=7.3 Hz, H^{b}), 6.88 (1H, s, H^{e}), 5.77 (1H, br s, C=C(SO_2NEt_2)C*H*), 6.83 (1H, s, H^{g}), 3.04 (3H, s, NCH_3), 2.84 (2H, dq, J=14.4, 7.3 Hz, CH_2CH$_3$), 2.70 (2H, dq, J=14.1, 7.0 Hz, CH_2CH$_3$), 2.53 (3H, s, H^{d}), 2.47 (3H, s, H^{g}), 2.25 (3H, s, H^{f}), 0.88 (6H, t, J=7.2 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.0 (*C*=C(SO_2NEt_2)CH), 139.0 (*C*C^{d}), 137.9 (*C*C^{f}), 137.2 (*C*C^{h}), 131.9 (C*C*HN), 131.6 (C^{e}), 131.0 (C^{c}), 129.6 (C^{g}), 129.5 (C^{a}), 128.2 (C^{b}), 127.0 (*C*C=C(SO_2NEt_2)), 108.5 (CC=*C*(SO_2NEt_2)), 74.3 (C=C(SO_2NEt_2)*C*H), 48.7 (N*C*H$_3$), 40.9 (*C*H$_2$CH$_3$), 21.0 (C^{f}), 20.8 (C^{h}), 19.7 (C^{d}), 14.2 (CH_2*C*H$_3$); LRMS (ES+) 415.21 (M+H$^+$, 100%); HRMS (ES+) calc'd for $C_{23}H_{31}N_2O_3S$ (M+H$^+$) 415.2055, found 415.2059.

_N_,_N_-Diethyl-2-methyl-5-phenyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydroisoxazole-4-sulfonamide

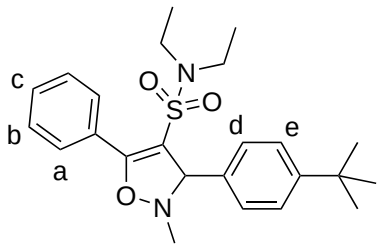
118



(Yellow oil, 82 mg, 88 %); ν_{max} (film)/cm^{-1} 2976, 1620, 1322, 1109, 1065; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.78 (2H, d*, J=7.1 Hz, H^{a}), 7.64 (2H, d, J=8.2 Hz, H^{e}), 7.61 (2H, d, J=8.4 Hz, H^{d}), 7.51 (1H, tt, J=7.4, 1.6 Hz, H^{c}), 7.45 (2H, t*, J=7.6 Hz, H^{b}), 5.11 (1H, br s, C=C(SO_2NEt_2)C*H*), 3.07 (3H, s, NCH_3), 2.98 (2H, dq, J=14.4, 7.3 Hz, CH_2CH$_3$), 2.85 (2H, dq, J=14.3, 7.1 Hz, CH_2CH$_3$), 0.90 (6H, t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.1 (*C*=C(SO_2NEt_2)CH), 144.4 (*C*CHN), 131.8 (C^{c}), 130.7 (q, J=32.9 Hz, *C*CF_3), 129.9 (C^{a}), 128.4 (C^{b}), 127.9 (C^{d}), 126.3 (*C*C=C(SO_2NEt_2)), 125.8 (q, J=3.8 Hz, C^{e}), 124.2 (q, J=273.8 Hz, CF_3), 110.9 (CC=*C*(SO_2NEt_2)), 77.2 (C=C(SO_2NEt_2)*C*H), 47.2 (N*C*H$_3$), 41.0 (*C*H$_2$CH$_3$), 13.8 (CH_2*C*H$_3$); LRMS (EI) 440.07 (M$^+$, 37 %), 295.07 (47 %), 105.00 (100 %); HRMS (EI) calc'd for $C_{21}H_{23}F_3N_2O_3S$ (M$^+$) 440.1382, found 440.1383.

3-(4-(*tert*-Butyl)phenyl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

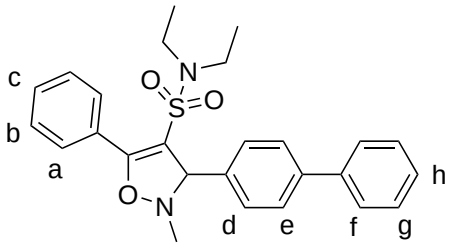
119



(Yellow oil, 90 mg, 80 %); ν_{max} (film)/cm^{-1} 2960, 2096, 1696, 1605, 1446, 1330, 1267, 1146, 1016, 929; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.78 (2H, d*, J=7.1 Hz, H^a), 7.49 (1H, tt, J=7.34, 1.6 Hz, H^c), 7.44 (2H, t*, J=7.5 Hz, H^b), 7.39 (2H, d, J=8.6 Hz, H^e), 7.36 (2H, d, J=8.5 Hz, H^d), 5.02 (1H, s, C=C(SO_2NEt_2)C*H*), 3.03 (3H, s, NCH_3), 2.91 (2H, dq, J=14.3, 7.2 Hz, CH_2CH$_3$), 2.78 (2H, dq, J=14.3, 7.0 Hz, CH_2CH$_3$), 1.30 (9H, s, C(CH_3)$_3$), 0.88 (6H, t, J=7.1 Hz, CH$_2$CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 158.9 (*C*=C(SO_2NEt_2)CH), 151.6 (*C*C(CH$_3$)$_3$), 137.2 (*C*CHN), 131.4 (C^c), 128.2 (C^b), 129.9 (C^a), 127.2 (C^d), 126.8 (*C*C=C(SO_2NEt_2)), 125.8 (C^e), 111.3 (CC=*C*(SO_2NEt_2)), 77.3 (C=C(SO_2NEt_2)*C*H), 47.4 (N*C*H$_3$), 41.1 (*C*H$_2$CH$_3$), 34.7 (*C*(CH$_3$)$_3$), 31.4 (C(*C*H$_3$)$_3$), 14.1 (CH$_2$*C*H$_3$); LRMS (ES+) 429.22 (M+H$^+$, 100 %); HRMS (ES+) calc'd for $C_{24}H_{33}N_2O_3S$ (M+H$^+$) 429.2212, found 429.2196.

3-([1,1'-Biphenyl]-4-yl)-*N*,*N*-diethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-sulfonamide

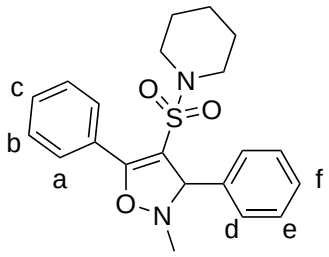
120



(Pale yellow solid, 83 mg, 88 %); m.p. 103-106 ^{o}C; ν_{max} (film)/cm^{-1} 2977, 1633, 1313, 1144, 1088, 933; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.81 (2H, d, J=7.8 Hz, 2xCH), 7.62 (2H, d, J=7.8 Hz, 2xCH), 7.59 (2H, d, J=7.8 Hz, 2xCH), 7.53 (2H, d, J=7.9

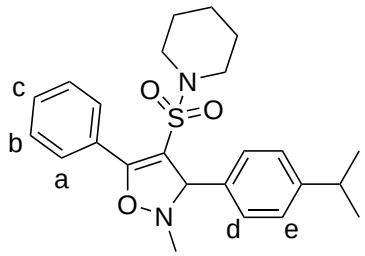
Hz, 2xCH), 7.50 (1H, d*, J=7.1 Hz, CH), 7.47 (2H, d, J=8.0 Hz, 2xCH), 7.44 (2H, d, J=7.7 Hz, 2xCH), 7.36 (1H, t, J=7.4 Hz, CH), 5.10 (1H, s, C=C(SO_2NEt_2)C*H*), 3.08 (3H, s, NCH_3), 2.97 (2H, dq, J=14.5, 7.3 Hz, CH_2CH_3), 2.85 (2H, dq, J=14.3, 7.1 Hz, CH_2CH_3), 0.92 (6H, t, J=7.1 Hz, CH_2CH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.0 (*C*=C(SO_2NEt_2)CH), 141.5 (q), 140.9 (q), 131.5 (Ar-C), 129.9 (2xCH), 129.1 (q), 128.9 (2xAr-C), 128.3 (2xAr-C), 128.0 (2xAr-C), 127.6 (2xAr-C), 127.5 (2xAr-C), 127.3 (Ar-C), 126.7 (*C*C=C(SO_2NEt_2)), 111.2 (CC=*C*(SO_2NEt_2)), 77.4 (C=C(SO_2NEt_2)*C*H), 47.2 (N*C*H_3), 41.2 (*C*H_2CH_3), 14.1 (CH_2*C*H_3); LRMS (ES+) 449.19 (M+H^+, 50 %), 325.23 (20 %), 173.12 (47 %); HRMS (ES+) calc'd for $C_{26}H_{29}N_2O_3S$ (M+H^+) 449.1899, found 449.1881.

2-Methyl-3,5-diphenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole 121



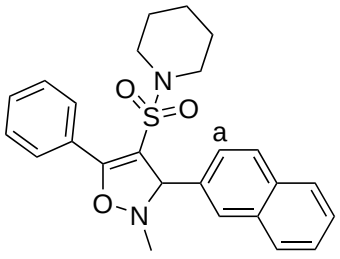
(Yellow oil, 50 mg, 66 %); ν_{max} (film)/cm^{-1} 2946, 2853, 2168, 1697, 1446, 1163, 1025, 932; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.81 (2H, d*, J=7.1 Hz, H^a), 7.51 (1H, tt, J=7.4, 1.6 Hz, H^c), 7.44-7.48 (4H, m, H^b, H^d), 7.40 (2H, t, J=7.5 Hz, H^e), 7.34 (1H, tt, J=7.3, 1.6 Hz, H^f), 5.07 (1H, s, NC*H*), 3.07 (3H, s, NCH_3), 2.72-2.84 (4H, m, SO_2NC$H^{ax}H^{eq}$), 1.25-1.31 (6H, m, N(CH_2CH_2C*H*)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.4 (C*C*=CS), 140.4 (C=CCH*C*), 131.5 (C^c), 130.0 (C^a), 128.9 (C^e), 128.6 (C^f), 128.3 (C^b), 127.6 (C^d), 126.7 (*C*C=CS), 110.2 (CC=*C*S), 77.8 (N*C*H_3), 47.4 (N*C*H_3), 45.9 (N*C*H_2), 25.3 (N(CH_2*C*H_2CH)$_2$), 23.7 (N(CH_2CH_2*C*H)$_2$); LRMS (ESI) 385.2 (95 %), 236.1 (10 %); HRMS (ESI) calc'd for $C_{21}H_{25}N_2O_3S$ (M+H^+) 385.1586, found 385.1587.

2-Methyl-3,5-diphenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole
122



(Yellow oil, 80 mg, 84 %); ν_{max} (film)/cm^{-1} 2959, 2939, 2857, 1631, 1448, 1147, 1107, 1049, 933; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.80 (2H, d*, J=7.1 Hz, H^a), 7.51 (1H, tt, J=7.5, 1.8 Hz, H^c), 7.45 (2H, tt, J=7.2, 1.2 Hz, H^b), 7.37 (2H, d, J=8.1 Hz, H^d), 7.25 (2H, d, J=8.1 Hz, H^e), 5.04 (1H, s, NC*H*), 3.06 (3H, s, NCH_3), 2.91 (1H, sept, J=6.9 Hz, C*H*$(CH_3)_2$), 2.68-2.82 (4H, m, NC$H^{ax}H^{eq}$), 1.25-1.31 (12H, m, CH(CH_3)2, N$(CH_2CH_2CH)_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.4 (C*C*=CS), 149.4 (*C*CH$(CH_3)_2$), 131.4 (C^c), 129.9 (C^a), 128.2 (C^b), 127.6 (C^d), 127.0 (C^e), 126.8 (*C*C=CS), 110.3 (CC=*C*S), 77.3 (NCH*C*C^d), 47.5 (NCH_3), 45.8 (N$(CH_2CH_2CH)_2$), 34.1 (*C*H$(CH_3)_2$), 25.3 (N$(CH_2CH_2CH)_2$), 24.1 (CH$(CH_3)_2$), 23.7 (N$(CH_2CH_2CH)_2$); LRMS (ESI+) 427.21 (100 %), 278.15 (11 %); HRMS (ESI+) calc'd for $C_{24}H_{31}N_2O_3S$ ($M+H^+$) 427.2055, found 427.2052.

2-Methyl-3-(naphthalen-2-yl)-5-phenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole
123

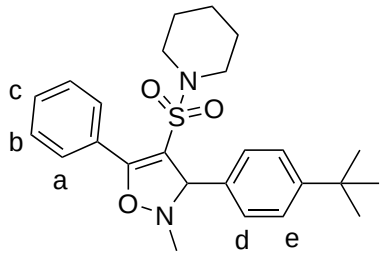


(Yellow oil, 76 mg, 83 %); ν_{max} (film)/cm^{-1} 3052, 2924, 2848, 1635, 1444, 1338, 934; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.83-7.96 (6H, m, aromatic H), 7.46-7.62 (5H, m, aromatic H), 7.61 (1H, dd, J=8.5, 1.5 Hz, H^a), 5.25 (1H, s, NC*H*), 3.12 (3H, s, NCH_3), 2.82 (2H, ddd, J=12.3, 6.4, 5.3 Hz, SO_2NCH_2), 2.75 (2H, ddd, J=12.2, 6.3, 5.3 Hz, SO_2NCH_2), 1.18-1.26 (6H, m, SO_2N$(CH_2CH_2CH)_2$); ^{13}C NMR (600

MHz, $CDCl_3$) δ_C 159.8 (C*C*=C), 154.2 (q), 133.5 (q), 133.3 (q), 131.6 (CH), 130.0 (CH), 128.9 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 126.8 (CH), 126.7 (*C*C=C), 126.4 (CH), 126.3 (CH), 125.1 (C^a), 110.7 (CC=*C*), 78.1 (N*C*H), 47.3 (N*C*H_3), 45.9 (N(*C*$H_2CH_2CH)_2$), 25.2 (N(CH_2*C*$H_2CH)_2$), 23.6 (N(CH_2CH_2*C*H)$_2$); LRMS (ESI) 891.32 (2M+Na^+, 35 %), 435.17 (M+H^+, 88 %); HRMS (ESI) calc'd for $C_{25}H_{27}N_2O_3S$ (M+H^+) 435.1737, found 435.1739.

3-(4-(*tert*-Butyl)phenyl)-2-methyl-5-phenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole

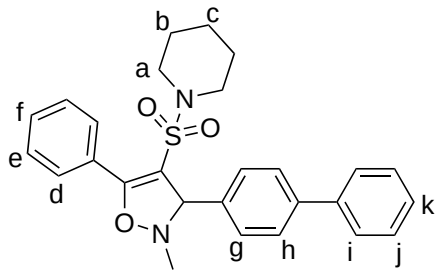
124



(Yellow oil, 64 mg, 68 %); ν_{max} (film)/cm^{-1} 3056, 2961, 2860, 1695, 1632, 1445, 1093, 935; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.80 (2H, d*, J=7.0 Hz, H^a), 7.50 (1H, t, J=7.4 Hz, H^c), 7.45 (2H, t, J=7.5 Hz, H^b), 7.41 (2H, d, J=8.5 Hz, H^e), 7.38 (2H, d, J=8.4 Hz, H^d), 5.04 (1H, s, N(CH_3)C*H*C), 3.06 (3H, s, NC*H*$_3$), 2.67-2.81 (4H, m, N(C*H*$_2CH_2CH)_2$), 1.31 (9H, s, C(C*H*$_3)_3$), 1.02-1.27 (6H, m, N(CH_2C*H*$_2$C*H*)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.4 (C*C*=CS), 151.6 (C^e*C*), 137.5 (CH*C*C^d)), 131.4 (C^c), 129.9 (C^a), 128.2 (C^b), 127.3 (C^d), 126.8 (C*C*C=CS), 125.8 (C^e), 110.2 (CC=*C*S), 77.1 (CH_3N*C*H), 45.8 (N(*C*$H_2CH_2CH)_2$), 34.7 (*C*($CH_3)_3$), 31.4 (C(*C*$H_3)_3$), 25.2 (N(CH_2*C*$H_2CH)_2$), 23.7 (N(CH_2CH_2*C*H)$_2$); LRMS (EI) 440.20 (24 %), 307.11 (100 %), 292.16 (39 %), 276.17 (41 %), 105.01 (61 %); HRMS (EI) calc'd for $C_{25}H_{32}N_2O_3S$ (M^+) 440.2134, found 440.2137.

3-(4-(*tert*-Butyl)phenyl)-2-methyl-5-phenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole

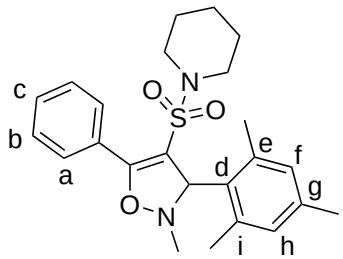
125



(Yellow oil, 78 mg, 80 %); ν_{max} (film)/cm^{-1} 3057, 3029, 2943, 2851, 1697, 1626, 1600, 1486, 1448, 1028, 927; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.83 (2H, d, J=8.6 Hz, H^d), 7.62 (2H, d, J=8.1 Hz, H^i), 7.58 (2H, d, J=7.3 Hz, H^g), 7.55-7.51 (3H, m, H^f, H^h), 7.43-7.48 (4H, m, H^e, H^j), 7.36 (1H, t, J=7.4 Hz, H^k), 5.12 (1H, s, N(CH_3)C*H*C), 3.10 (3H, s, NC*H*$_3$), 2.79-2.88 (4H, m, H^a), 1.27-1.31 (6H, m, H^b, H^c); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 168.6 (q), 159.5 (C*C*=CS), 141.6 (q), 141.0 (q), 131.6 (C^f), 130.0 (C^d), 128.9 (2xAr-C), 128.3 (2xAr-C), 128.0 (2xAr-C), 127.7 (C^h), 127.5 (C^i), 127.3 (C^g), 126.6 (*C*C=CS), 110.2 (CC=*C*S), 77.3 (CH_3N*C*H), 47.4 (N*C*H$_3$), 46.0 (C^a), 25.3 (C^b), 23.7 (C^c); LRMS (ESI) 461.19 (M+H$^+$, 100 %), 943.36 (2M+Na$^+$, 46 %); HRMS (ESI) calc'd for $C_{27}H_{29}N_2O_3S$ (M+H$^+$) 461.1893, found 461.1895.

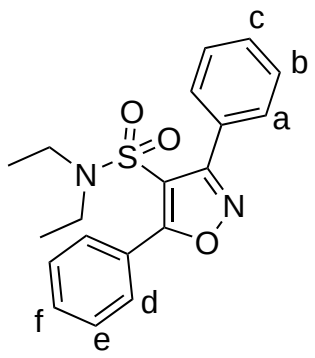
3-Mesityl-2-methyl-5-phenyl-4-(piperidin-1-ylsulfonyl)-2,3-dihydroisoxazole

126



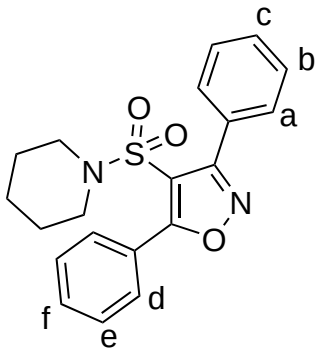
(Yellow oil, 48 mg, 53 %); $\nu_{\max}$ (film)/cm^{-1} 2944, 2920, 2850, 1640, 1440, 1321, 1277, 1150, 1102, 1047, 918; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.68 (2H, d, J=7.7 Hz, H^a), 7.49 (1H, t, J=7.4 Hz, H^c), 7.44 (2H, t, J=7.4 Hz, H^b), 6.90 (1H, s, H^f), 6.84 (1H, s, H^h), 5.76 (1H, s, CHN), 3.06 (NCH_3), 2.76 (2H, dq, J=11.3, 6.1 Hz, N(CH_2CH$_2$CH)$_2$), 2.64 (2H, dq, J=11.9, 6.4 Hz, N(CH$_2$CH_2CH)$_2$), 2.54 (3H, s, C^{e}CH_3), 2.47 (3H, s, C^{i}CH_3), 2.26 (3H, s, C^{g}CH_3), 1.20-1.30 (6H, m, N(CH$_2$CH_2CH)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 159.7 (CC=CS), 138.9 (C^e), 137.8 (C^g), 137.4 (C^i), 132.3 (C^d), 131.6 (C^f), 131.1 (C^c), 129.6 (C^a), 129.6 (C^h), 128.2 (C^b), 126.9 (CC=CS), 107.2 (CC=CS), 74.1 (CHN), 48.9 (NCH$_3$), 45.6 (N(CH$_2$CH$_2$CH)$_2$), 25.4 (N(CH$_2$$CH_2$CH)$_2$), 23.8 (N(CH$_2CH_2$$C$H)$_2$), 21.0 (C^g$CH_3$), 20.8 (C^i$CH_3$), 19.6 (C^e$CH_3$); LRMS (ESI) 427.21 (M+H$^+$, 100 %), 875.38 (2M+Na$^+$, 33 %); HRMS (ESI) calc'd for $C_{24}H_{31}N_2O_3S$ (M+H$^+$) 427.2055, found 427.2059.

***N*,*N*-Diethyl-3,5-diphenylisoxazole-4-sulfonamide 127**



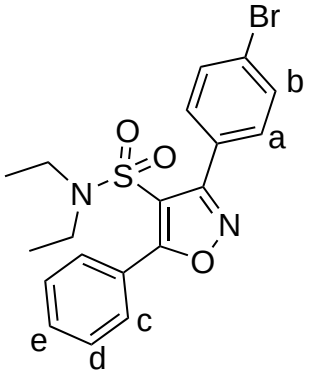
A mixture of alkynyl sulfonamide **39** (0.17 g, 0.72 mmol, 1.0 eq) and DIPEA (0.63 ml, 3.6 mmol, 5 eq) in toluene (2 ml) was refluxed in a sealed tube under argon with stirring whilst chloroxime (0.134 g, 0.86 mmol, 1.2 eq) in toluene (4 ml) added dropwise over 2 hours. The reaction was monitored by TLC until there was no further change in reaction equilibria (usually 1 hour after addition was complete), after which the mixture was reduced *in vacuo* to give a brown oil that was purified by column chromatography (0-20 % ether in petroleum ether) to give the title compound as white crystals, (154 mg, 60 %); m.p. 152-154 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 3063, 2979, 2935, 2872, 1566, 1445, 1342, 1201, 1171, 1119, 1017, 937; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.87 (2H, d*, J=7.2 Hz, H^{d}), 7.75 (2H, dd, J=7.5, 1.2 Hz, H^{a}), 7.58 (1H, tt, J=7.4, 1.7 Hz, H^{f}), 7.49–7.55 (5H, m, H^{b}, H^{c}, H^{e}), 2.84 (4H, q, J=14.4, 7.2 Hz, N(CH_2CH$_3$)$_2$), 0.85 (6H, t, J=7.2 Hz, (CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 173.1 (CC=CS), 162.0 (ON=CC), 131.8 (C^{f}), 130.5 (C^{e}), 130.1 (C^{d}), 129.8 (C^{a}), 128.5 (Ar-C), 128.4 (Ar-C), 127.8 (OCN=C), 126.3 (CC=CS), 117.2 (CC=CS), 41.0 (N(CH$_2$CH$_3$)$_2$), 13.5 (N(CH$_2$$CH_3$)$_2$); LRMS (ES+) 357.13 (100 %), 242.29 (20 %), 214.09 (29 %); HRMS (ES+) calc'd for $C_{19}H_{21}N_2O_3S$ (M^{+}) 357.1273, found 357.1266.

3,5-Diphenyl-4-(piperidin-1-ylsulfonyl)isoxazole 128



A mixture of alkynyl sulfonamide **78** (0.1 g, 0.42 mmol, 1.0 eq) and DIPEA (0.37 ml, 2.1 mmol, 5 eq) in toluene (2 ml) was placed in a sealed tube under argon with stirring whilst chloroxime (0.134 g, 0.86 mmol, 1.2 eq) in toluene (4 ml) added dropwise over 1 hour at room temperature. After being stirred for a further 2 hours at room temperature, the mixture was heated at 100 ^{o}C for an hour upon which TLC indicated there was no further change in reaction equilibria. The mixture was then reduced *in vacuo* to give a brown oil that was purified by column chromatography (0-20 % ether in petroleum ether) to give the title compound as white crystals, (154 mg, 60 %); m.p. 159-162 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 3060, 2943, 2856, 2180, 1563, 1486, 1444, 1349, 1279, 1174, 1125, 1054, 938; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.88 (2H, d, J=7.0 Hz, H^{d}), 7.76 (2H, d, J=7.0 Hz, H^{a}), 7.58 (1H, t, J=7.2 Hz, H^{f}), 7.49-7.55 (5H, m, H^{b}, H^{c}, H^{e}), 2.74 (4H, t*, J=5.4 Hz, N(CH_2CH$_2$CH)$_2$), 1.28-1.31 (2H, m, N(CH$_2$CH$_2$CH)$_2$), 1.19-1.23 (4H, m, N(CH$_2$CH_2CH)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 173.4 (OC=CS), 162.1 (N=CCS), 131.8 (C^{f}), 130.4 (C^{c}), 130.1 (C^{d}), 129.8 (C^{a}), 128.5 (C^{e}), 128.4 (C^{b}), 127.8 (OCCC), 126.3 (N=CCC), 115.4 (OC=CS), 46.0 (N(CH$_2$CH$_2$CH)$_2$), 25.1 (N(CH$_2$$CH_2$CH)$_2$), 23.5 (N(CH$_2CH_2$$C$H)$_2$); LRMS (ES+) 369.13 (52 %), 328.15 (93 %), 242.29 (100 %); HRMS (ES+) calc'd for $C_{20}H_{21}N_2O_3S$ (M+H^{+}) 369.1273, found 369.1260.

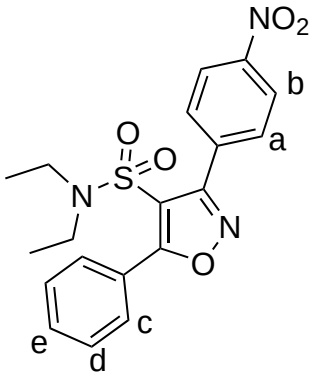
3-(4-Bromophenyl)-*N*,*N*-diethyl-5-phenylisoxazole-4-sulfonamide 129



A flame-dried RBF was charged with 4-bromobenzaldehyde (0.13 g, 0.71 mmol, 2.6 eq) and N-hydroxylamine.HCl (49 mg, 0.71 mmol, 2.6 eq) in DMF (1.5 ml) under argon. Triethylamine (0.1 ml, 0.71 mmol, 2.6 eq) was added dropwise and the mixture was stirred at room temperature for 30 minutes until the aldehyde was fully consumed. N-chlorosuccinimide (0.11 g, 0.82 mmol, 3 eq) was then added in one burst and the reaction was monitored by TLC for 1 hour until the intermediate was fully consumed. The DMF was removed by dissolving the mixture in DCM, and washing with lithium chloride solution. Any remaining product in the aqueous layer was extracted with ether and washed with brine, before the organic layers were dried with $MgSO_4$ and reduced to give a pale cream solid. Assuming a 100 % conversion, this chloroxime was dissolved in toluene (4 ml) and added dropwise to a stirring solution of alkynyl sulfonamide (0.064 g, 0.27 mmol, 1 eq) and DIPEA (0.05 ml, 0.27 ml, 1 eq) in toluene (1 ml) at 100 ^{o}C over 1 hour. After 1 further hour, TLC indicated that the chloroxime was fully consumed but that the Rf between the sulfonamide starting material and **129** in 20 % ether/petroleum ether and ethyl acetate/petroleum ether were too close to separate easily. DMA (1 ml), H_2O (1 ml) and THF (2 ml) were added, and the mixture was refluxed to ensure the sulfonamide was fully consumed. The mixture was cooled to room temperature, dissolved in DCM, washed with H_2O and dried with $MgSO_4$, before it was reduced in vacuo and purified by column chromatography in 0-10 % ethyl acetate in petroleum ether to afford the title compound as an off white solid, (56 mg, 47 %); m.p. 147-149 ^{o}C; ν_{max} (film)/cm^{-1} 2976, 2935, 2875, 1557, 1486, 1447, 1403, 1330, 1166, 1123, 1072, 1015, 943; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.85 (2H, d, J=7.4 Hz, H^c), 7.64 (2H, s*, H^a), 7.64 (2H, s*, H^b), 7.59 (1H, t, J=7.4 Hz, H^e), 7.54 (2H, t, J=7.4 Hz, H^d), 2.88 (4H, dq, N(CH_2CH$_3$)$_2$), 0.86 (6H, t, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$)

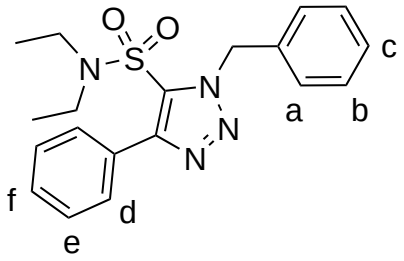
δ_C 173.1 (O*C*=CS), 161.2 (N=*C*CS), 131.9 (C^e), 131.7 (C^b), 131.4 (C^a), 130.0 (C^c), 128.5 (C^d), 126.7 (N=C*C*C), 126.1 (OC*C*C), 125.1 (*C*Br), 117.0 (OC=*C*S), 41.0 (N(*C*H$_2$CH$_3$)$_2$), 13.4 (N(CH$_2$*C*H$_3$)$_2$); LRMS (ES+) 437.04 (M+H$^+$, 100 %), 347.12 (35 %), 214.09 (40 %); HRMS (ES+) calc'd for $C_{19}H_{20}BrN_2O_3S$ (M+H$^+$) 435.0378, found 435.0368.

N,*N*-Diethyl-3-(4-nitrophenyl)-5-phenylisoxazole-4-sulfonamide 130



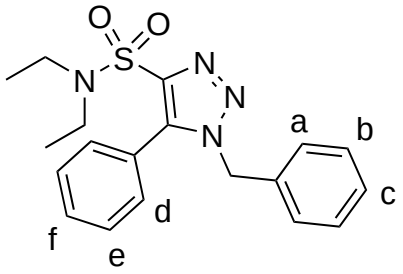
Using the same procedure and quantities for **129**, but with 4-nitrobenzaldehyde (0.11 g, 0.71 mmol, 2.6 eq), and without the need to separate the sulfonamide and product chemically as the Rf values were distinct. The title compound was purified by column chromatography in 100 % $CHCl_3$ to give a yellow oil, (42 mg, 49 %); ν_{max} (film)/cm^{-1} 2979, 2936, 1523, 1345, 1015, 854; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.37 (2H, d, J=8.8 Hz, H^b), 7.97 (2H, d, J=8.7 Hz, H^a), 7.87 (2H, d, J=7.2 Hz, H^c), 7.62 (1H, t, J=7.5 Hz, H^e), 7.56 (2H, t, J=7.5 Hz, H^d), 2.89 (4H, q, J=14.3, 7.2 Hz, N(C*H*$_2$CH$_3$)$_2$), 0.86 (6H, t, J=7.2 Hz, N(CH$_2$C*H*$_3$)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 173.0 (O*C*), 160.6 (ON*C*), 149.1 (*C*NO$_2$), 134.2 (ONC*C*), 132.2 (C^e), 131.1 (C^a), 129.9 (C^c), 128.7 (C^d), 125.8 (C*C*=CS), 123.5 (C^b), 117.3 (CC=*C*S), 41.0 (N(*C*H$_2$CH$_3$)$_2$), 13.4 (N(CH$_2$*C*H$_3$)$_2$); LRMS (ES+) 402.11 (100 %), 361.18 (10 %); HRMS (ES+) calc'd for $C_{19}H_{20}N_3O_5S$ (M+H$^+$) 402.1124, found 402.1136.

1-Benzyl-*N*,*N*-diethyl-4-phenyl-1*H*-1,2,3-triazole-5-sulfonamide 132



Alkynyl sulfonamide **39** (47 mg, 0.2 mmol, 1.3 eq) and benzyl azide (0.02 ml, 0.15 mmol, 1 eq) in toluene (5 ml) was refluxed until the starting material was fully consumed. The solvent was removed *in vacuo* to give a golden oil that was purified by column chromatography in 0-20 % ethyl acetate in petroleum ether to give the title compound as a yellow oil, (35 mg, 63 %); ν_{max} (film)/cm^{-1} 3064, 3035, 2976, 2937, 2875, 1455, 1333, 1173, 1145, 1014, 940; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.70 (2H, dd, J=6.3, 3.3 Hz, H^d), 7.43-7.44 (5H, m, H^a, H^e, H^f), 7.37 (2H, t, J=7.7 Hz, H^b), 7.33 (1H, t, J=7.3 Hz, H^c), 5.95 (2H, s, NCH_2), 2.70 (4H, dq, J=14.3, 7.2 Hz, N(CH_2CH$_3$)$_2$), 0.74 (6H, t, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 148.1 (CC=CS), 135.1 (NCH$_2C$), 132.8 (CC=CS), 130.0 (Ar-C), 129.7 (CC=CS), 129.6 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 54.4 (NCH$_2$), 41.4 (N(CH$_2$CH$_3$)$_2$), 13.6 (N(CH$_2C$H$_3$)$_2$); LRMS (ESI) 763.28 (2(M+Na+H)$^+$, 100 %), 371.15 (M+H$^+$, 83 %); HRMS (ESI) calc'd for $C_{19}H_{23}N_4O_2S$ (M+H$^+$) 371.1536, found 371.1535.

1-Benzyl-*N*,*N*-diethyl-5-phenyl-1*H*-1,2,3-triazole-4-sulfonamide 133

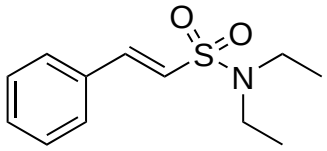


(Yellow oil, 15 mg, 27 %); ν_{max} (film)/cm^{-1} 3064, 3035, 2976, 2937, 1692, 1608, 1453, 1336, 1202, 1147, 1019, 938; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.51 (1H, t, J=7.5 Hz, H^{f}), 7.45 (2H, t, J=7.7 Hz, H^{e}), 7.25-7.30 (5H, m, H^{b}, H^{c}, H^{d}), 6.99 (2H, t, J=6.6 Hz, H^{a}), 5.40 (2H, s, NCH_2), 3.34 (4H, dq, J=14.3, 7.0 Hz, N(CH_2CH$_3$)$_2$), 1.16 (6H, t, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 145.7 (CC=*C*S), 138.1 (N*C*=CS), 134.3 (NCH$_2$*C*), 130.6 (C^{f}), 130.2 (C^{d}), 129.0 (C^{c}), 128.8 (C^{b}), 128.7 (C^{e}), 127.8 (C^{a}), 124.8 (*C*C=CS), 52.7 (N*C*H$_2$), 43.2 (N(CH_2CH$_3$)$_2$), 14.7 (N(CH$_2$*C*H$_3$)$_2$); LRMS (ES+) 371.15 (M+H$^+$, 20 %), 242.29 (100 %); HRMS (ESI) calc'd for $C_{19}H_{23}N_4O_2S$ (M+H$^+$) 371.1542, found 371.1532.

General method for the synthesis of alkenyl sulfonamides 134-137

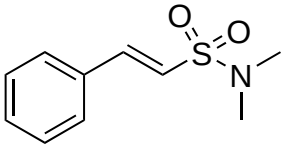
Trans-β-styrenesulfonyl chloride (2.5-5.0 mmol, 1.0 eq) was dissolved in DCM (25 ml) and stirred to form a brown solution. Amine (5.0-10.0 mmol, 2.0 eq) in DCM (10 ml) was added slowly over 2 minutes at 0 ^{o}C, before the mixture was warmed to room temperature and stirred for 30 minutes, becoming a pale yellow colour. The reaction was monitored by TLC and upon consumption of the starting material, was washed with 2M HCl (2x 50 ml) and brine (50 ml). The organic layer was dried with $MgSO_4$, reduced *in vacuo* and purified by column chromatography using ether in petroleum ether.

(*E*)-*N*,*N*-Diethyl-2-phenylethene-1-sulfonamide 134



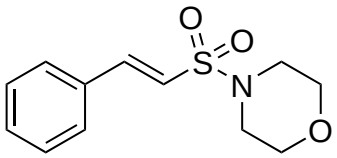
(White solid, 0.98 g, 82 %); m.p. 77-78 ^{o}C; ν_{max} (film)/cm^{-1} 2933, 1447, 1318, 1199, 1134, 1015, 978; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.47-7.49 (2H, m, H_{meta}), 7.44 (1H, d, J=15.4 Hz, C*H*), 7.40-7.42 (3H, m, H_{para}, H_{ortho}), 6.66 (1H, d, J=15.4 Hz, C*H*), 3.28 (4H, q, J=7.1 Hz, N(CH_2CH$_3$)$_2$), 1.22 (6H, t, J=7.2 Hz, N(CH$_2$$H_3$)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 140.9 (CC*C*S), 133.0 (*C*CCS), 130.7 (C_{para}), 129.2 (C_{ortho}), 128.2 (C_{meta}), 124.9 (C*C*CS), 41.9 (*C*H$_2$CH$_3$), 14.6 (CH$_2$*C*H$_3$); LRMS (EI) 240.1 (M+H$^+$, 1 %), 106.1 (100 %). Data in agreement with literature values.[145]

(*E*)-*N*,*N*-Dimethyl-2-phenylethene-1-sulfonamide 135



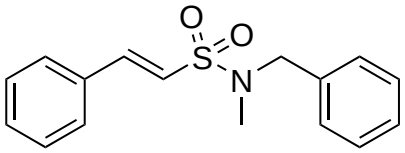
(White crystals, 0.68 g, 84 %); ν_{max} (film)/cm^{-1} 3049, 2967, 1616, 1326, 1137; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.50-7.52 (2H, m, H_{meta}), 7.48 (1H, d, J=15.3 Hz, C*H*), 7.42-7.44 (3H, m, H_{para}, H_{ortho}), 6.70 (1H, d, J=15.6 Hz, C*H*), 2.84 (6H, s, N(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 143.6 (CC*C*S), 132.7 (*C*CCS), 131.0 (C_{para}), 129.2 (C_{ortho}), 128.4 (C_{meta}), 120.4 (C*C*CS), 37.8 (CH_3); LRMS (EI) 211.3 (M$^+$, 21 %), 147.1 (100 %), 103.0 (73 %), 77.0 (29 %); HRMS (EI) calc'd for $C_{10}H_{13}NO_2S$ (M$^+$) 211.0661, found 211.0662.

(*E*)-4-(Styrylsulfonyl)morpholine 136



(White solid, 0.98 g, 82 %); m.p. 116 ^{o}C; ν_{max} (film)/cm^{-1} 3032, 2967, 2848, 1452, 1342, 1328, 1147, 1109; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.41-7.52 (6H, m, H_{meta}, H_{para}, H_{ortho}, CH), 6.78 (1H, d, J=15.5 Hz, CH), 3.79 (4H, t, J=4.7 Hz, $N(CH_2CH_2)_2$), 3.20 (4H, t, J=4.8 Hz, $N(CH_2CH_2)_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 144.5 (CC*C*S), 132.5 (*C*CCS), 131.3 (C_{para}), 129.3 (C_{ortho}), 128.5 (C_{meta}), 120.5 (C*C*CS), 66.4 (*C*O), 45.8 (*C*N); LRMS (ES+) 529.1 (2M+Na$^+$, 100 %), 507.1 (2M+H$^+$, 49 %), 254.1 (M+H$^+$, 60 %); HRMS (ES+) calc'd for $C_{12}H_{16}NO_3S$ (M+H$^+$) 254.0851, found 254.0853.

(*E*)-*N*-Benzyl-*N*-methyl-2-phenylethene-1-sulfonamide 137

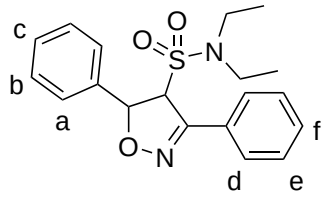


(White solid, 0.72 g, 82 %); m.p. 112 ^{o}C; ν_{max} (film)/cm^{-1} 3058, 1450, 1323, 1143; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.48-7.51 (3H, m, Ar-H, C*H*), 7.41-7.44 (3H, m, Ar-H), 7.37 (4H, d, J=4.4 Hz, Ar-H), 7.30-7.33 (1H, m, Ar-H), 6.68 (1H, d, J=15.6 Hz, CH), 4.31 (2H, s, CH_2), 2.74 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 142.7 (CC*C*S), 135.8 (NCH_2C), 132.8 (*C*CCS), 131.0 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 122.3 (C*C*CS), 54.1 (CH_2), 34.4 (CH_3); HRMS (LC-MS) calc'd for $C_{16}H_{18}NO_2S$ (M+H$^+$) 288.1053, found 288.1056.

General method for the synthesis of 4,5-dihydroisoxazoles 138-141

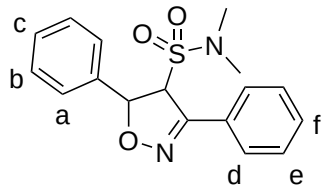
Alkenyl sulfonamide (0.39-47 mmol, 1 eq) and DIPEA (0.78-0.94 mmol, 2 eq) in toluene (3 ml) was refluxed under argon in a flame-dried sealed tube. Chloroxime (1.95-2.35 mmol, 5 eq) in toluene (2 ml) was added via syringe pump over 2 hours. The mixture was left overnight and reduced to give a brown oil which was purified by column chromatography using 0-20 % ethyl acetate in petroleum ether.

***N*,*N*-Diethyl-3,5-diphenyl-4,5-dihydroisoxazole-4-sulfonamide 138**



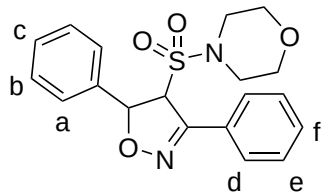
(White crystals, 90 mg, 60 %); m.p. 102-107 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 2987, 2958, 2938, 1701, 1587, 1562, 1496, 1448, 1329, 1200, 1134, 1012, 944, 907; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.84 (2H, dd, J=7.7, 1.3 Hz, H^{d}), 7.41-7.46 (3H, m, H^{e}, H^{f}), 7.32-7.38 (5H, m, H^{a}, H^{b}, H^{c}), 6.22 (1H, d, J=3.1 Hz, OC*H*), 4.98 (1H, d, J=3.1 Hz, SC*H*), 3.16 (4H, dq, J=13.9, 7.0 Hz, N(CH_2CH$_3$)$_2$), 1.13 (6H, t, J=7.2 Hz, N(CH$_2$CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 151.7 (*C*=N), 138.6 (*C*CHO), 130.9 (C^{e}), 129.2 (C^{b}), 128.9 (C^{f}), 128.8 (C^{c}), 127.9 (*C*C=N), 127.8 (C^{d}), 124.9 (C^{a}), 85.9 (C*C*HO), 78.3 (S*C*H), 42.58 (N(*C*H$_2$CH$_3$)$_2$), 14.5 (N(CH$_2$*C*H$_3$)$_2$); LRMS (ES+) 359.14 (100 %), 242.29 (32 %); HRMS (ES+) calc'd for $C_{19}H_{23}N_2O_3S$ (M+H^{+}) 359.1429, found 359.1417.

_N_,_N_-Dimethyl-3,5-diphenyl-4,5-dihydroisoxazole-4-sulfonamide 139



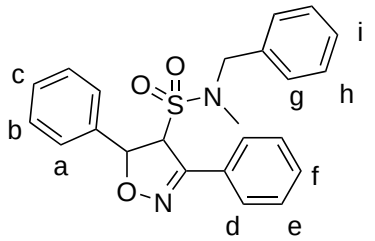
(White crystals, 92 mg, 59 %); m.p. 146-147 ^{o}C; ν_{max} (film)/cm^{-1} 3066, 2950, 2927, 1494, 1339, 1176, 1152, 1122, 980; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.85 (2H, dd, J=8.0, 1.9 Hz, H^{d}), 7.42-7.47 (3H, m, H^{e}, H^{f}), 7.31-7.38 (5H, m, H^{a}, H^{b}, H^{c}), 6.26 (1H, d, J=2.8 Hz, OC*H*), 5.00 (1H, d, J=2.8 Hz, SC*H*), 2.82 (6H, s, N(CH_3)$_2$); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 151.8 (*C*=N), 138.3 (*C*CHO), 131.0 (C^{e}), 129.2 (C^{a}), 129.0 (C^{f}), 128.9 (C^{c}), 127.9 (C^{d}), 127.8 (*C*C=N), 124.9 (C^{b}), 85.7 (C*C*HO), 77.5 (S*C*H), 38.3 (N(*C*H$_3$)$_2$); LRMS (ES+) 683.1 (2M+Na$^+$, 23 %), 331.1 (M+H$^+$, 100 %); HRMS (ES+) calc'd for $C_{17}H_{18}N_2O_3S$ (M+H$^+$) 331.1116, found 331.1118.

4-((3,5-Diphenyl-4,5-dihydroisoxazol-4-yl)sulfonyl)morpholine 140



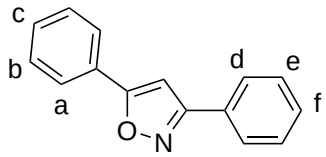
(Yellow crystals, 63 mg, 42 %); m.p. 156-157 ^{o}C; ν_{max} (film)/cm^{-1} 3064, 2966, 2921, 2861, 1494, 1447, 1348, 1261, 1200, 1143, 1113, 1074, 960; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.86 (2H, dd, J=8.3, 1.4 Hz, H^{d}), 7.42-7.48 (3H, m, H^{e}, H^{f}), 7.33-7.40 (5H, m, H^{a}, H^{b}, H^{c}), 6.20 (1H, d, J=2.8 Hz, OC*H*), 5.01 (1H, d, J=2.8 Hz, SC*H*), 3.62 (4H, t, J=4.6 Hz, N(CH$_2$CH_2)$_2$O), 3.27 (4H, s, N(CH_2CH$_2$)$_2$O); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 151.6 (*C*=N), 138.1 (*C*CHO), 131.2 (C^{e}), 129.2 (C^{a}), 129.0 (C^{f}), 129.0 (C^{c}), 127.9 (C^{d}), 127.5 (*C*C=N), 124.8 (C^{b}), 85.8 (C*C*HO), 77.8 (S*C*H), 66.8 (N(CH$_2$*C*H$_2$)$_2$O), 46.9 (N(*C*H$_2$CH$_2$)$_2$O); LRMS (ES+) 242.29 (100 %), 373.12 (5 %); HRMS (ES+) calc'd for $C_{19}H_{21}N_2O_4S$ (M+H$^+$) 373.1222, found 373.1223.

***N*-Benzyl-*N*-methyl-3,5-diphenyl-4,5-dihydroisoxazole-4-sulfonamide 141**



(White crystals, 29 mg, 19 %); m.p. 167-168 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 3065, 3031, 2937, 1453, 1334, 1191, 1138, 1119, 992, 938, 906; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.89 (2H, dd, J=8.0, 1.7 Hz, H^{d}), 7.42-7.47 (3H, m, H^{e}, H^{f}), 7.26-7.41 (10H, m, H^{a}, H^{b}, H^{c}, H^{g}, H^{h}, H^{i}), 6.33 (1H, d, J=2.6 Hz, OC*H*), 5.10 (1H, d, J=2.7 Hz, SC*H*), 4.16 (2H, s, NCH_2), 2.69 (3H, s, NCH_3); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 151.8 (*C*=N), 138.2 (*C*CHO), 135.4 (NCH$_2$*C*), 131.1 (C^{e}), 129.2 (*C*H), 129.1 (*C*H), 128.9 (C^{c}), 128.8 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 127.9 (C^{d}), 127.8 (*C*C=N), 124.9 (C^{b}), 85.8 (C*C*HO), 77.7 (S*C*H), 54.6 (N*C*H$_2$), 34.9 (N*C*H$_3$); LRMS (ES+) 437.03 (100 %), 407.14 (10 %); HRMS (ES+) calc'd for $C_{23}H_{23}N_2O_3S$ (M+H^{+}) 407.1429, found 407.1431.

3,5-Diphenylisoxazole 143



A flame-dried RBF was fitted with a condenser and charged with dihydroisoxazole **138** (40 mg, 0.11 mmol, 1 eq) and anhydrous THF (4 ml) under argon. Potassium *tert*-butoxide was added in one burst, upon which the reaction mixture changed colour from yellow to orange. The mixture was heated to reflux at 60 ^{o}C for 1 hour or until TLC indicated that the starting material was fully consumed. The solvent was removed *in vacuo* and the mixture was purified by column chromatography using 5 % ether in petroleum ether to give the title compound as colourless crystals, (18 mg, 74 %); m.p. 147-148 ^{o}C; $\nu_{\max}$ (film)/cm^{-1} 3113, 3048, 2955, 2918, 2851, 1666, 1611, 1592, 1570, 1486, 1449, 1385, 1340, 1259, 1074, 919; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.85-7.89 (4H, m, H^{a}, H^{d}), 7.45-7.52 (6H, m, H^{b}, H^{c}, H^{e}, H^{f}), 6.85

(1H, s, NCC*H*); ^{13}C NMR (600 MHz, $CDCl_3$) δ_C 170.5 (O*C*), 163.1 (N*C*), 130.4 (Ar-H), 130.2 (Ar-H), 129.2 (q), 129.2 (Ar-H), 129.1 (Ar-H), 127.6 (q), 126.9 (C^d), 126.0 (C^a), 97.6 (NC*C*H); LRMS (ES+) 222.09 (100 %); HRMS (ES+) calc'd for $C_{15}H_{12}NO$ ($M+H^+$) 222.0919, found 222.0990. Data in agreement with literature values.[146]

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