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The Synthesis of Benzothiadiazepines, Pyrrolobenzodiazepines and Pyrrolobenzothiadiazepines of Biological and Pharmaceutical Relevance

Nilesh Patel

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

University of Huddersfield
Department of Chemical & Biological Sciences

August 2006
I would like to dedicate this thesis to my mother Shantiben Patel and my father Manilal Patel with my deep appreciation for their love and patience. I hope that this achievement will complete the dream that you had for me all those many years ago when you chose to give me the best education you could.
Contents

<table>
<thead>
<tr>
<th>Acknowledgements</th>
<th>viii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>ix</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>xi</td>
</tr>
</tbody>
</table>

1 Introduction

1.1 An introduction to the pyrrolobenzodiazepines  1
1.2 Synthesis of pyrrolobenzodiazepines via azides  4
  1.2.1 Aza-Wittig based synthesis of pyrrolobenzodiazepines  4
  1.2.2 Azide reductive cyclisation  6
1.3 Synthesis of pyrrolobenzodiazepines via oxidation and reductive cyclisation  9
  1.3.1 Oxidation method  9
  1.3.2 Reductive cyclisation  10
  1.3.3 Synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines  12
1.4 Synthesis of pyrrolobenzodiazepine dimers  19
  1.4.1 Synthesis of C8-linked pyrrolo[2,1-c][1,4]benzodiazepine dimer via dethioacetalisation  19
  1.4.2 Synthesis of C8-linked pyrrolobenzodiazepine dimer via reductive cyclisation of \( \omega \)-azido/nitrocarbonyl compounds  21
  1.4.3 Synthesis of pyrrolobenzodiazepine dimers through a piperazine side armed alkane spacer  24
  1.4.4 Synthesis of C2/C2'-exo unsaturated pyrrolobenzodiazepine dimer  26
  1.4.5 Synthesis of A-C8/C-C2 linked pyrrolo[2,1-c][1,4]benzodiazepine dimers  28
1.5 Synthesis of pyrrolobenzodiazepine hybrids  33
1.6 Synthesis of pyrrolobenothiadiazepines  44
  1.6.1 Synthesis of other pyrrolobenothiadiazepine analogues  47
  1.6.2 Synthesis of tetracyclic pyrrolobenothiadiazepines  48
1.7 1,2-Thiazine 1-oxides  51
2 Discussion-Part I

2.1 Aims of research project 55
2.2 Synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides via 1,2-thiazine 1-oxides 57
  2.2.1 Synthesis of N-sulfinyl dienophiles 58
  2.2.2 Synthesis of 1,2-thiazine 1-oxides via hetero Diels-Alder reaction 60
  2.2.3 Synthesis of amines via an in situ Staudinger reaction 63
  2.2.4 Synthesis of allylic alcohols via amino allylic sulfoxides 65
  2.2.5 Synthesis of N-Fmoc protected amino alcohol 67
  2.2.6 Synthesis of N-Boc protected amino alcohol 69
  2.2.7 Synthesis of N-Fmoc protected amino ketones via Dess-Martin oxidation 71
  2.2.8 Synthesis of N-Boc protected amino ketone via Dess-Martin oxidation 72
  2.2.9 Synthesis of 1,2,5-benzothiadiazepines by deprotection/cyclisation 73
  2.2.10 Attempted deprotection/cyclisation of N-Boc protected amino ketone 78
2.3 Conclusion 79

3 Discussion-Part II

3.1 Attempted synthesis of tricyclic 1,2-thiazine 1-oxides 80
  3.1.1 Synthesis of hex-2,4-dien-1-ol 81
  3.1.2 Synthesis of the cyclisation precursor via 1-bromo-2,4-hexadiene 82
  3.1.3 Attempted synthesis of tricyclic 1,2-thiazine 1-oxide 83
3.2 Conclusion 84

4 Discussion-Part III

4.1 Synthesis of pyrrolobenzothiadiazepines using ring contraction approach 85
  4.1.1 Synthesis of 1,2-thiazine 1-oxides via the N-sulfinyl dienophile 86
4.2 Synthesis of pyrrole via ring contraction of the 1,2-thiazine 1-oxides

4.2.1 Synthesis of pyrrole from the 2-(aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide

4.2.2 Synthesis of pyrrole from 2-(azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides

4.3 Formylation of the pyrrole

4.4 Synthesis of 1-(2-formamidobenzenesulfonyl) pyrroles

4.5 Synthesis of pyrrolobenzothiadiazepines

4.6 Synthesis of tetracyclic systems

4.6.1 Synthesis of benzaldoxime

4.6.2 Synthesis of benzo hydroximoyl chloride

4.6.3 Synthesis of 1,2,4-oxadiazolopyrrolobenzothiadiazepine 5,5-dioxide via 1,3-dipolar cycloaddition reaction

4.7 Conclusion

5 Discussion-Part IV

5.1 Synthesis of aziridinobenzothiadiazocines and pyrrolobenzothiadiazines

5.1.1 Synthesis of homoallylic sulfonamides via hydrolysis of 1,2-thiazine 1-oxides

5.1.2 Attempted synthesis of pyrrolidine via 5-endo-trig iodo cyclisation

5.2 Synthesis of pyrrolidine via 5-endo-trig iodo cyclisation

5.2.1 Acid hydrolysis of 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxide and 2-(2-iminophosphoryl)-1,2-thiazine 1-oxide

5.2.2 Synthesis of 2-nitroaryl allylic systems via 2-(2-nitroaryl)-1,2-thiazine 1-oxides

5.2.3 Synthesis of 1-(2'-nitroaryl)-3-iodopyrrolidine via 5-endo-trig iodo cyclisation

5.3 Attempted alternative synthesis of aziridine fused benzothiadiazocines

5.3.1 Thermolysis of homoallylic sulfonamido aryl azide

5.4 Conclusion
6 Discussion-Part V

6.1 Attempted synthesis of aziridinopyrrolobenzodiazepines and pyrrolobenzodiazepines

6.1.1 Synthesis of N-Fmoc protected (S)-prolinol

6.1.2 Synthesis of N-Fmoc protected (S)-prolinal via oxidation

6.1.3 Synthesis of (2S)-N-(9'-fluorenylmethoxycarbonyl)-pyrrolidine-2-ethene via a Wittig reaction

6.1.4 Attempted synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene

6.2 Synthesis of aziridinopyrrolobenzodiazepines and pyrrolobenzodiazepines via N-ethyl ester

6.2.1 Synthesis of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-methanol

6.2.2 Synthesis of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde

6.2.3 Synthesis of (S)-(−)-1-ethenyl-1-ethoxycarbonylpyrrolidine

6.2.4 Synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene

6.2.5 Synthesis of the pyrrolobenzodiazepine targets

6.3 Synthesis of triazolopyrrolobenzodiazepines via alkyne

6.3.1 Corey-Fuchs approach to the alkyne

6.3.2 Synthesis of (2S)-N-(2-azidoaroyl)-2-ethynylpyrrolidine

6.3.3 Synthesis of (S)-(−)-1-β-butoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene)

6.3.4 Synthesis of (S)-(−)-1-β-butoxycarbonylpyrrolidine-2-prop-1-yne

6.3.5 Synthesis of (2S)-N-(2-azidoaroyl)-2-ethynylpyrrolidine

6.3.6 Synthesis of 1,2,3-triazolopyrrolo[2,1-c][1,4]benzodiazepine

6.4 Synthesis of tetrazolopyrrolobenzodiazepines via the nitrile

6.4.1 Oxidative conversion of alcohol to nitrile

6.4.2 Synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile

6.4.3 An alternative synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile

6.4.4 Synthesis of 1,2,3,4-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine

6.5 Conclusion
## 7 Experimental

### 7.1 Experimental-Part I

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1.1</td>
<td>Synthesis of 2-azidobenzenesulfonamide</td>
<td>151</td>
</tr>
<tr>
<td>7.1.2</td>
<td>Synthesis of 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides</td>
<td>152</td>
</tr>
<tr>
<td>7.1.3</td>
<td>Synthesis of 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides</td>
<td>154</td>
</tr>
<tr>
<td>7.1.4</td>
<td>Synthesis of 2-(2-aminobenzenesulfonyl)alkenols via phenyl allylic sulfoxides</td>
<td>156</td>
</tr>
<tr>
<td>7.1.5</td>
<td>Synthesis of {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenols</td>
<td>157</td>
</tr>
<tr>
<td>7.1.6</td>
<td>Synthesis of {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl} alkenones</td>
<td>159</td>
</tr>
<tr>
<td>7.1.7</td>
<td>Synthesis of 2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxides</td>
<td>160</td>
</tr>
<tr>
<td>7.1.8</td>
<td>Synthesis of 4-[(o-tert-butoxycarbonylamino)benzenesulfonamidyl]-2-methyl-but-1-en-3-ol</td>
<td>163</td>
</tr>
<tr>
<td>7.1.9</td>
<td>Synthesis of 4-[(o-tert-butoxycarbonylamino)benzenesulfonamidyl]-2-methyl-but-1-en-3-one</td>
<td>164</td>
</tr>
<tr>
<td>7.1.10</td>
<td>Synthesis of 2-aminobenzenesulfonamidyl-2-methyl-but-1-en-3-one</td>
<td>165</td>
</tr>
</tbody>
</table>

### 7.2 Experimental-Part II

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2.1</td>
<td>Synthesis of hex-2,4-dien-1-ol</td>
<td>166</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Synthesis of 1-bromo-2,4-hexadiene</td>
<td>166</td>
</tr>
<tr>
<td>7.2.3</td>
<td>Synthesis of cyclisation precursor</td>
<td>167</td>
</tr>
</tbody>
</table>

### 7.3 Experimental-Part III

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3.1</td>
<td>Synthesis of 1-(2-aminobenzenesulfonyl)pyrroles</td>
<td>168</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Synthesis of 1-(2-formamidobenzenesulfonyl)pyrroles</td>
<td>169</td>
</tr>
<tr>
<td>7.3.3</td>
<td>Synthesis of pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides</td>
<td>171</td>
</tr>
<tr>
<td>7.3.4</td>
<td>Synthesis of 11-phenyl-[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothia-diazepine 5,5-dioxides</td>
<td>172</td>
</tr>
<tr>
<td>7.3.5</td>
<td>Synthesis of ethyl-[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothia-diazepine 5,5-dioxide carboxylates</td>
<td>174</td>
</tr>
<tr>
<td>7.3.6</td>
<td>Synthesis of 1-(2-phosphoramidobenzenesulfonyl)pyrroles</td>
<td>175</td>
</tr>
<tr>
<td>7.3.7</td>
<td>Synthesis of (N-[o-(N',N'-\text{dimethylformamidiny}l)\text{benzenesulfonyl}]) formylpyrroles</td>
<td>177</td>
</tr>
<tr>
<td>7.3.8</td>
<td>Synthesis of 1-(2'-aminobenzenesulfonyl)-2-formylpyrrole</td>
<td>178</td>
</tr>
</tbody>
</table>

### 7.4 Experimental-Part IV

| 7.4.1 | Synthesis of 2-amino-\(N\)-(but-3-enyl)benzenesulfonamide | 180 |
| 7.4.2 | Synthesis of aziridino 1,2,6-benzothiadiazocine 1,1-dioxides | 182 |
| 7.4.3 | Synthesis of 2-azido-\(N\)-(but-3-enyl)benzenesulfonamides | 183 |
| 7.4.4 | Synthesis of pyrrolo-1,2,4-benzothiadiazine 1,1-dioxides | 185 |
| 7.4.5 | Synthesis of 2-triphenylphosphoranyl-\(N\)-(3-methylbut-3-enyl)benzenesulfonamide | 186 |
| 7.4.6 | Synthesis of 2-nitro-\(N\)-(but-3-enyl)benzenesulfonamides | 187 |
| 7.4.7 | Synthesis of \(N\)-(2-nitrobenzoyl)-3-iodo-3-methylpyrrolidine | 188 |

### 7.5 Experimental-Part V

| 7.5.1 | Synthesis of \(N\)-Fmoc protected pyrrolidine-2-methanol | 190 |
| 7.5.2 | Synthesis of \(N\)-Fmoc protected (S)-prolinal | 191 |
| 7.5.3 | Synthesis of (2S)-\(N\)-(9'-fluorenylmethoxycarbonyl)-pyrrolidine-2-ethene | 191 |
| 7.5.4 | Synthesis of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-methanol | 192 |
| 7.5.5 | Synthesis of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde | 193 |
| 7.5.6 | Synthesis of (S)-(-)-2-ethenyl-1-ethoxycarbonylpyrrolidine | 194 |
| 7.5.7 | Synthesis of (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-ethene | 196 |
| 7.5.8 | Synthesis of 11a-hydroxyl-11-methyl-pyrrolo[2,1-c][1,4]benzodiazepin-5-one | 197 |
| 7.5.9 | Synthesis of aziridinopyrrolobenzodiazepin-5-one | 198 |
| 7.5.10 | Synthesis of (2S)-\(N\)-(2-azidoaryl)-2-hydroxymethylpyrrolidine | 199 |
| 7.5.11 | Synthesis of (2S)-\(N\)-(2-azidoaryl)-pyrrolidine-2-carbaldehyde | 200 |
| 7.5.12 | Synthesis of \(N\)-protected dibromoalkene | 201 |
| 7.5.13 | Synthesis of \(N\)-protected alkyne | 202 |
| 7.5.14 | Synthesis of (2S)-\(N\)-(2'-azidoaryl)-2-ethynlypyrrolidine | 203 |
| 7.5.15 | Synthesis of 1,2,3-triazolopyrrolo[2,1-c][1,4]benzodiazepine | 205 |
| 7.5.16 | Synthesis of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbonitrile | 206 |
| 7.5.17 | Synthesis of (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile | 206 |
| 7.5.18 | Synthesis of 1,2,3,4-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine | 208 |
References 209
Appendix I-XV
Publications
Acknowledgements

There is a strong temptation to try to individually acknowledge everyone who has helped me to reach this point. Sadly, such a list would be much too long and it is inevitable that many people would be unintentionally omitted. I would thus like to thank everyone who, knowingly or otherwise, has provided support, encouragement and assistance along the way. However, there are others who have played a major role in the production of this thesis and who deserve a more personal note of gratitude.

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It would, of course, be completely amiss for me to end my acknowledgement without recognising the immense contribution that my family has made to my work. Despite living 110 miles away, they are constantly in my thoughts and their love and support has been a major stabilising force over these past four years. Their unquestioning faith in me and my abilities has helped to make all this possible and I hope that they will see this thesis as much their achievement as mine.
This thesis describes the applications of 1,2-thiazine 1-oxides as precursors for the synthesis of other heterocycles. The requisite 1,2-thiazine 1-oxides (2) were synthesised via a hetero-Diels-Alder reaction of the readily available dienophile (1).

Ring opening of the 1,2-thiazine 1-oxides (2, Y=NH₂) at the sulfur, with a Grignard reagent gave allylic sulfoxides, which after [2,3]-sigmatropic rearrangement and desulfurisation, furnished the unsaturated allylic alcohols (3, Y=NH₂). Oxidation and ring closure via Fmoc protection of the amine provided the 3-hydroxy-1,2,5-benzothiadiazepines (4) as the major products. Advantageously, the use of 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxides (2, Y=N₃) led to the 1-(2-aminobenzenesulfonyl)pyrrole (5, Y=NH₂) via a one-pot ring contraction, desulfurisation and aromatisation process, accompanied by concomitant same pot conversion of the azide to a primary amine through a Staudinger reaction. Subsequent N-formylation and Bischler-Napieralski ring closure gave pyrrolo[1,2-b][1,2,5]benzothiadiazepines (6), which were...
good templates for 1,3-dipolar cycloaddition reactions. Furthermore, hydrolysis of (2) gave homoallylic systems (7), which underwent iodine promoted cyclisation (Y=NH₂) to give aziridino-1,2,7-benzothiadiazocines (8) and thermolytic cyclisation (Y=N₃) to furnish pyrrolo-1,2,4-benzothiazine 1,1-dioxides (9).

Finally, thermolytic cyclisations of the precursors (10a-c) were explored. Intramolecular 1,3-dipolar cycloaddition of azide to the nitrile or alkyne was shown to provide efficient routes to triazolo- (11b, X=CH) and tetrazolo- (11c, X=N) fused pyrrolobenzodiazepines. Intramolecular ring closure of alkene (10a) gave aziridinopyrrolobenzodiazepine (12) and pyrrolobenzodiazepine (13) as an inseparable mixture at lower reaction temperatures or hydroxy pyrrolobenzodiazepine (14) at high temperature.
Abbreviations

Å  Angstrom
aq  aqueous
AIBN 2,2'-azobisisobutyronitrile barbituric acid
Alloc allyloxycarbonyl
Ar aryl
b/br broad (IR/NMR)
B base
BAIB [bis(acetoxy)iodo]benzene
Bn/Bnz benzyl [PhCH₂]
Boc t-butoxycarbonyl [t-BuCO₂]
Bu butyl [CH₃(CH₂)₃]
c. concentrated
cat. Catalytic
Cbz carboxbenzylxy [PhCH₂CO₂]
CDI carbonyl-bis(imidazol-1-yl)
CI chemical ionization (MS)
CNS central nervous system
d doublet (NMR)
DAST diethylaminosulfur trifluoride
DBF dibenzofulvene
DBU 1,8-diazabicycloundec-7-ene
DCC 1,3-dicyclohexylcarbodiimide
DCM dichloromethane
DIBAL-H diisobutylaluminum hydride
DIPEA N,N-diisopropylethylamine
DMA N,N-dimethacacetamide
DMF N,N-dimethylformamide
DMSO dimethylsulfoxide
DNA deoxyribonucleic acid
DPPE 1,3-bis(diphenylphosphino)ethane
EDCI N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide
EDTA ethylenediaminetetraacetic acid
EI electron impact (MS)
eq. equivalent(s)
ESI electrospray ionization (MS)
Et ethyl [CH₃CH₂]
FMO frontier molecular orbital
Fmoc 9-fluorenylethoxycarbonyl
GABA γ-aminobutyric acid
hr hour(s)
HIV human immunodeficiency virus
HMDST hexamethyldisilathiane
HOBt 1-hydroxybenzotriazole
HOMO highest occupied molecular orbital
HRMS high-resolution mass spectrum
hv photolysis
IR infrared
LDA lithium diisopropylamide
lit literature
LRMS low-resolution mass spectrum
LUMO lowest unoccupied molecular orbital
m multiplet (NMR)/ medium (IR)
m- meta-
M⁺ molecular ion (MS)
m-CPBA m-chloroperbenzoic acid
Me methyl [CH₃]
min minute(s)
mp melting point
MS mass spectrometry
NBS N-bromosuccinimide
NCS N-chlorosuccinimide
NMO 4-methylmorpholine N-oxide
NMR nuclear magnetic resonance
NNRTI non-nucleosidic reverse transcriptase inhibitor
O- ortho-
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$p$-</strong></td>
<td><em>para-</em></td>
</tr>
<tr>
<td><strong>PBD</strong></td>
<td>pyrrolo[2,1-$c$]benzo[1,4]diazepine</td>
</tr>
<tr>
<td><strong>PBTD</strong></td>
<td>pyrrolo[1,2-$b$][1,2,5]benzothiadiazepine</td>
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<tr>
<td><strong>PCC</strong></td>
<td>pyridinium chlorochromate</td>
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<tr>
<td><strong>PE</strong></td>
<td>petroleum ether</td>
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<td><strong>PG</strong></td>
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<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td><strong>t</strong></td>
<td>triplet (NMR)</td>
</tr>
<tr>
<td><strong>TBAF</strong></td>
<td>tetrabutylammonium fluoride</td>
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<tr>
<td><strong>TBDMS</strong></td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td><strong>TBTU</strong></td>
<td>O-(benzotriazol-1-yl)-$N,N,N',N'$-tetramethyluroniumtetrafluoroborate</td>
</tr>
<tr>
<td><strong>TEA</strong></td>
<td>triethylamine</td>
</tr>
<tr>
<td><strong>TEMPO</strong></td>
<td>2,2,6,6-tetramethylpiperidinyloxy</td>
</tr>
<tr>
<td><strong>tert-$t$-</strong></td>
<td>tertiary</td>
</tr>
<tr>
<td><strong>Tf</strong></td>
<td>triflate [CF$_3$SO$_2$]</td>
</tr>
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</tr>
<tr>
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</tr>
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<td>tetramethylsilyl chloride</td>
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<td><strong>TNF</strong></td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td><strong>TosMIC</strong></td>
<td>$(p$-toluenesulfonyl)methylisocyanide</td>
</tr>
<tr>
<td><strong>TPAP</strong></td>
<td>tetra-$n$-propy lammonium perruthenate</td>
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<tr>
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<td>triphenylphosphine</td>
</tr>
<tr>
<td><strong>Troc</strong></td>
<td>2,2,2-trichloroethoxycarbonyl</td>
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<tr>
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</table>
1

Introduction
1 Introduction

1.1 An introduction to the pyrrolobenzodiazepines

The increase in cancer awareness has led to the discovery of many natural and synthetic anticancer agents with the ability to interact with DNA, but most have little sequence-specificity and often exhibit severe toxicity to normal tissue. Thus, there has been considerable interest within molecular biology and human medicine to find small molecules that can alkylate the DNA in a sequence-specific manner and modify the function of nucleic acids irreversibly. The tricyclic pyrrolo[2,1-c][1,4]benzodiazepines (1) which are structurally related to the well-known 1,4-benzodiazepine (2) pharmacore are amongst the few that have been shown to recognize and bind to specific sequences of DNA (Figure 1.1). Thus, such compounds have potential as regulators of gene expression with possible applications as therapeutic agents in the treatment of certain genetic disorders including some cancers.

![Figure 1.1: The tricyclic and bicyclic benzodiazepine](image)

The pyrrolobenzodiazepines represent a remarkable core structure, which has many attributes. The most important feature is the electrophilic centre at the N10-C11 position, and the presence of an imine, carbinolamine/amide moiety in the central B-ring is essential for the alkylation of the guanine residues in the minor groove DNA. The binding to the DNA can exist in at least three different interchangeable forms (Figure 1.2) and thus three possible mechanisms may be envisaged for the reaction of these species with the 2-amino functionality of guanine.

Route (a) via a direct S_N2 type attack of the protonated carbinolamine (3) or its 11-methyl ether (4) by the biological nucleophile. A second mechanism (b) involving Schiff's base formation between N2-guanine functionality and the acyclic amino aldehyde, followed by intramolecular cyclisation and finally the third mechanism (c) via a direct attack of biological nucleophile on the imine function. Molecular modelling, solution NMR, fluorimetry, and DNA footprinting experiments indicate that PBD monomers are generally sequence-specific with a binding site preference for 5'-puGpu (particularly 5'-AG or 5'-GA) sequences. Additionally, the S-
stereochemistry of the C11a-H gives these molecules their right-handed twist; a characteristic that makes them isohelical with B-DNA.  

![Figure 1.2: DNA binding mechanism](image)

Another important aspect of the PBD skeleton is the nature of the substituents on the aromatic A-ring. Electron donating substituents increase the electrophilicity of the N10-C11 centre, whilst electron-withdrawing substituents attenuate biological activity arising from covalent DNA binding. Bulky substituents at C9 and N10 also eliminate biological activity and DNA binding affinity of the pyrrolobenzodiazepine. A significant increase in DNA binding affinity, cytotoxicity and in vivo antitumour activity has been observed when there is unsaturation present in the C-ring, specifically when C2 is sp² hybridised, i.e. by the inclusion of an exocyclic double bond or a C2-C3 double bond. However, complete unsaturation of the C-ring deactivates the compounds because of the involvement of the N10-C11 centre in the conjugated system, which leads to a decrease in the electrophilicity of this centre.

In recent years much effort has been put into extending the pyrrolobenzodiazepines so that they span a greater number of base pairs and have enhanced sequence selectivity. One approach has involved attaching different substituents on the pyrrolobenzodiazepines, such as ethylenediaminetetraacetic acid (EDTA), epoxide, polyamide, oligopyrrole, and cyclopropylpyrroloindole (CPI) moieties, which have exhibited sequence selective DNA-cleaving and cross linking properties. Furthermore, there have been attempts to develop more potent compounds that could enhance the sequence selectivity as in the case of C8 diether-linked
PBD dimers DSB-120,19 SJG-136 (9a),20 DRG-16 (9b)21 [Figure 1.3] and C2-C3/C2'-C3' endo unsaturated PBD dimer.22 It has been observed that there has been extensive improvement in the biological activity due to the cross-linking property by the presence of two imine functionalities. One example, SJG-136 (9a) which is presently under clinical evaluation, spans six base pairs of DNA and has a preference for a Pu-GATC-py or Py-GATC-Pu sequence.23,20

Figure 1.3: Pyrrolobenzodiazepine dimer

A detailed review of the synthetic literature of the pyrrolobenzodiazepines appeared in 1994.5 The purpose of the present review is to survey the most recent developments towards the synthesis of pyrrolobenzodiazepines. The synthesis of other classes of pyrrolobenzodiazepine such as tri/tetracyclic sulphur and heterocyclic analogues will be looked at in more detail than in the 1994 paper, since their synthesis is significant to this project. Further, in this review an effort is being made to outline the various synthetic routes developed since 1994 with their merits and limitations. Most of the advances that have occurred since 1994 have been in the synthesis of "dimeric" PBDs and "hybrid" PBDs and so they will be dealt with in separate sections of this introduction.
1.2 Synthesis of pyrrolobenzodiazepines via azides

1.2.1 Aza-Wittig based synthesis of pyrrolobenzodiazepine

A number of synthetic routes have been developed for the preparation of the pyrrolobenzodiazepines antibiotics and have met with varying degrees of success; some however found the general problem to be the introduction of the sensitive imine at the N10-C11 position. Since 1994, there has been considerable interest in the use of aza-Wittig reactions as a tool for the construction of carbon-nitrogen double bonds under mild and neutral conditions. The key intermediate iminophosphoranes have been generated from both azides and primary amines, and their aza-Wittig reaction with a variety of carbonyl compounds provides a valuable method for the regiospecific formation of the cyclic imine, a feature often not available via the classical amine-carbonyl group cyclisation where double bond shifts are possible.

The intramolecular aza-Wittig reaction of N-(2-azidobenzoyl) α-amino acid esters and their application to the synthesis of benzylated DC-81 (13) as well as the natural antibiotic DC-81 (14) has been reported by Molina, Eguchi et al. Both the groups have employed triphenylphosphine for their intramolecular aza-Wittig reaction as illustrated in the following scheme:

Parallel with these studies, O’Neil et al. prepared a series of functionalised pyrrolo[2,1-c][1,4]benzodiazepines (18-23) bearing a variety of A-ring substituents, using a Staudinger/ aza-Wittig sequence (Scheme 1.2). Thus, treatment of the azido aldehydes (17) with either
tributylphosphine or triphenylphosphine generated the corresponding iminophosphoranes, which underwent an *in situ* intramolecular aza-Wittig cyclisation to give the desired pyrrolo[2,1-c][1,4]benzodiazepines (18-23) in up to 90% yield.

![Scheme 1.2](image)

Furthermore, the same group later reported a novel synthesis of C2-fluoro-substituted pyrrolobenzodiazepines (32a-c), using the Staudinger/aza-Wittig methodology. The key strategy was the synthesis of Boc-protected fluoro and difluoro methyl esters (Scheme 1.3). The cis- and trans 4-fluoropropyl methyl ester (25) was readily obtained from compound (24) with DAST. Oxidation and difluorination of compound (24) gave the 4,4'-difluoropropyl methyl ester (27).

![Scheme 1.3](image)

Reduction of the esters with DIBAL-H followed by removal of the Boc-protecting group afforded compounds (28a-c) in respectable yields. Coupling followed by oxidation of the 4-fluoro substituted prolinol (30) afforded the desired azido aldehyde (31), which underwent a Staudinger/aza-Wittig cyclisation upon treatment with DPPE to provide the fluoro-substituted pyrrolobenzodiazepines (32a-c) in 71%, 80% and 62% yields, respectively (Scheme 1.4).
1.2.2 Azide reductive cyclisation

In addition to the ongoing research towards the synthesis of pyrrolo[2,1-c][1,4]benzodiazepine and analogues via the azide, Kamal et al. have reported a new modified approach based on an in situ cyclisation of an amine with the pendant carbonyl through an azido reductive process (Scheme 1.5). A wide range of reagents such as hexamethyldisilathiane, FeSO₄·7H₂O/NH₃, trimethylsilyl iodide, hydriodic acid (HI), FeCl₃-NaI, and zinc with ammonium formate have been used under extremely mild conditions to successfully produce both the pyrrolobenzodiazepine dilactam ring system and the DNA interactive pyrrolobenzodiazepine imine, bearing the S-conformation at the chiral C₁₁a position. The results are summarized in table 1.0.
<table>
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<th>Entry</th>
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<th>Reaction conditions</th>
<th>Final PBD product</th>
<th>Yield/ %</th>
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<td>Time</td>
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<td>MeOH</td>
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<td>4 h</td>
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<tr>
<td>2</td>
<td>FeSO₄.7H₂O/NH₃</td>
<td>DCM</td>
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<td>3</td>
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<tr>
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**Table 1.0**
Chandrsekaran et al.\textsuperscript{37} have reported another azido reductive cyclisation in the synthesis of seven membered cyclic imine using benzyltriethylammonium tetrathiomolybdate. The methodology was extended to a successful synthesis of pyrrolo[2,1-c][1,4]benzodiazepine (39a) and also the benzylated DC-81 (39b) [Scheme 1.6].

![Scheme 1.6](image-url)
1.3 Synthesis of pyrrolobenzodiazepines via oxidation and reductive cyclisation

1.3.1 Oxidation method

An early approach of using very active manganese dioxide for the oxidation of the readily prepared pyrrolobenzodiazepine secondary amine (40) to its corresponding imine has been subject to little scrutiny due to lack of control to selectively achieve oxidation at only the N10-C11 position (Scheme 1.7), the isolated product being the fully unsaturated product (41).

Similarly, Rault et al. reported the use of thionyl chloride in the presence of base to readily aromatise 2-hydroxypyrrolo[2,1-c][1,4]benzodiazepines (42) into 11-chloropyrrolo[2,1-c][1,4]benzodiazepines (43a-d) in high yield. The chloroimine moieties are interesting analogues to the imine and carbinolamine found in the antitumour antibiotic DC-81. Thus, the chlorine group at the C11 position could reinforce the electrophilic character and enhance the ability to react with nucleophiles, whilst on the other hand the chloroimine could also act as a scaffold for the preparation of numerous tricyclic derivatives by substitution.

However, Kamal et al. have reported a new mild oxidant, TPAP in the presence of N-methylmorpholine N-oxide as a co-oxidant, which can selectively oxidise the secondary amine to the imine without over oxidation and without any racemisation at the C11a position. This
methodology has many advantages, but the most significant is that it is devoid both of side products and aqueous work-up for the sensitive imine moiety. Also, in this study the pyrrolobenzodiazepine secondary amine was synthesized by a new approach involving the reductive desulfurisation of the pyrrolobenzodiazepine-5-one-11-thione by Raney nickel (Scheme 1.9).

Furthermore, the same workers showed that oxidation of the cyclic secondary amine (49) using activated Me$_2$SO gave the desired pyrrolobenzodiazepine in the imine form (50) in 40-45% yield.

\[ \text{47} \]

Raneynickel, EtOH, $\Delta$ 5-6h

\[ \text{48} \]

Scheme 1.9

1.3.2 Reductive cyclisation

Reductive cyclisation of acyclic nitro aldehydes has been by far the most important approach of synthesizing the pyrrolobenzodiazepine imine. However, earlier studies have showed that using such routes generally gave large amounts of the secondary amine along with the desired carbinolamine, methyl ether or imine in moderate yield. Current studies by Kamal et al. have
showed that reduction of the nitro aldehyde (54) using iron powder\textsuperscript{41} in acetic acid, results in the formation of the desired pyrrolobenzodiazepine imine (55) in high yield with no by products (Scheme 1.10). The limitation in this methodology has been that the pyrrolobenzodiazepine imine is produced with an optical rotation value somewhat lower than the product obtained though other routes. This is believed to be a direct result of racemisation taking place in acidic reaction conditions. Further, the method was extended towards the synthesis of 5-thio pyrrolobenzodiazepine imine derivatives. Thus thiation of nitro aldehyde (54) with Lawesson’s reagent resulted in (56) and reductive cyclisation with iron and acetic acid in THF afforded the desired 5-thio PBD imines (57) in good yields.

\[ \text{Scheme 1.10} \]

In addition, a new one-pot reductive cyclisation\textsuperscript{42} of the acyclic nitro aldehyde in the synthesis of benzylated DC-81 and the natural product DC-81 has been reported by the same group. Thus, reduction of (2S)-N-(2-nitrobenzoyl)pyrrolidin-2-carboxaldehyde (58) with ferric chloride hexahydrate and \textit{N}, \textit{N}-dimethylhydrazine resulted in the corresponding methylether of the pyrrolobenzodiazepine carbinolamine (59), via a hydrazone intermediate, which upon column chromatography (silica gel, chloroform:methanol. 9.8:0.2) afforded the pyrrolobenzodiazepine imine (60a-c) [Scheme 1.11].
A new class of heterocyclic quinone (64) from 3,6-dimethoxy-2-nitrobenzoic acid (61) has been reported by Tapia et al. Thus treatment of (61) with thionyl chloride and subsequent reactions of the resulting acid chloride with (L)-proline methyl ether furnished the amide (62) as a 1:1 mixture of syn and anti rotamers. Reductive cyclisation of compound (62) with iron(II) sulphate and ammonium hydroxide yielded the pyrrolobenzodiazepine (63) in 86% yield. Oxidative demethylation of (63) with ammonium cerium(IV) nitrate afforded the pyrrolobenzodiazepinequinone (64) in 75% yield [Scheme 1.12].

1.3.3 Synthesis of C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines

Ongoing investigations into the chemistry and structure activity relationship (SAR) of the pyrrolobenzodiazepine ring systems have established that compounds possessing endo-exo unsaturation in their C-rings combined with conjugated planar C2-substituents, such as the acrylamide side chain found in anthramycin, have the greatest cytotoxicity and DNA binding affinity. It is also well known in the literature that C-ring hydroxy substitution plays an important role in biological activity, examples being naturally occurring pyrrolobenzodiazepines such as chicamycin A and B, neothramycin A and B, and abbeymycin. On the basis of these studies Kamal et al. reported an elegant and efficient solid-phase synthesis of N10-C11 imine containing pyrrolobenzodiazipines and the dilactam with C2-hydroxy substituents via a reductive cyclisation procedure. Thus, the Wang trichloroacetamidate resin (66) was coupled with Fmoc-protected 4-
hydroxyproline methyl ether (67). The product, after Fmoc deprotection using 20% piperidine/DMF, was coupled with 2-azidobenzoic acid in presence of DCC and DMAP to provide the amide (71). Reductive cyclisation of (71) using TPP afforded the pyrrolobenzodiazepine-5,11-dione (75), which upon cleavage from the resin yielded 2-hydroxy-7,8-substituted pyrrolobenzodiazepine-5,11-dione (76). Furthermore the reduction of (71) by DIBAL-H followed by reductive cyclisation and cleavage afforded 2-hydroxy-7,8-substituted pyrrolobenzodiazepine imine (74) (Scheme 1.13).
Thurston et al.\textsuperscript{46} have reported a simple coupling reaction in the synthesis of a C2-vinyllic pyrrolobenzodiazepine imine. Thus, the pre-formed C-rings (78) were coupled to the nitrobenzoic acid fragment (77) using oxalyl chloride in presence of potassium carbonate to provide compounds (79). Reduction followed by treatment with 4-nitrobenzyl chloroformate and pyridine of the resultant amine (80) afforded the N10-protected intermediates (81), which were cyclised with TPAP/NMO to give (82). Removal of the N10-protecting group resulted in the C2-vinyllic pyrrolobenzodiazepine imine (83).

\begin{center}
\begin{tikzpicture}
% Diagram code goes here
\end{tikzpicture}
\end{center}

Scheme 1.14

Another approach reported\textsuperscript{47} by the same group involves the use of the Suzuki reaction to introduce the C2-aryl substituents (Scheme 1.15). Thus, the pre-formed C-ring (85) was coupled to 4,5-dimethoxy-2-nitrobenzoic acid (84) to provide compound (86). Reduction followed by cyclisation of the resultant amine provided the pyrrolobenzodiazepine dilactam (87). Protection of the C2 alcohol as the TBDMS ether (88), followed by treatment with SEM-Cl under strongly basic conditions provided the SEM substituted analogue (89). Selective deprotection of the C2-TBDMS
ether, followed by Swern oxidation of (90) furnished the C2 ketone (91), which was converted to the C2-C3 enoltriflate (92) using trifluoromethanesulfonic anhydride in the presence of pyridine. Suzuki reactions on the enoltriflate (92) with various arylboronic acids provided C2-substituted analogues (93-95). Reduction of the dilactam in the presence of the N10-SEM group with sodium borohydride, followed by spontaneous cleavage of the unstable N10-SEM protected carbinolamine in presence of wet silica gel afforded C2-aryl pyrrolobenzodiazepines (96-98) in their imine form.

Scheme 1.15

In continuation, Thurston et al. reports the use of Stille coupling in the synthesis of C-ring endo-exo unsaturated C2-substituted pyrrolo[2,1-c][1,4]benzodiazepines. Thus, the key enoltriflate (92) was coupled to a number of commercially available organotin reagents under Stille conditions to provide vinylic, acetylenic and heteroaromatic moieties at the C2 position of the pyrrolobenzodiazepine dilactams (99a-d). Reduction of the dilactam with sodium borohydride afforded the SEM-protected carbinolamine intermediate, which converted to the
pyrrolobenzodiazepine imines (100a-d) upon exposure to moist silica gel. An attempt to convert the enoltriflate to the more versatile trimethylstannyl alkene failed and instead afforded the simple unsubstituted endo-2,3-unsaturated product (101) in 41% yield.

Scheme 1.16

The same group later reported an alternative synthetic strategy where trifluorosulphonation/Suzuki coupling are carried out prior to the B-ring closure (Scheme 1.17). Thus, coupling of 4-(L)-trans-hydroxyproline (102) with 4,5-dimethoxy-2-nitrobenzoic acid to give (103) followed by oxidation with BAIB/TEMPO resulted in compound (104) in 90% yield. Triflation of compound (104) with NaHMDS afforded almost exclusively the 1,2-unsaturated product (105), which underwent Suzuki coupling in presence of arylboronic acid to give compound (106) in high yield, but needed heating, unlike the Suzuki reaction involving the dilactam-based enoltriflate reported above. Reduction of the nitro and protection of the resultant amine (107) gave compound (108). TBDMS group removal and oxidation of (109) with BAIB/TEMPO achieved B-ring closure to compound (110) in 80% yield. Finally, removal of the allyl carbamate afforded the C2-aryl substituted 1,2-unsaturated pyrrolobenzodiazepine imine (111) in 80% yield. The advantages of this synthetic route in comparison to the one mentioned above is that it avoids a reductive step, thus removing the risk of N10-C11 secondary amine formation and allows a reduction sensitive group to be included on the C2-aryl ring.
More recently, Mori et al. reported\(^5\) a novel synthesis of an anthramycin derivative via reductive cyclisation of a pyrrolidine (Scheme 1.18). The key strategy includes the ring closing enyne metathesis and cross metathesis via the use of ruthenium carbene complex. Thus, enyne metathesis of compound (112) and 5 mol% of ruthenium carbene complex at room temperature under ethylene gas gave pyrrolidine (113) in 76% yield. Condensation of the deprotected pyrrolidine with 2-nitro-3-benzyloxy-4-methyl-benzoyl chloride (114) afforded compound (115), which upon reduction with zinc in acetic acid and treatment with dilute hydrochloric acid gave (116) in 86% yield. Cross metathesis of (116) with ethyl acrylate using (117) followed by treatment of the resultant (118) with RhCl\(_3\)\(\cdot\)3H\(_2\)O in ethanol resulted in the formation of the double bond shifted compound (119). Debenzylation followed by protection of the resultant phenol (120) as a benzylidene acetal gave (121), which was reduced via NaBH\(_4\) to give aminal (122), the final product.
Scheme 1.18
1.4 Synthesis of pyrrolobenzodiazepine dimers

Recently, there has been tremendous interest in the design and synthesis of DNA interstrand cross-linking agents that are likely to enhance the sequence selectivity and which in turn could increase selectivity for tumour cells. In this context a large number of PBD dimers have been designed and synthesized with a view to exploring their DNA cross-linking ability and their sequence selectivity. These PBD dimers have been joined through different positions such as A-C8/A-C8', A-C7/A-C7', C-C2/C-C2' and A-C8/C-C2. Amongst these, A-C8/A-C8' linked PBD dimers have shown promising cytotoxicity and efficient cross-linking properties.

1.4.1 Synthesis of C8-linked pyrrolo[2,1-c][1,4]benzodiazepine dimer via dethioacetalisation

An efficient convergent synthesis of the C8-linked pyrrolobenzodiazepine dimer via a versatile approach of joining two vanillic acid units with α,ω-dihaloalkanes has been reported by Thurston and co-workers. Thus, refluxing vanillic acid (123) with diiodoalkanes of varying length in the presence of aqueous sodium hydroxide afforded the dimer acids (124a-d) in 60-84% yield. Following conversion to their corresponding methyl esters (125a-d), nitration using SnCl₂/HNO₃ in DCM proceeded smoothly at -20°C to provide the corresponding aryl nitro esters (126a-d) in 65-75% yield. Mild hydrolysis of the esters followed by coupling of the corresponding nitro acids (127a-d) with (2S)-pyrrolidinecarbaxaldehyde diethyl dithioacetal afforded the bis-amides (128a-d). Reduction of the nitro thioacetal intermediates and cyclisation of the resultant aryl amino thioacetal (129) with HgCl₂/CaCO₃ gave the target C8-linked dimers (130a-d) in 60-83% yield (Scheme 1.19).
Kamal et al., have reported an improved and versatile route to the DC-81 dimer via a less expensive starting material, i.e., vanillin instead of vanillic acid. The use of this approach means that the additional step of esterification and deesterification of the vanillic acid has been eliminated which in turn reduces the number of steps, as well as improving the yields. Thus, vanillin (131) was dimerised with dibromo-alkanes followed by the nitration with SnCl₄/HNO₃ to obtain the nitroaldehyde dimers (132). Oxidation of the aldehydes with NaClO₂ gave the nitro acids (133) in 78-84% yield. Treatment of nitro acids (133) with thionyl chloride and coupling of the resultant acid chloride with (S)-proline gave compound (134), which upon esterification followed by reduction of the ester (135) with DIBAL gave the aldehyde (136). Treatment of the aldehyde (136) with TMSiCl and EtSH provided the advanced intermediate (137). Reduction of this nitro thioacetal intermediate and cyclisation of the resultant amino thioacetal (138) with HgCl₂/CaCO₃ afforded the DSB-120 (139a: n=3) and other DC-81 dimers (139b-c) in 22-25% yields (Scheme 1.20).
The same group later reported a simple procedure for the conversion of the thioacetals (138a-c) to the carbonyl compounds using FeCl₃·6H₂O and have further demonstrated subsequent cyclisation to give DSB-120 (139a; n=3) and other DC-81 dimers in 18-22% yield (Scheme 1.21).
Very recently, Kamal et al. synthesized and tested a new sequence selective imine-amide pyrrolobenzodiazepine dimer,\textsuperscript{57} comprised of DC-81 and dilactam of the DC-81 subunits tethered to their C8 positions through alkanedioxy linkers. Thus, oxidation of vanillin followed by benzylation and nitration provided the starting material (145). Coupling of the (L)-proline methyl ester and debenzylation of the resultant (146) with BF\textsubscript{3}.OEt\textsubscript{2}-EtSH afforded compound (147), which upon hydrogenation over a palladium catalyst gave the dilactam precursor (148). Esterification of vanillic acid methyl ester (149), followed by nitration, ester hydrolysis and coupling with (2S)-pyrrolidinecarboxaldehyde diethyl thioacetal afforded the other precursor (153) (Scheme 1.23).

Linking compounds (147) and (153) resulted in the key intermediate (154), while the alternative key intermediate (155) has been prepared by linking (153) and (148). Reduction of both compound (154) and (155) with tin (II) chloride provided (156), which upon treatment with
HgCl₂/CaCO₃ gave the target C8-linked dimers (157) containing the imine and dilactam moiety in 55-61% yield (Scheme 1.24).

Similarly, the same group later reported⁵⁸ the synthesis of the mixed imine-amine PBD dimers employing compound (146). The key step involves the synthesis of compound (160) which was obtained in moderate yield via reduction to alcohol (158) and subsequent oxidation to give aldehyde (159) followed by hydrogenation and ring closure. Linking compound (160) and (153a-b) resulted in the key intermediate (161), which upon reduction to compound (162) and treatment with HgCl₂/CaCO₃ gave the target C8-linked dimers (163) containing the imine and amine moiety in 50-51% yield (Scheme 1.25).

23
1.4.3 Synthesis of pyrrolobenzodiazepine dimers through a piperazine side armed alkane spacer

During the last decade, many piperazine derivatives have been synthesized as useful chemotherapeutic agents for various diseases. Bis-1,4-dialkyl-piperazines have been extensively investigated and have been reported as anti-bacterial\textsuperscript{59,60} and antineoplastic agents.\textsuperscript{59,61,62} Michejda and co-workers\textsuperscript{63} reported symmetrical bifunctional agents as a promising antitumour class of compounds with remarkable selectivity against colon cancers that possess a piperazine moiety in its linker spacer. Recently, Kamal \textit{et al.} synthesised and tested a series pyrrolobenzodiazepine dimers linked through a piperazine moiety.\textsuperscript{64} Access to the pyrrolobenzodiazepine dimer linked through piperazine (166) was accomplished \textit{via} an initial dimerisation of the compound (153a-d) with piperazine in the presence of potassium carbonate in refluxing acetone to access dimer (164), followed by reduction to (165) and treatment with HgCl\textsubscript{2}/CaCO\textsubscript{3} to furnish the target C8-piperazine linked dimers (166a-d) in 61-65% yield (Scheme 1.26).
Lown and co-workers\textsuperscript{65} adopted a similar method for the synthesis of pyrrolo[2,1-c][1,4]benzodiazepine dimers (174) linked with pyrrole and imidazole polyamides. Thus, the key intermediate (169) was obtained in 70\% yield from compound (167) \textit{via} a condensation reaction with [2-[N-(benzyloxycarbonyl)amino]ethyl]amine and subsequent deprotection of the Cbz group in intermediate (168). Access to the alternative precursor (172) was accomplished \textit{via} an initial coupling reaction between compound (167) and (170) followed by hydrolysis of intermediate (171) with sodium hydroxide (Scheme 1.27). Additional coupling of compound (169) and (172) in the presence of EDCI and HOBt afforded compound (173), which upon reduction and treatment with HgCl\textsubscript{2}/HgO cyclised to afford the desired bis-PBD-pyrrole and imidazole dimer (174) in 40-45\% yield.
1.4.4 Synthesis of C2/C2'-exo unsaturated pyrrolobenzodiazepine dimer

In an attempt to further extend base-pair span and recognition behavior, Thurston et al. investigated the inclusion of C2/C2' substituents and reported a novel synthesis of SJG-136\textsuperscript{66,67} (189), a C2/C2' \textit{exo}-methylene analogue of DSB-120. Thus, the key PBD C-ring coupling fragment (182) was prepared in seven high yielding steps (via 176→181) from \textit{trans}-4-hydroxy-\textit{L-}
proline (175) as shown in Scheme 1.28. Subsequent coupling to compound (183) provided the bis-nitro-amide (184) in 74% yield, which under mild conditions using TBAF to rapidly remove the TBDMS protecting group afforded the bis-nitro-alcohol (185) in 94% yield. Reduction of the nitro group followed by Alloc protection and oxidation with TPAP/NMO resulted in ring closure to provide compound (188) in moderate 32% yield. Cleavage of the Alloc protecting group with Pd(PPh)₄/PPh₃/pyrrolidine afforded the desired PBD dimer (189) in 77% yield. Alternatively, under Swern's conditions, compound (187) oxidised to give compound (190) and upon Alloc deprotection gave the dilactam dimer (191). The same group further extended the study to include the synthesis of the homologous diether-linked dimers (i.e. -O-(CH₂)ₙ-O- where n=3 and 5) via a similar route.⁶⁸

In addition, Kamal et al. have reported a series of C2-exo-fluorounsaturated pyrrolobenzodiazepine dimers employing the deprotective cyclisation of an amino thioacetal approach.⁶⁹,⁷⁰ Thus, etherification of 4-fluorosubstituted pyrrolidine-2-carboxaldehyde diethyl thioacetal (192) with dibromoalkanes provided compound (193). Reduction of compound (193) with SnCl₂.2H₂O resulted in the corresponding amino diethyl thioacetal (194), which upon

![Scheme 1.28](image-url)
deprotection via HgCl₂/CaCO₃ cyclised to give C2/C2'-exo-fluorosubstituted PBD dimers (195a-c) in 60-70% yield (Scheme 1.29).

1.4.5 Synthesis of A-C8/C-C2 linked pyrrolo[2,1-c][1,4]benzodiazepine dimers

Recently, Thurston and co-workers have reported the first example of A-C8/C-C2 amido-linked pyrrolobenzodiazepine dimers via convergent routes involving C8-amino and C2-methyleneacarboxy pyrrolobenzodiazepine monomers. Thus, N-protection of the commercially available 4-nitroanthranilic acid (196) as its allyl carbamate (197) followed by coupling to (S)-(+) 2-pyrrolidinemethanol provided compound (198). Reduction of the nitro using SnCl₂ in refluxing methanol and treatment of the resultant amine (199) with 9-fluorenylmethyl chloroformate in the presence of aqueous sodium carbonate resulted in compound (200). Swern oxidation of (200) provoked B-ring cyclisation to give compound (201), which upon treatment with N,N-dimethylamine in methanol removed the Fmoc protecting group to provide the key C7-desmethoxyaniline (202). The desired A-C8/C-C2 amide-linked PBD dimers (205) were prepared by coupling compound (202) with compound (203) and subsequent treatment of compound (204).
with palladium in the presence of pyrrolidine cleaved the Alloc protecting group to give the novel N10-C11 imine PBD dimer (205) in 70 % yield (Scheme 1.30).

Scheme 1.30

The synthesis of a new A-C8/C-C2 alkoxyamido-linked pyrrolo[2, 1-c][1,4]benzodiazepine dimer has been described by Kamal et al. 72 The key A-C8 components (208a-c) were prepared by etherification of compound (206) with methyl bromoalkanoates, followed by basic hydrolysis of the resultant esters (207a-c) to give the desired intermediate acids (208a-c) in 78% yield (Scheme 1.31).

Scheme 1.31

The other key C-C2 amino components were prepared via a coupling reaction between compound (209) and trans-4-hydroxy-L-proline methyl ester hydrochloride to give the nitro ester
Treatment with TBDMS-Cl followed by reduction with DIBAL-H produced the corresponding aldehyde (212), which upon protection with EtSH/TMS-Cl resulted in the protection of the aldehyde and deprotection of the TBDMS in the same step to give compound (213). Mesylation upon C2 hydroxy group gave compound (214), followed by azidation to compound (215) and reduction of the azide to afford compound (216). Reaction of compound (208a-c) and compound (216) gave coupled product (217), which after reduction with SnCl2·2H2O in methanol gave (218a-c). Deprotection of the diaminothioacetal precursor using HgCl2/CaCO3 afforded the PBD dimers (219a-c) in 56-60% yield (Scheme 1.32).

In a variation on this procedure, intermediates (224a-c) were prepared by coupling compounds (208a-c) with compound (223) prepared as shown in Scheme 1.33, which upon reduction gave the aminothioacetal precursors (225a-c). Treatment with HgCl2/CaCO3 provided the imine-dilactam PBD dimers (226a-c) in 51-55% yield.
Moreover, the same group have reported the first example of A-C8/C-C2-exo unsaturated alkoxyamido linked pyrrolo[2,1-c][1,4]benzodiazepine dimer.\(^{73}\) Thus, debenzylation of precursor methyl 4-benzyloxy-5-methoxy-2-nitrobenzoate (227) with BF\(_3\).OEt\(_2\)-EtSH gave compound (228), which upon etherification with Boc-protected bromoalkylamine provided (229a-b). Hydrolysis and subsequent coupling of acid (230) with (2S)-pyrrolidinecarboxaldehyde diethyl thioacetal gave (231a-b) and Boc deprotection with trifluoroacetic acid provided the key C8 alkoxyamine intermediate (232a-b) (Scheme 1.34).
The C-C2-exo unsaturated acid components (240) required for coupling to (232) were synthesized via an initial coupling reaction between 4-benzyloxy-5-methoxy-2-nitrobenzoic acid (233) and trans-4-hydroxy-(L)-proline methyl ester hydrochloride to afford compound (234). Protection of the hydroxy group with TBDMS-Cl followed by reduction of the resultant (235) with DIBAL-H gave aldehyde (236). Subsequent treatment with EtSH/TMS-Cl resulted in the protection of aldehyde and deprotection of the TBDMS group in one step to provide compound (237). Oxidation followed by treatment of the resultant product (238) with methyl diethyl phosphonoacetate resulted in compound (239), which upon hydrolysis yielded the corresponding acid (240). Amidation of compound (240) with (232) yielded the key intermediate (241a-b), which upon reduction with SnCl₂·2H₂O gave the amino diethyl thioacetal (242a-b) and deprotection of the amino diethyl thioacetal with HgCl₂/CaCO₃ provided the target molecules (243a-b) and (244a-b) (Scheme 1.35).

Further, the group also prepared the PBD dimer (250a-b) with amide and imine functionality at the N10-C11 positions. Thus, amidation of compound (240) from above with
(247) prepared as shown below, and subsequent reduction of coupled product (248) followed by deprotection of the diethyl thioacetal group in intermediate (249) afforded the imine/dilactam PBD dimer (250a-b) in 51-53% yield (Scheme 1.36).

1.5 **Synthesis of pyrrolobenzodiazepine hybrids**

The development of conjugates and hybrid molecules between two types of cytotoxic moieties represent a new approach in the discovery of new antitumour agents, as they possess not only high potency but also different alkylating sites, with both the aspects being useful for tumour treatment. Thus in the past few years, several active moieties of known antitumour compounds leading to novel hybrids tethered to pyrrolobenzodiazepines have been designed, synthesized and
evaluated for their biological activity. Thurston and coworkers\textsuperscript{74} have synthesized PBD analogues with an epoxide group attached at the C8 position with an objective of producing PBD system with DNA cross-linking activity. In this method a 9-fluorenylmethylcarbonyl (Fmoc) group has been employed to protect the amino intermediate (253) before dithioacetal deprotection to allow the Fmoc-protected carbinolamine (254) to be formed in order to carry out epoxidation on the C8-propenoxy group with \textit{m}-CPBA. Finally, the Fmoc is cleaved by tetrabutyl-ammonium fluoride in DMF to produce the N10-C11 imine while leaving the epoxide intact, thus affording the target expoxide-PBD (256) in 79\% yield (Scheme 1.37).

![Scheme 1.37](image)

The same group has also focused on the development of a GC-specific agent, due to the sequence being a major site of action of a number of clinically useful antitumour drugs, such as nitrogen mustard and mitomycin.\textsuperscript{75} Consequently, an EDTA (cleaving moiety) conjugated pyrrolobenzodiazepine has been synthesized \textit{via} the thioacetal cyclisation route.\textsuperscript{76} The crucial strategy includes the attachment of the EDTA moiety to the pyrrolobenzodiazepine skeleton prior to the unstable electrophilic N10-C11 imine. The key to this was compound (259) which was accessed by coupling acid (258) to a diethyl thioacetal. Next, deprotection of compound (259) with Me\textsubscript{3}SiI, followed by attachment of the EDTA triester through its free carboxylic group using CDI afforded the nitro amide (261). Reduction of compound (261) through catalytic hydrogenation provided the amine (262), which cyclised upon treatment with HgCl\textsubscript{2}/CaCO\textsubscript{3} to the desired EDTA-DC-81 (263) in 12\% yield (Scheme 1.38). The EDTA moiety was then exploited to produce, for example, the iron complex (264).
The synthesis of pyrrolobenzodiazepine ring systems linked to methanesulphonate, which is an alkylating part of busulphan, used in treatment of chronic myeloid leukemia, has been described by Kamal and coworkers.\(^7\) Thus etherification of compound (265) with bromoalkanols, followed by mesylation of the resultant (266) provided the desired precursors (267). Reduction and subsequent treatment of the amine (268) with HgCl\(_2\)/CaCO\(_3\) in aqueous acetonitrile resulted in the deprotection of the thioacetal group to provide the target compound (269a-b) (Scheme 1.39).
A series of novel pyrrolobenzodiazepine analogues (277-280) resulting from conjugation to cyclic amines, such as pyrrolidine, piperidine, indoline and isoindoline, via a standard coupling approach has been reported by Thurston and coworkers. Thus, the key core building block (276) was obtained from an initial etherification of compound (270) with benzyl alcohol and p-toluenesulfonic acid to provide the nitro monoester (271). Treatment of (271) with oxalyl chloride generated the acid chloride which readily coupled to (2S)-(+)–pyrrolidinemethanol in presence of triethylamine to give compound (272), which upon reduction, followed by treatment of the resultant amine (273) with di-t-butyldicarbonate, gave the Boc-protected amine (274). Oxidation with pyridinium dichromate resulted in the ring closure to compound (275) and finally removal of the benzyl ester protecting group provided the target building block (276), which was conjugated to each of the four amines using standard coupling methodology (EDCI/DMAP). Removal of the Boc group and accompanying dehydration gave the target analogue (277-280) (Scheme 1.40).
With the aim of finding novel anticancer agents Kamal et al. synthesized numerous PBD hybrids and conjugates that exhibited not only good DNA binding affinity, but also represented promising \textit{in vitro} anticancer activity. The key step involves the initial etherification of (2S)-N-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde diethyl thioacetal derivatives (281, substrate in Tables 1.2a-b) with the DNA interactive moieties such as benzimidazole,\textsuperscript{79} anthraquinone,\textsuperscript{80} fluoroquinolone,\textsuperscript{81} flavone,\textsuperscript{82} naphthalimide,\textsuperscript{83} chrysene,\textsuperscript{84} acridone/acridine,\textsuperscript{85} and pyrene\textsuperscript{86} through different alkyl chain spacers to give the C8-linked nitro thioacetal intermediate (282). Reduction of the nitro to its corresponding amine (283) and subsequent deprotection of the thioacetal group provided the desired PBD hybrids (284) [Tables 1.2a-b].

\begin{center}
\includegraphics[width=\textwidth]{Scheme_1.41}
\end{center}

\begin{center}
\textbf{Scheme 1.41: General reaction}
\end{center}

<table>
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<th>Substrate</th>
<th>Hybrid</th>
<th>Reaction conditions</th>
<th>Final PBD product</th>
</tr>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2. SnCl$_2$, $\text{H}_2\text{O}$</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>1. K$_2$CO$_3$, acetone, reflux</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2. SnCl$_2$, $\text{H}_2\text{O}$, MeOH, reflux</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3. HgCl$_2$/CaCO$_3$, MeCN/$\text{H}_2\text{O}$, r.t.</td>
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<td>3</td>
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<td></td>
<td>1. K$_2$CO$_3$, acetone, reflux</td>
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<td></td>
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<td>2. SnCl$_2$, $\text{H}_2\text{O}$, MeOH, reflux</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. HgCl$_2$/CaCO$_3$, MeCN/$\text{H}_2\text{O}$, r.t.</td>
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\begin{center}
\textbf{Table 1.2a}
\end{center}
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<th>Reaction conditions</th>
<th>Final PBD product</th>
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<td><img src="image5.png" alt="Image" /></td>
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<td><img src="image8.png" alt="Image" /></td>
<td>1. isobutyl chloroformate, Et$_3$N, r.t 2. SnCl$_2$, 2H$_2$O, EtOAc, reflux 3. HgCl$_2$/CaCO$_3$, MeCN/H$_2$O, r.t</td>
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<tr>
<td>7</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td>1. EDCI, HOBT, DMF, r.t 2. SnCl$_2$, 2H$_2$O, MeOH, reflux 3. HgCl$_2$/CaCO$_3$, MeCN/H$_2$O, r.t</td>
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<td><img src="image14.png" alt="Image" /></td>
<td>1. EDCI, HOBT, DMF, r.t 2. SnCl$_2$, 2H$_2$O, MeOH, reflux 3. HgCl$_2$/CaCO$_3$, MeCN/H$_2$O, r.t</td>
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<td><img src="image17.png" alt="Image" /></td>
<td>1. isobutyl chloroformate, Et$_3$N, r.t 2. SnCl$_2$, 2H$_2$O, EtOAc, reflux 3. HgCl$_2$/CaCO$_3$, MeCN/H$_2$O, r.t</td>
<td><img src="image18.png" alt="Image" /></td>
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</table>

Table 1.2b

The same group also reported the synthesis of C2 and C2-C8 linked pyrrolobenzodiazepine-naphthalimide hybrids$^{87a,87b}$ to explore its DNA binding potential. Synthesis of the C2 linked PBD-naphthalimide hybrids have been carried out via the deprotective cyclisation of an amino thioacetal approach to introduce the sensitive N10-C11 imine. Thus,
treatment of the nitro ester (285) with TBDMS-Cl resulted in the protection of the hydroxy group. Reduction of compound (286) with DIBAL-H, followed by protection of the corresponding aldehyde (287) with EtSH/TMS-Cl gave compound (288) in 72% yield. Oxidation of the C2 hydroxy group with TPAP/NMO provided compound (289), which upon treatment with methyl (diethyl phosphono) acetate afforded compound (290). Subsequent treatment with 1M LiOH gave compound (291). Amidation of compound (291) with corresponding naphthalimide (292) provided the key intermediate (293), which upon treatment with SnCl2.2H2O afforded the corresponding amino diethyl thioacetal (294). Deprotection of amino diethyl thioacetal with HgCl2/CaCO3 provided the target C2 linked PBD-naphthalimide (295) in 56-58% yield (Scheme 1.42).

Synthesis of the C2-C8 linked PBD-naphthalimide87a,87b involved a similar approach, but employing compound (296) as starting material. Thus protection with TBDMS-Cl, reduction of the resultant intermediate (297) followed by ethanethiol protection of intermediate (298) afforded
compound (299). Coupling of this compound with 1,8-naphthalimide afforded the intermediate (300), which gave compound (301) upon oxidation. Treatment with methyl (diethyl phosphono) acetate and ester hydrolysis of the resultant intermediate (302) gave compound (303). Further amidation of compound (303) with amine (304) provided compound (305). Subsequent reduction gave the amine (306) which followed by deprotection of the diethyl thioacetal group provided the desired C2-C8 linked PBD-naphthalimide (307) in 52% yield (Scheme 1.43).
Furthermore, Baraldi et al. have reported the synthesis of a new hybrid,88 a combination of a PBD and the naturally occurring antitumour agent distamycin A. Thus, the key pyrrolobenzodiazepine (315) was prepared via a new general route involving oxidative cyclisation of the N10-Troc-protected intermediate (314), which was readily made available through coupling of nitro monoester (311) and (2S)-(+)-pyrrolidinylmethanol, followed by catalytic hydrogenation of compound (312) and subsequent protection of the resultant amine (313) with Troc-Cl. The final assembly of the desired hybrids (318) was achieved in two steps involving acid hydrolysis of the ester (315) to give acid (316), which was then coupled with deformyl distamycin in the presence of EDCI as condensing agent to provide Troc protected hybrid molecule (317a-d). Deprotection of the Troc afforded the free N10-C11 imine moiety of the target molecule (318a-d) (Scheme 1.44).

Similarly, Lown et al. have reported a convenient strategy for the design and synthesis of the first example of a pyrrolobenzodiazepine conjugated with a lexitropsin hybrid.89 The precursor carboxylic acid (322) was assembled from vanillin (319) as shown in Scheme 1.45. Coupling of carboxylic acid (322) with (2S)-pyrrolidine-2-carboxaldehyde diethyl thioacetal via the acid chloride resulted in the nitro ester (323). Hydrolysis produced nitro acid (324), which was then
coupled with the amine moiety of lexitropsin to give compound (325). Hydrogenation of the nitro lexitropsin hybrid (325) to the corresponding amine (326), followed by deprotection of the thioacetal group with HgCl₂/H₂O in aqueous acetonitrile afforded the desired imine (327) in 40% yield together with the methoxy derivative (328).

Scheme 1.45

Finally in this section, Hurley et al. have designed a new PBD hybrid (UTA-6026 n=3; see entry 1, table 1.3) containing two alkylating moieties with the potential to alkylate G and A sequence tracts of DNA. To achieve this a similar methodology to that discussed above was used whereby DC-81 was combined to (+)-cyclopropapyrroloindole [(+)-CPI], which is a DNA-DNA alkylating moiety that selectively alkylates N3 of adenine. The key strategy involved synthesizing the N10-Fmoc protected PBD analogue first and coupling it to (+)-seco-CPI-indole.
with EDCI/DMA and removing the Fmoc group in the final step to introduce the sensitive PBD imine bond (entry 1) [Table 1.3]. A similar approach was also undertaken by Tercel and coworkers\textsuperscript{92} to combine the seco-1,2,9,9a-tetrahydrocyclopropa[c]benz[e]indol-4-one (seco-CBI) and PBD units to construct a new class of unsymmetrical minor groove cross linking agents (entry 2-5) [Table 1.3].

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Hybrid</th>
<th>Reaction conditions</th>
<th>Final PBD product</th>
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<td>Pd(PPh₃)₄ pyrrolidine DCM, 20°C</td>
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<td><img src="image11.png" alt="Hybrid 4" /></td>
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Table 1.3
1.6 Synthesis of pyrrolobenzothiadiazepines

Recent searches for novel anti-HIV agents endowed with low toxicity has led to the synthesis of the tricyclic derivatives possessing a 7-membered diazepine ring, which is representative of a novel class of non-nucleosidic reverse transcriptase inhibitors. Amongst the benzodiazepine derivatives, the first non-nucleoside reverse transcriptase inhibitors with clinical potential have been tetrahydroimidazobenzodiazepinone (TIBO, 329), followed by the dipyridodiazepine nevirapine (330) and nevirapine-like tricyclic pyrido- (331) or benzo- (332) derivatives. Analogues of nevirapine and TIBO with thiadiazepine moieties have attracted numerous interest. The related pyrrolo (333) derivatives have also attracted attention as thiadiazepines with the potential to act as non-nucleosidic reverse transcriptase inhibitors. This, together with their structural relationship to the antitumour antibiotic pyrrolobenzodiazepines has made the pyrrolobenzothiadiazepines attractive targets, and thus a brief review of methods used to synthesise them follows.

With a view to investigating pyrrolobenzodiazepines as anti-HIV agents Artico and coworkers reported the synthesis of pyrrolobenzothiadiazepines using reductive cyclisation of a nitro in the presence of a pendant carbonyl functionality. Thus, condensation reaction of 2-nitrobenzenesulfonyl chloride (334) with compounds (335a-b) using potassium tert-butoxide and 18-crown-6 provided the key compounds (336a-b), which upon reduction with iron powder in the presence of acetic acid furnished the aminoaldehyde intermediate with concomitant ring closure to the desired pyrrolobenzothiadiazepines (337a-b) in 92-100% yield (Scheme 1.46).
Artico et al. further extended their studies and synthesized compound (337a) via a phosphorus oxychloride mediated Bischler-Napieralski cyclisation reaction of the formylated precursor 1-(2-formamidobenzenesulfonyl)pyrrole (339),97,99 which was quantitatively derived from the reaction of acetic formic anhydride with 1-(2-aminobenzenesulfonyl)pyrrole (338), which in turn was readily made available from a condensation reaction between the corresponding sulfonyl chloride and pyrrole (Scheme 1.47).

Recent studies by Artico and coworkers100 described the synthesis of pyrrolo[1,2-b][1,2,5]benzothiadiazepin-4-one 1,1-dioxides via an intermolecular cyclisation101 of an ester. Thus, reduction of the nitro compound (340) on heating in the presence of iron in acetic acid afforded the key amino ester compound (341) in high yield, which upon treatment with 2-hydroxypyridine as a bifunctional catalyst resulted in the intramolecular cyclisation of the amino ester to provide pyrrolobenzothiadiazepin-4-one (342) in 42-54% yield. Additionally, treatment of the ester (341) with hydrazine resulted in the 1-(2-amino-5-chlorobenzenesulfonyl)pyrrole-2-carbohydrazide (343), which underwent loss of hydrazine upon heating with 2-hydroxypyridine in acetic acid to provide compound (342) in 38% yield (Scheme 1.48).
An approach to the cyclopropyl and benzyl substituted pyrrolobenzothiadiazepines (348a-b) has been established in high yields via intermolecular cyclisation of the corresponding fluoro carboxyamides. Thus, coupling 2-ethoxycarbonyl-1H-pyrrole with 2-fluorobenzenesulfonyl chloride (344) resulted in the ester (345), which upon alkaline hydrolysis with KOH gave the acid (346). Treatment of the acid (346) with cyclopropylamine and benzylamine in the presence of EDC and DMAP and subsequent treatment of corresponding amides (347a-b) with sodium hydride/cuprous iodide provided the 5-cyclopropyl- (348a) and 5-benzyl- (348b) substituted pyrrolobenzothiadiazepine, respectively, in 80-94% yield (Scheme 1.49).

An example of a saturated pyrrole (i.e. pyrrolidine) derivative (351) was prepared from 2-ethoxycarbonyl-1-(2-nitrobenzenesulfonyl)pyrrolidine (349) and reported by Artico and
coworkers. Thus, reduction of the nitro (349) to the corresponding amino ester (350) with iron powder, followed by treatment of compound (350) with 2-hydroxypyridine on heating afforded the pyrrolo[1,2-\(b\)][1,2,5]benzothiadiazepin-1,1-one 5,5-dioxide (351) (Scheme 1.50).

\[
\begin{array}{c}
\text{Fe, AcOH, } 60^\circ\text{C, 2 h} \quad 349: R=\text{NO}_2 \\
\text{Ph}_2\text{O, } 180^\circ\text{C, 18 h} \quad 350: R=\text{NH}_2 \\
\rightarrow \quad 351
\end{array}
\]

**Scheme 1.50**

1.6.1 Synthesis of other pyrrolobenzothiadiazepine analogues

In the course of investigations into the synthesis of cyclic sulfones, Silvestri *et al.* synthesized a series of novel pyrrolobenzothiazepine 1,1-dioxide derivatives (355) and (358) via oxidation of the corresponding pyrrolobenzothiazepines. Thus, coupling of 2-aminothiophenol (352) with 1\(H\)-pyrrole in the presence of iodine and potassium iodide gave a mixture of 2-(2-aminobenzenesulfenyl)-1\(H\)-pyrrole (353) and 3-(2-aminobenzenesulfenyl)-1\(H\)-pyrrole (356), which upon treatment with triphosgene in the presence of triethylamine afforded pyrrolobenzothiazepines (354) and (357). Oxidation of compound (354) and (357) with hydrogen peroxide provided the desired dioxides (355) and (358) (Scheme 1.51).

\[
\begin{array}{c}
\text{352} \\
\text{I}_2, \text{KI} \\
\text{353} \\
\text{354} \\
\text{355} \\
\text{356} \\
\text{357} \\
\text{358}
\end{array}
\]

**Scheme 1.51**

The same group also adopted a similar approach in the synthesis of diester pyrrolobenzothiadiazepine (363). Thus, coupling of 2-nitrobenzenesulfenyl chloride (359) with
1H-pyrrole in presence of potassium tert-butoxide and 18-crown-6 furnished 1-(2-nitrobenzenesulfonyl)-1H-pyrrole (360), which upon reduction with iron powder gave the corresponding amino derivative (361). Condensation of compound (361) with diethyl oxalacetate resulted in the cyclised precursor (362), which was then oxidised to the desired dioxide in the presence of 3-chloroperoxybenzoic acid (Scheme 1.52).

1.6.2 Synthesis of tetracyclic pyrrolobenzothiadiazepines

On studies into the new antidepressant agent, aptazapine, Artico and coworkers synthesized a novel tetracyclic pyrrolobenzothiadiazepine (367) via cyclisation and double amide reduction. Thus, reaction of the unsubstituted pyrrolobenzothiadiazepine (364) with bromoacetyl bromide furnished 10-bromoacetyl-10,11-dihydro-11-ethoxycarbonylpyrrolo[1,2-h][1,2,5]benzothiadiazepine-5,5-dioxide (365), which in the presence of benzylamine provided the precursor N5-substituted pyrrolobenzothiadiazepine (366). Treatment of precursor (366) with lithium aluminium hydride resulted in cyclisation and amide reduction to afford the desired tetracyclic pyrrolobenzothiadiazepine (367) (Scheme 1.53).
The same group also demonstrated the conversion of compound (365) into a series of useful tetracyclic pyrrolobenzothiadiazepine derivatives, namely (368), (369), and (371). The former derivatives (368) and (369) resulted through treatment of 10-bromoacetyl-11-ethoxycarbonyl-10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine (365) with an equimolar amount of aqueous methylamine in the presence of triethylamine. The latter dioxopiperazinyl derivative (371) was accomplished through thermal cyclisation of the benzylaminoacetyl intermediate (370), which was in turn attained by reacting compound (365) with benzylamine.

Alternatively, treatment of compound (365) with sodium hydrogen carbonate allowed a high yielding access to the tetracyclic β-lactam derivative (368). Opening of the β-lactam ring
with excess methylamine furnished the bis-amide (372), which underwent ring closure in the presence of 2-hydroxypyridine to provide the spiro pyrrolobenzothiadiazepine derivative (373) in 50% yield (Scheme 1.55).

Access to the imidazolo-fused tetracyclic system (377) via cycloaddition of tosylmethyl isocyanide (TosMIC) to the N10-C11 imine of pyrrolobenzothiadiazepine (337a) in the presence of butyllithium has also been established by the same author. Such tetracyclic systems were envisaged as sulfonyl analogues of flumazenil, which has found clinical and commercial success as a cognition enhancer. The same tetracycle (377) has also been synthesized in 39% yield through oxidation of the dihydroimidazole precursor (376), which was in turn obtained from treatment of the aminomethyl derivative (375) with triethyl orthoformate. The aminomethyl derivative (375) was obtained from the reaction of pyrrolobenzothiadiazepine (337a) with nitromethane and subsequent Raney nickel reduction of the intermediate nitro compound (374) (Scheme 1.56).
1.7 1,2-Thiazine 1-oxides

In the context of our interest in the synthesis of pyrrolobenzodiazepines, pyrrolobenzothiadiazepines and analogues, including other tricycles, some tetracycles and even bicycles, this introduction will conclude with a brief introduction to the synthesis and chemistry of 1,2-thiazine 1-oxides, as the major aim of this thesis is to synthesise pyrrolobenzodiazepines, pyrrolobenzothiadiazepines and analogues from 1,2-thiazine 1-oxides.

1.7.1 Chemistry of 1,2-thiazine 1-oxides

1,2-Thiazine 1-oxides are cyclic six-membered ring compounds containing an S-N bond, which emanate from the [4+2] cycloaddition reaction of N-sulfinyl dienophile (378) with a conjugated 1,3-diene (379), in a Diels-Alder fashion. In principle the N-sulfinyl nitrogen-sulfur double bond, embraced with four electrons, is very similar to the carbon-carbon double bond, and thus has sufficient polarity to enter into conjugative interaction with adjacent π-electron systems. Subsequently, the hetero Diels-Alder reaction of nitrogen-sulfur double bonds in a variety of N-sulfinyl compounds (378; R=Ar, SO₂Ar, CO₂R, COR, CN, SR₂, PO(OR)₂) has provided a valuable method for the synthesis of 3,6-dihydro-1,2-thiazine 1-oxides (380) [Figure 1.5].
Since the discovery of this reaction by Wichterle and Rocek in 1953, a number of Diels-Alder cycloadditions have been reported for a variety of N-sulfinyl compounds bearing electron-withdrawing groups on the nitrogen and generally proceed rapidly at relatively low temperatures. Conversely, in the absence of an electron-withdrawing group these reactions are slow and require high pressure conditions or Lewis acids to proceed efficiently. In general these Diels-Alder reactions show excellent regio- and stereospecificity. A few examples of asymmetric hetero Diels-Alder reactions, using either chiral N-sulfinyl dienophiles or chiral dienes, have been reported to proceed with high diastereoselectivities, while the application of chiral Lewis acid complexes as catalysts has been demonstrated to give excellent chiral induction.

### 1.7.2 Reactivity of 1,2-thiazine 1-oxides

Although 3,6-dihydro-1,2-thiazine 1-oxides are stable enough to be handled and isolated, the N-S bond is very easily cleaved with variety of nucleophiles. This reactivity is, in fact, a very important and useful aspect of 3,6-dihydro-1,2-thiazine chemistry given that they can, in turn, be transformed into a variety of useful structures, such as allylic sulfoxides, sulfenyl esters, allylic alcohols, homoallylic amines, pyrroles, sultams, N-unsubstituted thiazine derivatives and other important compounds as shown below in Figure 1.6.
Chapter 1

Introduction

(i) Homoallylic amines

The acid- or base hydrolysis of 3,6-dihydro-1,2-thiazine 1-oxides results in the formation of the unsaturated amine derivatives via the S-N bond cleavage (Figure 1.6, route a). Based on deuterium labeling experiments, Mock and Nugent propose that such a conversion involves a concerted retro-ene reaction of the allylic sulfinic acid, derived from ring opening of the thiazine ring, generating the corresponding homoallylic amines via extrusion of SO₂.

(ii) Allylic alcohols

The conversion of 3,6-dihydro-1,2-thiazine 1-oxides to allylic alcohols proceeds via a sequence of steps by the use of carbon nucleophiles. The bond rupture with a Grignard reagent initially affords the allylic sulfoxide (Figure 1.6, route b), which later undergoes a reversible [2,3]-sigmatropic rearrangement to produce the sulfenate esters (Figure 1.6, route c). Upon treatment with a thiophilic reagent (e.g trimethyl phosphite), the sulfenate esters produce the corresponding allylic alcohols (Figure 1.6, route d).

(iii) 4-amino-2-alkenyldisulfanes

Reaction of 3,6-dihydro-1,2-thiazine 1-oxide cycloadducts of TosNSO with PhSH in an alkaline medium yields 4-amino-2-alkenyldisulfanes (Figure 1.6, route e).
(iv) 4-amino-2-alkenesulfonic acid derivatives

Treatment of the cycloadducts of TosNSO with base, followed by oxidation with hydrogen peroxide and acidification provides the 4-amino-2-alkenesulfonic acid (Figure 1.6, route f).\(^{125}\)

(v) 3,6-dihydro-[2H]-1,2-thiazine 1-oxides

\(\text{N-}\)Unsubstituted derivatives of 3,6-dihydro-1,2-thiazine 1-oxides can be obtained via the reduction of the cycloadducts of \(\text{CCl}_3\text{CH}_2\text{O}_2\text{CNSO}\) with zinc in refluxing \(\text{t-BuOH}\) (Figure 1.6, route g).\(^{125-127}\)

(vi) 3,6-dihydro-1,2-thiazine 1,1-dioxides (sultams)

Oxidation of 3,6-dihydro-1,2-thiazine 1-oxides tends to be complicated since oxidation can occur at both the carbon-carbon double bond, as well as at the sulfur. Usually, oxidation at sulfur is accomplished with milder oxidising agents, such as \(m\)-CPBA (peracid) to afford 3,6-dihydro-1,2-thiazine-1,1-dioxides (sultams) (Figure 1.6, route h). However, a stronger oxidising agent, such as trifluoroperacetic acid, can lead to oxidation at both centres to produce epoxysultams.\(^{108-115}\)

(vii) 3,6-dihydro-1,2-thiazines

\(\text{N-}\)Aryl-3,6-dihydro-1,2-thiazine 1-oxides can be reduced to the corresponding 3,6-dihydro-1,2-thiazines by treatment with lithium aluminium hydride in ether (Figure 1.6, route i). However, 3,6-dihydro-1,2-thiazine oxides that have a strong electron-withdrawing group on nitrogen yield only products derived from N-S bond cleavage.\(^{109-116}\)

(viii) pyrroles

Heating the 3,6-dihydro-1,2-thiazine 1-oxide in a strong alkaline methanolic solution appears to be a complex process. Nevertheless there is literature precedent,\(^{107}\) which shows that 3,6-dihydro-1,2-thiazine 1-oxides can be transformed into pyrroles. More recent precedence has shown an alternative route, which makes use of triethylamine/trimethylphosphite in methanol to convert the cycloaddition adduct via ring contraction to the corresponding pyrrole (Figure 1.6, route j).\(^{109-115,122}\)
Discussion-Part I
2.1 Aims of research project

As can be seen from the introduction, considerable effort continues to be focused on the chemistry of pyrrolobenzodiazepines and the related pyrrolobenzothiadiazepines. Due to the immense biological importance of these tricyclic systems, there is always scope to discover new synthetic routes and modified ring systems with new potential pharmacokinetic properties. Consequently, in this thesis novel approaches to PBDs/ PBTDs and related analogues using 1,2-thiazine 1-oxide chemistry will be discussed.

The first part of this research is focused on exploiting route “b” of Figure 2.1 to gain access to the allylic alcohol (383) via a ring-opening/ [2,3]-sigmatropic rearrangement/ desulfurisation.
sequence of the starting 1,2-thiazine 1-oxide precursor (382)\textsuperscript{109,128-130}. 1,2-Thiazine 1-oxides are easily made by intermolecular hetero Diels-Alder reaction of the N-sulfinyl precursor (381) with 1,3-diene\textsuperscript{109,128-130} as shown in Figure 2.1 route “a”. Oxidation of the corresponding allylic alcohols prior to N-protection followed by deprotection and an intramolecular ring closure should furnish the bicyclic system (384), a useful target in itself, but also useful as a template for further reaction to form analogues of the PBDs/ PBTDs such as structure (385).

The next aim of the project was to use similar chemistry to routes “a” and “b” as an approach to some novel tricyclic systems involving intramolecular cyclisation. The concept of this strategy, as depicted in Figure 2.1 route “c”, relies upon the initial construction of cyclisation precursor (386). Treatment of compound (386) with thionyl chloride and pyridine should generate the N-sulfinyl dienophile, which is anticipated to undergo intramolecular hetero Diels-Alder cycloaddition to provide the key tricyclic 1,2-thiazine 1-oxide fused system (387), a useful target in itself, as an interesting tricyclic benzodiazepine and benzothiadiazepine. Furthermore, compound (387) may serve as an excellent template for a variety of chemistry, and importantly a route through to PBDs/ PBTDs (389) via ring contraction-sulfur expulsion reaction\textsuperscript{122} or through ring opening and subsequent cyclisation of the corresponding allylic alcohol (388).

Almost all reported syntheses of the PBDs/ PBTDs rely upon proline as the source of the 5-membered ring,\textsuperscript{5,29,34,66,78,96,93} with only a few methods relying upon a de novo pyrrole construction methodology,\textsuperscript{4c,5,130-132} and no methods which construct the pyrrole from a diene. Although relatively unexploited, the synthesis of simple (unfused) pyrroles from dienes has proven its importance to the synthetic chemist.\textsuperscript{122,133} In the view of this, the synthesis of PBTD through 1,2-thiazine 1-oxide precursors is the next aim of this research. We envisioned exploiting route “d” which should allow access to the pyrroles (390) via a ring contraction-sulfur expulsion reaction\textsuperscript{122,134} of the 1,2-thiazine 1-oxides, followed by a ring closure procedure to propagate the tricyclic PBD/ PBTD nucleus (389).

The next route to be explored was to utilise a third reaction of 1,2-thiazine 1-oxide, that of homoallylic amine (391) formation via hydrolysis\textsuperscript{109-115} as shown in Figure 2.1 route “e”. The idea here was to close the homoallylic systems to form a pyrrole (392) and then study ring closure possibilities for the system, with a view to generating analogues of PBDs/ PBTDs.

Finally, the thesis describes work that will look at the extension of the tricyclic PBTDs to their tetracyclic analogues (393) via performing a final cycloaddition reaction on the reactive N10-C11 imine bond as shown in Figure 2.1 route “f”. As discussed previously in the introduction, such tetracyclic systems are of enormous potential utility. For this reason significant effort was
put into exploring route “g” of Figure 2.1, whereby the azides (394) are closed onto alkenes, nitriles and alkynes derived from proline to give the tetracycles (393) via “click” ring closure, a method hitherto unknown for the synthesis of the PBD/ PBTD nucleus.

2.2 Synthesis of 1,2,5-benzothiadiazepine 1,1-dioxide via 1,2-thiazine 1-oxides

As stated in the aims, the initial plan of this project involved the synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides via a novel 1,2-thiazine 1-oxide based approach. The target is represented by structure (395) [Figure 2.2]. 1,2,5-Benzothiadiazepines are 1,4-benzodiazepine analogues possessing a sulfonyl moiety at the 5-position of the 7-membered benzothiadiazepine ring, and have attracted attention as analogues of the benzodiazepines because of their CNS, diuretic, hypolipidemic, and antiarrhythmic activities, their ability to inhibit metalloproteinases and farnesyl protein transferase enzymes, and their activity as potent tumour necrosis factor-α (TNF-α) converting enzyme (TACE) inhibitors. Some typical examples are the antiarrhythmic agents (396) and the TACE inhibitors (397), as shown in Figure 2.3. Although target (395) is useful in its own right, our intention was, however, to further explore its utility as a precursor for tricyclic systems. In the event, the bicyclic compound (395) was not formed, but some interesting chemistry, producing a 1,2,5-benzothiadiazepine 1,1-dioxide resulted nonetheless and will be discussed in this chapter.

![Figure 2.2](image)

The concept of this strategy, as depicted in Scheme 2.1, relies upon the conversion of the 1,2-thiazine 1-oxide functionality into the amino ketone (408) and its subsequent intramolecular cyclisation to generate the target compound (395). Access to the required amino ketone precursor (408) was to be accomplished via a hetero Diels Alder reaction of the N-sulfinyl dienophile (399) produced in situ from the 2-azidobenzenesulfonamide (398) by treatment with thionyl chloride in the presence of pyridine. The reduction of the azide via a Staudinger reaction provides the amine (402), followed by treatment with a Grignard reagent to afford the allylic sulfoxide (403), which upon subsequent heating with methanolic trimethyl phosphite, would furnish the
allylic alcohol (405) via a [2,3]-sigmatropic rearrangement/desulfurisation sequence.\textsuperscript{109-115} It was observed previously\textsuperscript{141} that direct oxidation of such allylic alcohols was unfeasible with a variety of oxidants and, therefore, protection of the amine group was essential, a process that had been performed previously in the group, but was not optimized. It was, therefore, the preliminary aim of this project to improve upon this route, and, in addition, to investigate the ring closure reaction to allow access to target (395) and hopefully therefore to tricyclic analogues of the PBTDs. This work will now be discussed in detail in this chapter.

Scheme 2.1: Reagents and conditions: (i) SOCl\textsubscript{2}, pyridine, THF, rt, 4h; (ii) R\textsuperscript{1}CH=CH-CR\textsuperscript{3}=CHR\textsuperscript{2}, THF, rt, 18h; (iii) PPh\textsubscript{3}, THF, rt; (iv) H\textsubscript{2}O, THF, reflux; (v) PhMgBr, THF, -40°C; NH\textsubscript{4}Cl(aq); (vi) P(OMe\textsubscript{3}), MeOH, 60°C; (vii) Protection; (viii) Oxidation; (ix) Deprotection; (x) Cyclisation.

2.2.1 Synthesis of N-sulfinyl dienophiles

The N-sulfinylamines containing a quadrivalent dicoordinate sulfur atom are highly reactive heterocumulenes,\textsuperscript{146} which have attracted many interests as starting material for the synthesis of a diverse range of organic compounds.\textsuperscript{108-116,146-150} Of particular interest are the products from their reactions with dienes, which are readily formed and can, in turn, be used for the preparation of a series of acyclic and heterocyclic compounds as discussed previously.\textsuperscript{110-115,134} The classical means of preparing these hetero dienophiles are via sulfinylation of compounds containing an NH\textsubscript{2} group or a ‘masked’ NH\textsubscript{2} group with thionyl chloride in the presence of
The resulting N-sulfinyl derivatives can often be distilled or crystallized, but are water sensitive and are usually prepared in situ. Accordingly, the generation of N-sulfinyl dienophile through sulfinylation of the commercially available 2-aminobenzenesulfonamide was examined first. It was observed that the 2-amino nitrogen of 2-aminobenzenesulfonamide (409) has the greater reactivity towards thionyl chloride. Consequently, the 2-amino nitrogen was converted into its corresponding azide, with a view to the subsequent conversion of the azide back to the amine at a later stage in the synthesis. Thus, diazotization of 2-aminobenzenesulfonamide (409) in aqueous hydrochloric acid solution at 0°C resulted in the corresponding diazonium chloride (410), which was used without isolation in an azidation reaction with sodium azide in aqueous sodium acetate solution at 0°C to give a reproducible 90% yield of the 2-azidobenzenesulfonamide (398) [Scheme 2.2]. The structure of the product was confirmed by NMR, IR and MS spectroscopic analysis, with IR showing the characteristic azide band at ν max 2135 cm⁻¹.

\[ \text{Scheme 2.2} \]

Under these conditions the diazotization takes place with an initial attack of the protonated nitrosating agent (HNO₂) by the free aromatic amine nitrogen, followed by proton loss from the NH₂⁺ group, transfer of a proton onto the oxygen and subsequent loss of water to provide the diazonium salt (410). Finally, a nucleophilic displacement of N₂ by an azide ion gave access to the 2-azidobenzenesulfonamide (398), as shown in the scheme below:

\[ \text{Scheme 2.3: Mechanism of diazotization/azidation of primary amine} \]
Sulfinylation of the 2-azidobenzenesulfonamide (398) with thionyl chloride using rigorously dry conditions in the presence of pyridine, proceeds rapidly at 0°C, to provide the desired N-sulfinyl-2-azidobenzenesulfonamide (399), which was used without purification in a Diels Alder reaction, as described in the following section. One should note that the pyridine is required in large excess under these conditions. Pyridine functions as both a nucleophilic catalyst and as a scavenger to trap the liberated hydrogen chloride and precipitates it as the hydrochloride salt and thus the following mechanism is envisaged (Scheme 2.4).

Scheme 2.4: Mechanism of sulfinylation of sulfonamides in the presence of pyridine

2.2.2 Synthesis of 1,2-thiazine 1-oxides via hetero Diels-Alder reaction

Embarking on the synthetic methodology set out in Scheme 2.1, we examined the hetero Diels-Alder reaction of the N-sulfinyl-2-azidobenzenesulfonamide (399), which was generated in situ, as discussed in the previous section, with isoprene to produce the 1,2-thiazine 1-oxide (400b). The cycloaddition reaction was carried out by employing an excess of diene and was allowed to proceed to completion by stirring at 0°C for 16 hours, whilst being monitored by TLC (Scheme 2.5).

Scheme 2.5

In the event of purification by column chromatography of the crude reaction mixture, it was found that two major product fractions were isolated. The structure of both compounds were confirmed by spectroscopic analysis and were found to the homoallylic amine (501b) [see
discussion-part IV] formed in 23% yield and the desired 1,2-thiazine 1-oxide (400b) isolated in 75% yield.

Specifically, the $^1$H NMR spectrum of compound (400b) provided evidence of cycloaddition of the diene by the occurrence of the methyl peak at $\delta_H$ 1.83 ppm (3H, s, CH$_3$), the presence of the axial and equatorial protons of the thiazine ring as four pairs of doublets of multiplets, in the region of $\delta_H$ 3.20-4.10 ppm [3.24 (1H, dd, J 16.2, 1.8, CH$_2$S=O), 3.56-3.67 (1H, dt, J 16.2, 1.1, CH$_2$S=O), 3.75-3.85 (1H, dm, J 16.8, CH$_2$N)], 4.05-4.15 (1H, dm, J 17.1, CH$_2$N)]. The vinylic CH appeared more deshielded at $\delta_H$ 5.65 (1H, d, J 1.9, MeC=CH), indicating coupling with the adjacent CH proton. Lastly, four aromatic protons were present, as expected in the region of $\delta_H$ 7.20-8.10 ppm [7.28 (1H, t, J 7.4, ArH), 7.34 (1H, d, J 8.0, ArH), 7.65 (1H, td, J 7.9, 1.3, ArH), 8.01 (1H, dd, J 8.0, 1.3, ArH)]. Furthermore, the $^{13}$C NMR spectrum of the molecule showed a single CH$_3$ group at $\delta_C$ 22.1 ppm and two CH$_2$ groups at $\delta_C$ 39.3, 54.2, while the vinylic, aromatic and quaternary carbon atoms appeared more downfield at $\delta_C$ 117.6-139.6 ppm. These data combined with IR spectroscopy [$N_3$ absorption at $\nu_{max}$ 2131 cm$^{-1}$], MS [m/z (ESI+): [M+H]$^+$, 313] and correct accurate mass measurement supported the structure assignment.

The symmetrical 1,3-butadiene was next selected to react with N-sulfonyl-2-azidobenzenesulfonamide (399) [Scheme 2.6]. 1,3-Butadiene is highly volatile and readily evaporates at room temperature. Consequently, a large excess of 1,3-butadiene was condensed at low temperature (<-10°C) and was subsequently introduced to the cooled reaction mixture containing the dienophile. The cycloaddition was found to proceed readily and the 1,3-butadiene adduct (400a) was obtained in 75% yield after purification via column chromatography.

![Scheme 2.6](image)

The structure of the product was confirmed by the presence of the two CH$_2$ groups in the $^1$H NMR spectrum (400 MHz), shown as four complex sets of signals in the region of $\delta_H$ 3.45-4.17 ppm, with the more downfield CH$_2$ being, presumably, next to the more electronegative nitrogen atom. Furthermore, the appearance of two multiplets at $\delta_H$ 5.77-5.97 ppm as the two complex vinylic CH groups, each split both by their neighbouring CH$_2$ and vinylic CH group, confirmed the assignment. Spectroscopic analysis by $^{13}$C NMR (100 MHz) [(DEPT-135) $\delta_C$ 39.0, 50.6 ppm]
and IR spectra [N₃ absorption (strong) at \( \nu_{\text{max}} \) 2137 cm\(^{-1}\)], along with a consistent MS [m/z (ESI+): [M+NH₄]+, 316] and accurate mass measurement further supported the desired structure.

The mechanism of such cycloaddition reactions is open to debate. Mock and Nugent\(^{123}\) proposed a non-concerted, stepwise mechanism, whereas, later, Hanson and Stockburn\(^{155}\) proposed that such cycloadditions were concerted processes in accord with Frontier Molecular Orbital theory.\(^{156}\) Both proposals can rationalize the observed regioselectivity of these reactions, such as that observed above with isoprene. The mechanistic situation is further complicated by the fact that there is no clear evidence as to whether the (E)- or (Z)-sulfinyl dienophile (Figure 2.3) is involved.\(^{109-110,112,130}\)

![Figure 2.3: (Z)- and (E)-isomers of N-sulfinyl compounds](image)

Whilst investigating the regioselectivity of the Diels-Alder reaction of N-sulfinyl-p-toluenesulfonamide with several unsymmetrical dienes, Kresze and Wagner\(^{157}\) observed that the cycloaddition with 2-substituted dienes yields only the 5-substituted dihydrothiazine oxides, whereas in the case of 1-substituted dienes the regiochemistry of the adduct is dependent on the reaction temperature; at low temperatures, 3-substituted dihydrothiazine oxides are usually formed, but at higher temperatures the 6-substituted heterocycles are produced (Scheme 2.7).\(^{109,129,157}\)

![Scheme 2.7](image)
Based on their finding, Kresze and Wagner\textsuperscript{157} offered a mechanistic model for the \([4+2]\)-cycloadditions of \(N\)-sulfinyl dienophiles to rationalise the kinetically formed regioisomeric products. They proposed a concerted reaction mechanism \textit{via} a transition state which has dipolar character. For 2-substituted dienes, transition states A and B may be considered (Scheme 2.8).\textsuperscript{109,129,157} If R is an electron-donating group, which stabilises the cationic center, a 5-substituted product will result. Thus, the isoprene used above, behaves entirely as predicted, a prediction that was confirmed by subsequent reactions (see later in this chapter). A similar argument can be made for 1-substituted and more complex dienes (Scheme 2.8).\textsuperscript{109,129,157}

\begin{center}
\textbf{Scheme 2.8}
\end{center}

### 2.2.3 Synthesis of amines \textit{via} an \textit{in situ} Staudinger reaction

The reduction of azides to amines is an important reaction for the synthesis of variety of organic compounds.\textsuperscript{158} Amongst the large number of methods reported, the Staudinger/hydrolysis reaction remains one of the more extensively used approaches owing to its simplicity, high selectivity and mild conditions.\textsuperscript{159} Developed in 1919 by Staudinger and Meyer,\textsuperscript{159a} the reaction engages a primary imination reaction of an azide (412) and tertiary phosphine (411) to form phosphazide. Interestingly, phosphazides are sometimes isolable or stable, or can be trapped either \textit{via} intermolecular reactions, or through formation of a transition metal complex. However, as a rule they lose nitrogen at ambient temperature or at even lower temperatures to give the corresponding iminophosphoranes (418)\textsuperscript{159b,159c} in practically quantitative yields (Scheme 2.9).
Mechanistic studies on the Staudinger reaction revealed that the nucleophilic attack of the tertiary phosphine on the azide occurs with the formation of an $E$-phosphazide (413) which possesses zwitterionic character. Isomerisation of the $E$-phosphazide gives the $Z$-phosphazide (415)/intermediate (416), the formation of which results in cyclisation to (417) and then elimination of nitrogen and formation of the iminophosphorane (418).

![Scheme 2.9](image)

While iminophosphoranes (418) are powerful synthetic intermediate for aza-Wittig reactions, they can also be rapidly hydrolysed to the corresponding amine (419) under acidic\cite{163-165} and basic\cite{166-167} conditions as shown below.

![Scheme 2.10](image)

In this respect, both 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxides (400a-b) were treated with triphenylphosphine in anhydrous tetrahydrofuran at ambient temperature. The resultant iminophosphorane intermediates (401a-b) were employed in situ in a hydrolysis reaction in refluxing tetrahydrofuran in the presence of a slight excess of water (Scheme 2.11). In both cases the hydrolysis step proceeded readily, yielding the amines (402a-b) in almost quantitative yields (98-99%).
Spectroscopic analysis by $^1$H and $^{13}$C NMR of the 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (402) confirmed their proposed structure. In particular, the presence of an amine group was manifested by the appearance in the $^1$H NMR spectrum (400 MHz) of a broad signal integrating to two protons at $\delta_H \sim 4.91-5.06$ ppm. Further analysis by IR spectroscopy revealed the disappearance of the azide band, together with the existence of two broad NH stretch peaks, the primary band appearing at $\nu_{\text{max}} \sim 3432-3476$ cm$^{-1}$ and the secondary band at $\nu_{\text{max}} \sim 3338-3373$ cm$^{-1}$, while the NH bending absorption appeared at $\nu_{\text{max}} \sim 1560-1598$ cm$^{-1}$. Both $^{13}$C NMR (100 MHz) and MS (ESI+), as well as accurate mass measurements were consistent with the structure of the products.

### 2.2.4 Synthesis of allylic alcohols via amino allylic sulfoxides

Following the synthetic methodology shown in Scheme 2.1, the next step involved the generation of the allylic alcohol$^{168-169}$ via cleavage of the 1,2-thiazine 1-oxide ring by a Grignard reagent to produce an allylic sulfoxide, which would furnish the allylic alcohol via [2,3]-sigmatropic rearrangement$^{170-172}$ and subsequent desulfurisation in the presence of a thiophile, as outlined in Scheme 2.12.
Accordingly, the 2-(2-aminobenzenesulfonyl)-1,2-thiazine 1-oxides (402a-b) were treated at \(-78^\circ\text{C}\) with an ethereal solution of phenylmagnesium bromide in anhydrous tetrahydrofuran under rigorously dry conditions (Scheme 2.13). The reaction was allowed to proceed to completion by stirring at \(-50^\circ\text{C}\), whilst being monitored by TLC. Thiazine bond rupture proceeded very cleanly under these conditions to give the crude allylic sulfoxides (403a-b), which were heated with trimethylphosphite in refluxing methanol to give the desired \(N\)-(2-aminobenzenesulfonyl)-1,2-vicinal amino alcohols (405a-b). The allylic alcohols (405) were purified by column chromatography and were obtained in excellent yields (80-89%). The structures of the products were confirmed by spectroscopic analysis.

More specifically, the \(^1\)H NMR spectrum of the \(N\)-(2-aminobenzenesulfonyl)-1,2-vicinal amino alcohol (405b) showed the methyl peak at \(\delta_1 \text{H} 1.61 \text{ (3H, s, } CH_3)\), together with a characteristic signal for the two protons next to the sulfonamide (SO\(_2\)NCH\(_2\)) group which were split by each other and the neighbouring CH and NH groups as two sets of doublets of double doublets at \(\delta_1 \text{H} 2.84 \text{ (1H, ddd, } J \text{ 13.0, 8.5, 4.3, } CH_2\text{NH) and 3.09 (1H, ddd, } J \text{ 13.1, 6.9, 3.8, } CH_2\text{NH). The resonance of the alcohol appeared as a broad singlet at 3.02 (1H, s, br, } OH)\) and its neighbouring CH-OH appeared as doublet of doublets 4.02 (1H, dd, \( J \text{ 8.1, 3.0, } CHOH)\), indicating coupling with the adjacent two CH protons. In the vinylic region of the \(^1\)H NMR, the vinylic CH\(_2\) group appeared as two separate singlets at \(\delta_1 \text{H} 4.86 \text{ (1H, s, } MeC=CH_2)\), and 4.95 (1H, s, MeC=CH\(_2\)), followed by a broad singlet integrating at two, which corresponded to the NH\(_2\) at \(\delta_1 \text{H} 4.97 \text{ (2H, s, br, } NH_2)\). Evidence for a successful ring opening was provided by the presence of a broad peak at \(\delta_1 \text{H} 5.59 \text{ ppm (1H, quartet, } J \text{ 4.1, SO}_2\text{NH})\), corresponding to the sulfonamide NH proton. Lastly, four aromatic protons were present, as expected in the region of \(\delta_1 \text{H} 6.70-7.70 \text{ ppm [6.78 (1H, d, } J \text{ 7.7, ArH), 6.79 (1H, t, } J \text{ 7.8, ArH), 7.31 (1H, td, } J \text{ 7.7, 1.4, ArH), 7.69 (1H, dd, } J \text{ 7.9, 1.4, ArH). Further}\)more, the \(^{13}\)C NMR (100 MHz) supported the assignment, showing, amongst other peaks, the vinylic CH\(_2\) present at \(\delta_{13} \text{C} 112.2 \text{ ppm (DEPT-135). The IR spectrum also showed two broad bands at } \nu_{\text{max}} 3474 \text{ cm}^{-1} \text{ (OH stretch) and } \nu_{\text{max}} 3378 \text{ cm}^{-1} \text{ (NH stretch) and a NH}}\)
bend at $v_{\text{max}}$ 1522 cm$^{-1}$, which, together with a consistent MS analysis (ESI+) and accurate mass measurement, confirmed the anticipated structure.

2.2.5 Synthesis of N-Fmoc protected amino alcohol

As mentioned in the introduction to this chapter, previous work in this group$^{145}$ showed that a direct oxidation of the hydroxy group in the allylic alcohol proved unsuccessful under a variety of conditions (for example, Dess-Martin, Swern, TPAP, Corey's reagent, and MnO$_2$) possibly due to a competing reaction of the primary amine. Protection of the amino group was essential in order to carry out the subsequent oxidation step. Therefore, an investigation on amine protecting groups that could apply to our synthesis was undertaken. The protecting group chosen would need to protect the amine in the presence of the alcohol group.

Fortunately, recent work by Wijkmans et al.$^{173}$ into the investigation of the cyclisation strategies for the construction of the 3-methoxycarbonyl-2-N-methyl-1,2,5-benzothiadiazepine 1,1-dioxide (424) via an aniline derivative (423), demonstrated the use of 9-fluorenylmethyl chloroformate as a protecting group for the generation of the Fmoc-protected aniline (421), a species which, like compound (405), contains an alcohol. Thus, in Wijkman's work treatment of the amine (420) with 9-fluorenylmethyl chloroformate in the presence of sodium bicarbonate afforded the Fmoc-protected compound (421) in 45% overall yield (Scheme 2.14). At the deprotection step, these workers anticipated that removal of the Fmoc-group of the $\alpha,\beta$-unsaturated ester (422) using standard conditions, such as piperidine in DMF, would rapidly lead to the formation of the piperidyl adduct (425), the product of Michael addition. Therefore, alternative conditions for the deprotection of Fmoc derivative (422) were studied. It was found that refluxing a mixture of (422) in a 1:1 solution of dichloromethane and $N,N$-diisopropylethylamine (DIEA) afforded aniline derivative (423) in 70% yield.$^{173}$ Cyclisation of compound (423) with sodium tert-butoxide in THF furnished the desired benzothiadiazepine dioxide (424).
Accordingly, the allylic alcohols (405a-b) were treated with 9-fluorenylmethyl chloroformate and sodium hydrogen carbonate in anhydrous dichloromethane at ambient temperature under nitrogen (Scheme 2.15). In both cases the protection proceeded readily and the purification of the crude mixture yielded the Fmoc-protected arylamino alcohols (406a-b) in 63-71% yields.

The incorporation of the Fmoc group was confirmed by $^1$H and $^{13}$C NMR spectroscopic analysis of the products. Significantly, in each case, the $^1$H NMR spectrum (400 MHz) indicated the additional presence of the 9-fluorenylmethoxycarbonyl CH and CH$_2$ groups, split by each other as a triplet at $\delta_H \sim 4.33$ ppm (1H, t, $J_{7.1}$ Hz, CHCH$_2$OCONH) and a doublet at $\delta_H \sim 4.52$ ppm (2H, d, $J_{7.2}$ Hz, CHCH$_2$OCONH), respectively. In the aromatic region, the fluorenyl CH groups appeared in the region of $\delta_H \sim 7.36$-7.44 ppm and $\delta_H \sim 7.65$-7.81 ppm, while, more downfield in the spectrum, a broad signal at $\delta_H \sim 8.70$ ppm verified the presence of the deshielded carbamate NH group. Additionally, $^{13}$C NMR spectra (100 MHz) of the products showed the 9-fluorenylmethoxycarbonyl CH and CH$_2$ groups in the region of $\delta_C \sim 46.9$-54.2 ppm and $\delta_C \sim 67.6$
ppm, respectively, together with the expected fluorenyl carbons in the aromatic region and the deshielded carbamate C=O group at δC ~153.2 ppm. Further evidence of the carbamate protection was provided by the occurrence, in the IR spectrum of each of the products, of a C=O stretching absorption at νmax 1738 cm⁻¹, while analysis by MS (ESI+) and accurate mass determination were in full agreement with the proposed structures.

2.2.6 Synthesis of N-Boc protected amino alcohol

Having, successfully, protected the allylic alcohol with a base-labile Fmoc protecting group, our next aim was to improve the yield of the protection with the use of an alternative protecting group. Among the various protecting groups, we became interested in the acid labile tert-butyl carbamate (Boc) group,¹⁷⁴-¹⁷⁷ which has been the most utilized protecting group for ₁° and ₂° amines in the literature.¹⁷⁴-¹⁷⁷ Various different reagents with a general structure Boc-X (426) have been synthesized for introducing the Boc group onto the amines (Figure 2.4). However, owing to the instability of the corresponding tert-butyl chloroformate (429) and the explosive properties of the tert-butylazido formate (428), the di-tert-butyl carbonate (430, Boc₂O) reagent is the most widely used for protecting the amines.¹⁷⁴-¹⁷⁸

![Figure 2.4](image)

The conventional means of introducing the tert-butoxy carbonyl group using Boc₂O involve treatment of the parent amine with Boc anhydride in the presence of triethylamine, a procedure which well documented in literature.¹⁷⁴-¹⁷⁷ However, the efficiency and selectivity of such conditions depends very much on the nature of the compound which is being protected, as described by Hassner et al.¹⁷⁹ whilst investigating the reaction of Boc₂O in the presence and absence of DMAP as a route to protecting primary aliphatic and aromatic alcohols, amino alcohols and aminothiols. The study showed that the reaction of di-tert-butyl dicarbonate (Boc₂O) with amines or alcohols, in the presence or absence of DMAP leads to N-Boc protected amines or
alcohols, usually in high yield (Scheme 2.16). Furthermore, in the presence of triethylamine, aromatic amines can be converted to their N-Boc derivatives.  

\[
\text{RNH}_2 + \text{Boc}_2\text{O} \xrightarrow{\text{DMAP}} \text{RNHBoc} + \text{RHNCONHR} + \text{RN=CO}
\]

\[
\text{ROH} + \text{Boc}_2\text{O} \xrightarrow{\text{DMAP}} \text{ROCO} + \text{ROOR}
\]

**Scheme 2.16**

Accordingly, compound (405b) was initially treated with a solution of Boc₂O and triethylamine in anhydrous acetonitrile at ambient temperature under nitrogen (Scheme 2.17). However, several attempts to perform the amine protection were unsuccessful, yielding only the starting allylic alcohol (405b).

Consequently, the reactivity of compound (405a) with Boc₂O in the presence and absence of DMAP and triethylamine was carefully examined under different conditions. Several attempts to form the N-Boc protected amine (431b), led to the formation of the N,O-diBoc product (432b) as a result of the concomitant protection of the OH group. The best conditions leading to the highest yield of the desired N-Boc protected amine (431b) were found to be when the reaction was carried out at low temperatures (<-10°C, Scheme 2.18) in DMAP/ MeCN, although, even then the ratio of the N-Boc product (431b) to the N,O-diBoc product (432b) was just less than 1:1. The desired N-Boc protected amine (431b) was easily separated by column chromatography in 50% yield.

\[
\text{NH}_2 \xrightarrow{\text{Boc}_2\text{O}, \text{MeCN}} \xrightarrow{-10°C} \text{NH Boc}
\]

**Scheme 2.18**
The incorporation of the Boc group was confirmed by $^1$H and $^{13}$C NMR spectroscopic analysis of the products. Significantly, in each case, the $^1$H NMR spectrum (400 MHz) indicated the additional presence of the tert-butyl carbonyl (CH$_3$)$_3$ groups as a singlet, integrating as 9 protons in the region of $\delta_H \sim$1.35-1.38 ppm (9H, s, (CH$_3$)$_3$). Evidence of the N,O-diBoc product (432b) was provided by the disappearance of the OH group in the $^1$H NMR of compound (432b), which is present in the N-Boc compound (431b) at $\delta_H \sim$2.81 ppm (1H, s, OH). Additionally, $^{13}$C NMR spectra (100 MHz) of both products showed the tert-butyl carbonyl (CH$_3$)$_3$ and the carbamate C=O group in the region of $\delta_C \sim$27.7 ppm and $\delta_C \sim$151.0-153.3 ppm, respectively, together with the expected doubling of the carbamate peak in the $^{13}$C NMR of compound (432b), which is indicative of two Boc groups in the product. Further evidence of the carbamate protection was provided by the occurrence, in the IR spectrum, of a C=O stretching absorption at $v_{\text{max}}$ 1738 cm$^{-1}$, while analysis by MS (ESI+) and accurate mass determination were in full agreement with the proposed structures.

2.2.7 Synthesis of N-Fmoc protected amino ketones via Dess-Martin oxidation

Having successfully synthesised the N-protected Fmoc and Boc allylic alcohols, the next step involved the generation of a ketone via an oxidation. The oxidation of allylic alcohols to the corresponding ketones can be achieved using a variety of oxidising reagents, with the most common being Dess-Martin periodinane, TPAP, Corey’s reagent and MnO$_2$, as well as Swern oxidation. The ease of use and ready availability made Dess-Martin periodinane the first reagent to be tried. Furthermore, its use as an effective oxidant for similar conversions had already been established in previous work by this group.

Therefore, a solution of the Fmoc protected allylic alcohols (406a-b) in dry dichloromethane was added to a suspension of Dess-Martin periodinane in dry dichloromethane at room temperature under nitrogen (Scheme 2.19). In both cases the oxidation proceeded smoothly and the desired ketone (407a-b) was isolated in 80-90% yield.

![Scheme 2.19](image)
The mechanism of such oxidation processes is not known for certain, but it is considered to involve an initial exchange of an acetate ligand on the iodine with the alcohol functionality to give an intermediate (433)<sup>180</sup>, which then collapses to form the carbonyl functionality as outlined in Scheme 2.20.

![Scheme 2.20](image)

The structural assignment of the Fmoc-protected amino ketones (407a-b) was performed in view of their <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS and IR spectroscopic analysis. In both cases (407a-b) the <sup>1</sup>H NMR spectrum (400 MHz) indicated a dramatic change in the CH<sub>2</sub> group adjacent to the NH proton, which appeared as a doublet split by the adjacent NH proton in the region of δ<sub>H</sub> ~4.05-4.17 ppm (J ~4.7 Hz). The disappearance of both CH and OH groups (CH-OH) and the presence of the ketone moiety in the <sup>13</sup>C NMR spectra (100 MHz) in the region of ~192.1-193.3 ppm confirms successful oxidation. Additionally, the disappearance of the CHOH group and the presence of a new carbonyl C=O stretch in the range of ν<sub>max</sub> ~1733-1740 cm<sup>-1</sup> of the IR spectra gave further confirmation of the desired structure, while analysis by MS (ESI+) and accurate mass determination were in full agreement with the proposed structures.

2.2.8 Synthesis of N-Boc protected amino ketone via Dess-Martin oxidation

The effectiveness of the Dess-Martin periodinane in oxidising the allylic alcohols was also examined on the N-Boc-protected allylic alcohol (431b). Thus, a solution of the N-Boc protected allylic alcohols (431b) in dry dichloromethane was added to a solution of Dess-Martin periodinane in dry dichloromethane at room temperature under nitrogen. Similarly, the reaction proceeded smoothly and the reagent successfully oxidised the alcohol to give the corresponding N-Boc-protected ketone (434b) in 94% yield (Scheme 2.21).
Chapter 2 Discussion-Part I

Specifically, the $^1$H NMR spectrum evidence of oxidation of the alcohol was indicated by the dramatic change in the nature of the $CH_2$ group adjacent to the NH proton, which appeared as a singlet at $\delta_H 5.03$ ppm (2H, s, $CH_2CO$). The disappearance of both $CH$ and $OH$ groups ($CH-OH$) and the presence of the ketone moiety in the $^{13}$C NMR spectra (100 MHz) at $\delta_C 193.9$ ppm confirms successful oxidation. Additionally, the disappearance of the $CHOH$ group and the presence of a carbonyl $C=O$ stretch in the range of $v_{\text{max}} 1692$ cm$^{-1}$ of the IR spectra provided further confirmation for the desired product, while analysis by MS (ESI+) and accurate mass determination were in full agreement with the proposed structures.

2.2.9 Synthesis of 1,2,5-benzothiadiazepines by Fmoc deprotection/cyclisation

Following the successful oxidation of the Fmoc-amino alcohols to the corresponding ketones, the final requirement was to cleave the Fmoc functionality and generate the amino ketone cyclisation precursor for the synthesis of 1,2,5-benzothiadiazepines.

In general, Fmoc deprotection proceeds readily in mildly basic conditions by means of a variety of $1^o$, $2^o$ and some $3^o$ amines, most rapidly via unhindered secondary amines, such as piperidine. The amine serves two purposes in this reaction, initially to drive the reaction by removing the acidic $\beta$-proton of the fluorenyl ring to generate a cyclopentadienyl anion, which undergoes elimination reaction to form dibenzofulvene (DBF) and the desired amine via the loss of carbon dioxide from the carbamate anion precursor. Secondly, the purpose of the amine is its function as a scavenger to trap the liberated DBF via a Michael type addition thereby ruling out competing reaction with the product amine as illustrated in the Scheme 2.22.

Scheme 2.21

![Scheme 2.21](image-url)
Preliminary studies\textsuperscript{145} in our group have shown that the standard Fmoc deprotection methods (using secondary amines such as diethylamine, dicyclohexylamine and piperidine) were unsuccessful in cleaving the Fmoc group and instead led to the formation of the product of Michael addition to the $\alpha,\beta$-unsaturated ketone. Such competing reaction has also been noted by Wijkmans \textit{et al.}\textsuperscript{140} whilst attempting to remove the 9-fluorenemethyloxycarbonyl group with piperidine in the presence of a Michael acceptor. Subsequently, the bulky and sterically hindered $N,N$-diisopropylethylamine (DIEA) was employed in an attempt to circumvent the potential difficulties of piperidine acting as a Michael donor.\textsuperscript{140,186-188}

Thus, heating the Fmoc ketone (407b) in a 1:1 solution of $N,N$-diisopropylethylamine and dichloromethane resulted in the isolation of two new products, which were not the deprotected compound (408) nor the expected cyclisation product (395), but were in fact 3-hydroxy-1,2,5-benzothiadiazepine (435) and, tentatively assigned epoxybenzothiadiazine (436), obtained in 24\%, and 23\% yield, respectively (Scheme 2.23).
The structures of all products were assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, IR spectroscopy and further supported by an accurate mass measurement. Specifically, the $^1$H NMR spectrum (400 MHz) of the 3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxide (435) showed the two methyl groups split as doublets at $\delta_H$ 0.80 ppm (3H, d, $J=6.8$, CH$_3$) and 1.01 (3H, d, $J=6.9$, CH$_3$) together with a quartet of quartets at $\delta_H$ 2.25 ppm (1H, quartquart, $J=6.8$, 3.4, Me$_2$CH), diagnostic of the isopropyl group. The two methyl groups appeared as two doublets, as a result of their diastereoisotopic nature by virtue of the chiral centre. Further enlightenment was given by the presence of a sp$^3$ CH group at $\delta_H$ 4.28 (1H, d, $J=3.2$, CHOH), which is consistent with the chemical shift expected of the CH-OH grouping. In addition, $^{13}$C NMR spectra (100 MHz) showed a methine (CHOH) carbon together with a resonance at $\delta_C$ 160.8 ppm, diagnostic of an imine, which was also inferred by inspection of the IR spectrum via the presence of a C=N stretching absorption at $\nu_{\text{max}}$ 1602 cm$^{-1}$. The presence of an OH group was also indicated in the IR spectrum ($\nu_{\text{max}}$ 3475 cm$^{-1}$) and further confirmation of the proposed structures was provided by MS analysis and accurate mass measurement.

With regards to a possible mechanism, the 3-hydroxy-1,2,5-benzothiadiazepine (435) may arise as a result of a series of tautomermisms involving an initial base catalysed enolisation of the starting ketone (407b), followed by enamine/imine tautomerism to provide the imine tautomer (438) and further enol tautomerism to reveal the crucial isopropyl grouping present in compound (439), as illustrated in Scheme 2.24.

![Scheme 2.24](image)

With the isopropyl grouping now in place, deprotection of the Fmoc functionality and subsequent cyclisation of the corresponding free amine (440) under the basic reaction conditions would produce the carbinolamine (441), which could then give the isolated 3-hydroxy-1,2,5-benzothiadiazepine (435), possibly via an intermolecular process involving the intermediate epoxide (442) as outlined in Scheme 2.25.
The structure of the final product (436) was tentatively assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, IR spectroscopy and further supported by an accurate mass measurement. Specifically, the $^1$H NMR spectrum (400 MHz) of the epoxybenzothiadiazepine (436) showed the methyl groups as two singlets at $\delta_H$ 1.80-1.90 ppm, indicative of the gem dimethyl group. In addition, $^{13}$C NMR spectra (100 MHz) showed a resonance at $\delta_C$ 150.7 ppm, diagnostic of a carbonyl, which was also inferred by inspection of the IR spectrum via the presence of a C=O stretching absorption at $\nu_{max}$ 1767 cm$^{-1}$. Further evidence for the proposed structure was provided by MS analysis and accurate mass measurement, which, critically, showed the presence of an extra carbonyl group (28 mass units) over that expected for simple loss of Fmoc.

With reference to the mechanistic details, it is thought that the extra C=O unit is incorporated via the carbamate carbonyl by the sulfonamide nitrogen, to give an intermediate (443), which then collapses to cleave the remainder of the Fmoc functionality to reveal benzothiadiazine (445) and compound (446) as illustrated in the scheme below.
Compound (445), could then undergo a series of rearrangements, involving an initial keto/enol tautomerism to give intermediate (447), which further undergoes an enamine/imine tautomerism to reveal the crucial dimethyl group present in compound (448). Further intermolecular rearrangement would give the isolated product (436). Attempts to grow crystals of compound (436) in order to confirm this unusual structure were unsuccessful.

Scheme 2.27

It was thought that the vigorous conditions employed (N,N-diisopropylamine, dichloromethane, 1:1, 48 hrs at reflux) might be responsible for the failure to isolate the deprotected amine (408) [see Scheme 2.23, above]. Hence, a number other tertiary amines were investigated as replacements for diisopropylamine. In the event, triethylamine turned out to be the best base, as its use led to a single product in reasonable yields. Thus, treatment of the Fmoc ketones (407a-b) with excess triethylamine in anhydrous dichloromethane at reflux resulted in the isolation, in each case, of a major new product. Again the new products were not the deprotected free amines, but were in fact the 3-hydroxy-1,2,5-benzothiadiazepines (435a-b) which were isolated in 57-69% yield. With triethylamine as base, no other products were isolated (Scheme 2.28), and these represent the best conditions for the deprotection and cyclisation of the Fmoc-amine (407).

Scheme 2.28

77
Attempted deprotection/cyclisation of N-Boc protected amino ketone

Next, the deprotection/cyclisation of the Boc-protected ketone (434b) was investigated. Unlike the Fmoc group, the Boc group is stable towards hydrolysis under basic conditions as well as to many nucleophilic reagents. Thus, deprotection generally proceeds readily in mildly acidic conditions by means of a variety of acidic reagents, including ceric ammonium nitrate, HCl/dioxane (4M) solution, BF₃OEt₂/4Å sieves, acetyl chloride and most commonly TFA. It is considered that under acidic conditions, protonation of the carbonyl oxygen of the tert-butyl carbamate results in degradation to initially produce the unprotected amine, carbon dioxide, and the highly reactive tert-butyl cation, which can decompose to isobutylene in the absence of suitable trapping reagents (Scheme 2.29).

However, several attempts to perform the deprotection using HCl/dioxane (4M) or BF₃OEt₂/4Å sieves proved unsuccessful in yielding either the desired cyclised product, or the deprotected amine. When TFA was used, the deprotected product (408) was isolated in 68% yield (Scheme 2.30). Unfortunately, no cyclisation was observed under these conditions. It was found, however, that the amine (408) underwent widespread degradation to give a multi-spot TLC profile. Given this difficulty, together with the successful Fmoc results and the long synthetic procedure to produce compound (434b), this route was not pursued further.
2.3 Conclusion

The alcohols (405a-b) were easily produced from the 1,2-thiazine 1-oxides (402a-b) in a good yielding, reproducible and facile manner. The failure of the alcohols (405a-b) to undergo oxidation meant that protection of the aniline nitrogen was necessary prior to oxidation as it appeared that N-oxidation was the problem. Fmoc and Boc groups were successfully introduced, where the former was selective for the nitrogen and the latter gave mixtures of N-Boc and di-Boc products.

On attempted deprotection, Fmoc again showed itself the best group, allowing reasonable yields of 1,2,5-benzothiadiazepine to be obtained, although isolation of the deprotected amine proved impossible. Conversely, Boc allowed the deprotected amine to be isolated, but did not result in any cyclisation.

It is of note that compound (395), the target of this section of the work, and the target from which tricyclic systems would be built was not obtained. Consequently, this thesis will now describe some other routes by which attempts to produce tricyclic systems were made.
Discussion-Part II
3.1 Attempted synthesis of tricyclic 1,2-thiazine 1-oxides

As described in the previous section, the attempt to use the Fmoc-amino ketone deprotection-cyclisation strategy as a route to making tricyclic benzothiadiazepines was not successful, due to the involvement of some complex rearrangement reactions in the final step of the synthesis leading to 5-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxides, which are not suitable building blocks for tricyclic systems. In the view of this finding and our continuing quest to develop novel synthetic strategies for the synthesis of tricyclic systems, including the pyrrolobenzothiadiazepine and pyrrolobenzodiazepine heterocycles, we embarked upon a modified route, which relies upon the incorporation of a pyrrole moiety via intramolecular 1,2-thiazine 1-oxide formation, followed by conversion to the pyrrole, either via ring opening of the 1,2-thiazine ring to form the allylic alcohol (388), which then closes to pyrrolo-fused system (453) or via a direct ring contraction process to give (452), as shown in Scheme 3.1.

We began this part of our investigation with the aim of applying the 1,2-thiazine 1-oxide methodology employed previously, to the synthesis of pyrrolobenzothiadiazepine, starting from the readily available 2,4-hexdienal (449). The idea was to construct the tricyclic 1,2-thiazine 1-oxide system (387) via an in situ intramolecular hetero Diels-Alder reaction of the corresponding N-sulfinyl dienophile, generated from the cyclisation precursor (386) upon treatment with thionyl chloride (Scheme 3.1). Access to the cyclisation precursor (386) would be accomplished in three steps from the commercially available dienal (449) involving reduction, followed by halogenation and finally a coupling reaction of the resultant 1-bromo-2,4-hexadiene (451) with 2-aminobenzamide in presence of triethylamine. Ring contraction of the 1,2-thiazine 1-oxide ring (387) would give the desired pyrrole (452), whereas opening to allylic alcohol (388) and closure via an SN2' process would hopefully afford (453).
3.1.1 **Synthesis of hex-2,4-dien-1-ol**

The initial requirement was to reduce the aldehyde functionality to the corresponding alcohol, which would subsequently be used to produce the 1-bromohexa-2,4-diene. The reduction of carbonyl groups to the corresponding alcohol is an important reaction for the synthesis of variety of organic compounds. Amongst the large number of reagents reported, sodium borohydride remains one of the most frequently used owing to its ease of use under mild conditions.

Accordingly, the 2,4-hexadienal was treated with a milky fine suspension of sodium borohydride and sodium methoxide in methanol at 0°C. The reaction was found to have proceeded smoothly and upon purification of the crude mixture yielded the desired alcohol in 74% yield (Scheme 3.2).
3.1.2 **Synthesis of the cyclisation precursor via 1-bromo-2,4-hexadiene**

Following the successful reduction of the aldehyde to the corresponding primary alcohol, the next requirement was to replace the alcohol group with a halide atom to produce the desired alkenyl halide. Primary alcohols can be converted to the corresponding alkyl halide (HX) with several reagents, the most common of which are halogen acids, inorganic acid and halides such as SOCl₂, PBr₅, PBr₃, POBr₃, and so PBr₃ was used. The mechanism as outlined in Scheme 3.3, involves initial activation of the alcohol oxygen by the electrophilic phosphorus (to form a good leaving group), followed by an SN₂ substitution at the alcohol carbon (Scheme 3.3).

Accordingly, phosphorus tribromide was selected and reacted with the hexa-2,4-dien-1-ol (450) in anhydrous ether at 0°C under an atmosphere of dry nitrogen, to give 1-bromo-2,4-hexadiene (451) [Scheme 3.4], one spot pure by TLC, which was used without purification at the next stage.

Subsequently, the crude 1-bromo-2,4-hexadiene (451) was added to a solution of 2-aminobenzamide in anhydrous dichloromethane in presence of triethylamine and DMF and furnished the desired coupled cyclisation precursor (386), presumably via a simple substitution reaction (Scheme 3.5).
The reaction proceeded smoothly and the cyclisation precursor (386) was isolated, after purification by column chromatography in 32% yield. The structure of the compound was confirmed by NMR, IR, and mass spectroscopy. Specifically, the $^1$H NMR spectrum provided evidence by the presence of the methyl peak split into a doublet at $\delta_H$ 1.76 ppm (3H, d, $J_6.7$, CH$_3$) and the presence of the CH$_2$ at $\delta_H$ 3.86 ppm (2H, d, $J_5.5$, NHCH$_2$) split into doublets indicating coupling to the neighbouring group. The four vinylic CH groups appeared more deshielded in the region of $\delta_H$ 5.62-6.27 ppm, together with the four aromatic protons as expected in the region of $\delta_H$ 6.56-7.41 ppm. Lastly, both the NH$_2$ group and the NH group were present and appeared as broad singlets at $\delta_H$ 5.97 ppm and $\delta_H$ 7.92 ppm respectively. Furthermore, the $^{13}$C NMR spectra (100 MHz) of the product showed the 2,4-hexadiene CH$_3$ and CH$_2$ groups at $\delta_C$ 18 ppm and $\delta_C$ 44.6 ppm, respectively, together with the four expected vinyl CH group in the aromatic region and the deshielded C=O group at $\delta_C$ 172.3 ppm. These data combined with IR spectroscopic, which indicated the existence of three broad N-H stretch peaks at $v_{\text{max}}$ 3486-3340 cm$^{-1}$, and the presence of a C=O stretching absorption at $v_{\text{max}}$ 1735 cm$^{-1}$, together with MS [m/z (ESI+) : [M+H]$^+$, 217] further supported the structure assignment.

3.1.3 Attempted synthesis of tricyclic 1,2-thiazine 1-oxide

Following the synthetic plan shown in Scheme 3.1, we proceeded to the attempted synthesis of the tricyclic 1,2-thiazine 1-oxide (387) via an intramolecular cyclisation reaction, adopting the N-sulfinyl dienophile. Thus, preparation of the N-sulfinyl dienophile $^{108-109}$ (454) was attempted via sulfinylation of the cyclisation precursor (386) with thionyl chloride under our standard pyridine conditions. Unfortunately, this proved unsuccessful in generating the desired tricyclic product (387), and resulted only in the recovery of the starting cyclisation precursor (386). In the quest for successful cyclisation, a variety of different conditions were explored as shown in Scheme 3.6. However, despite the initial disappearance of the starting material, no identifiable product was obtained under a variety of times, concentrations and reactant ratios. This is perhaps because compound (454) does form, does not cyclise, but rather hydrolysces back to compound (386) on attempted isolation.
3.2 Conclusion

The above synthetic plan proved to be unsuccessful in providing the desired tricyclic 1,2-thiazine 1-oxide template for the construction of pyrrolobenzodiazepines and pyrrolobenzothiadiazepines. The failure to produce the desired 1,2-thiazine 1-oxide by intramolecular cycloaddition meant that the $S_N2'$ route and the direct ring contraction route to pyrrolobenzodiazepines and pyrrolobenzothiadiazepines could not be attempted. The next strategy for synthesizing the desired pyrrolobenzodiazepine and pyrrolobenzothiadiazepine that was attempted was to perform the pyrrole ring formation on a 1,2-thiazine formed in an intermolecular sense and this is described in the next section.
Discussion-Part III
4.1 Synthesis of pyrrolobenzothiadiazepines using ring contraction approach

As depicted in the previous chapter, attempted intramolecular cyclisation reaction to acquire the corresponding tricyclic 1,2-thiazine 1-oxide template as a precursor to the pyrrolobenzodiazepines had failed. In continuation of our pursuit to develop novel synthetic strategies for the synthesis of the pyrrolobenzothiadiazepine and pyrrolobenzodiazepine heterocycles, we thought to explore the possibility of using 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides in a ring contraction reaction to access the pyrrole moiety, with a view to generate the pyrrolobenzothiadiazepines. The modification of utilizing 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides was envisaged as a means to circumvent the difficulties encountered in the previous chapter, where intramolecular construction of the 1,2-thiazine 1-oxide ring was unsuccessful. The methodology is illustrated in Scheme 4.1.

![Scheme 4.1](image)

In summary, access to the 1,2-thiazine 1-oxide (400), was accomplished via a hetero Diels-Alder reaction of a sulfanylamine (399) produced in situ from the 2-azidobenzenesulfonamide (398) by treatment with thionyl chloride. Treatment of the 1,2-thiazine 1-oxide (400) with an equimolar mixture of triethylamine_trimethylphosphite in methanol furnished the desired pyrrole (455), whilst subsequent N-formylation\(^{97}\) using a preformed mixture of acetic anhydride and formic acid provided the N-formylated product (456). Finally, ring closure reaction using the Bischler-Napieralski approach\(^{97}\) gave the desired pyrrolobenzothiadiazepine (457). Approaches
via the amine (402) through an iminophosphorane (401) also successfully gave the pyrrole (455). The detail of this route will be discussed in the remainder of this chapter.

4.1.1 Synthesis of 1,2-thiazine 1-oxides via the N-sulfinyl dienophile

The initial requirement was to synthesize 1,2-thiazine 1-oxides via the hetero Diels-Alder cycloaddition, as established in section 2.2.2 of this thesis. We initially explored this methodology using 2,3-dimethylbutadiene as the diene. Accordingly, treatment of the N-sulfinyl-2-azidobenzenesulfonamide, which was generated in situ as discussed in section 2.2.1, with excess 2,3-dimethylbutadiene produced the desired 1,2-thiazine 1-oxide (400c), which was isolated upon purification via column chromatography in 77% yield (Scheme 4.2).

![Scheme 4.2](image)

The structure of the product was confirmed by the presence of the two \( \text{CH}_2 \) groups in the \( ^1\text{H} \) NMR spectrum (400 MHz), shown as four sets of doublet signals in the region of \( \delta_{\text{H}} \approx 3.23-3.86 \) ppm, with the more downfield \( \text{CH}_2 \) being, presumably, next to the more electronegative nitrogen atom. Furthermore, the appearance of two singlets at \( \delta_{\text{H}} 1.71 \) ppm and 1.79 ppm as the two \( \text{CH} \) groups, confirmed the assignment. Spectroscopic analysis by \( ^{13}\text{C} \) NMR (100 MHz) [(DEPT-135) \( \delta_{\text{C}} 16.9, 19.7 \) (2x \( \text{CH}_3 \)) and \( \delta_{\text{C}} 42.9, 55.5 \) (2x \( \text{CH}_2 \))] and IR spectra [azide (\( \text{N}_3 \)) absorption at \( \nu_{\text{max}} 2134 \) cm\(^{-1} \)], along with a consistent MS \([m/z (\text{ESI}+)]: [\text{M}+\text{H}]^+, 326\) and accurate mass measurement further support the proposed structure.

Having successfully established the 1,2-thiazine 1-oxide (400c) using the 2,3-dimethylbutadiene, a further two examples (400a) and (400b) were synthesized using butadiene and isoprene via the same route.
4.2 Synthesis of pyrroles via ring contraction of the 1,2-thiazine 1-oxides

Amongst the various methods developed for the synthesis of pyrroles (461), the use of 1,2-thiazine 1-oxide as a source of the five membered ring via a ring contraction approach has proven its use in the synthesis of simple (unfused) pyrroles,121-122,134 although the method seems little used. The method for this ring contraction transformation requires base catalyzed ring opening of the 1,2-thiazine 1-oxide, and was classically achieved by simply heating the 1,2-thiazine 1-oxides (458) in a strong alkaline methanolic solution.121 However, this procedure was only applied to derivatives of 1,2-thiazine 1-oxides, where the 2-position is substituted by an ester group, hence limiting it to pyrroles (459). Conversely, various other 2-substituted 1,2-thiazine 1-oxides were shown to exclusively yield homoallylic amines (460) under alkaline hydrolysis108,121,130 (Scheme 4.3). Subsequent to this work, Harrington122 showed that a tertiary amine base in the presence of trimethylphosphite furnished good yields of pyrroles (461) without the need for ester group substitution.

![Scheme 4.3](image)

4.2.1 Synthesis of pyrroles from 2-(aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides

In the context of our interest in the application of the 1,2-thiazine 1-oxide methodology to heterocyclic synthesis, particularly directed towards the synthesis of pyrrolobenzothiadiazepines, we envisioned a versatile synthetic approach utilizing a similar methodology to that above, via the conversion of 1,2-thiazine 1-oxide to a pyrrole. It is thus the aim of this section of the work to explore more fully this interesting transformation, utilizing 2-(aminobenzenesulfonyl)- and 2-
(azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (402) and (400) [see Scheme 4.1, pp. 86], respectively for the construction of the pyrrole moiety.

To test the feasibility of this process a solution of 2-(aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (402c) in methanol was treated with a 1:1 molar equivalent mixture of triethylamine:trimethylphosphite in methanol, under an atmosphere of nitrogen at room temperature, and monitored by TLC. The reaction was found to have proceeded readily, and was complete in two hours, with TLC indicating two new products. After purification by column chromatography of the crude reaction mixture, the upper product, the desired pyrrole (455c), was isolated in 21% yield, whilst the lower product, compound (462c), was obtained in 38% yield (Scheme 4.4). The structure of both compounds was confirmed by spectroscopic analysis.

Specifically, the $^1$H NMR spectrum (400 MHz) of the 1-(2-aminobenzenesulfonyl)pyrrole (455c) showed the two CH$_3$ groups as one singlet at $\delta_{H}$ 1.91 ppm (6H, s, 2x CH$_3$) and also the two pyrrole CH groups appeared as one singlet at $\delta_{H}$ 6.84 ppm (2H, s, 2x pyrrole-H), thus indicating a symmetrical pyrrole. Further enlightenment was given by the presence of the NH$_2$ group at $\delta_{H}$ 4.60 ppm (2H, br, s, NH$_2$). In addition, the $^{13}$C NMR spectrum (100 MHz) showed five CH resonances in the aromatic region ($\delta_{C}$ 117.4-135.0 ppm), diagnostic of the presence of the pyrrole and the aromatic ring. The presence of the NH$_2$ group was further verified by the IR spectrum, which indicates two NH stretching absorptions at $\nu_{\max}$ 3457 and 3377 cm$^{-1}$. MS (ESI+) and accurate mass measurements were in full agreement with the proposed structure.

Similarly, in the case of the second product (462c), the structure was confirmed by the $^1$H NMR spectrum as the N-phosphoramidate. This time, the presence of two extra sets of CH$_3$ as singlets at $\delta_{H}$ 3.71 ppm (3H, s, OCH$_3$) and 3.74 ppm (3H, s, OCH$_3$) and the disappearance of the NH$_2$ functionality and the appearance of the NH group as a broad singlet at $\delta_{H}$ 6.57 ppm (1H, s, br, NH), allowed the assignment of the structure (462c). The product was also analysed by $^{13}$C NMR (100 MHz) with the DEPT-135 showing the extra CH$_3$ resonances as expected. Further
confirmation was gained from the IR spectrum which indicates $P=O$ absorption at $\nu_{\text{max}}$ 1280 cm$^{-1}$, together with MS (ESI+) showing the expected mass peak.

With regards to a possible mechanism, the $N$-phosphoramidate (462c) may have arisen as a result of the nucleophilic amine reacting with the phosphate, PO(OMe)$_3$, the side product of the pyrrole formation reaction, as shown in Scheme 4.5 below.

![Scheme 4.5](image)

Although the necessary ring contraction reaction of the 2-aminobenzenesulfonyl-3,6-dihydro-1,2-thiazine 1-oxides with triethylamine in the presence of trimethylphosphite proved successful, the yields of the desired pyrrole were low. The observed reaction of the amino nitrogen with phosphorus species formed during the reaction is clearly problematic, and for this reason we turned attention to the use of the azides (400), with the hope that it would behave differently.

### 4.2.2 Synthesis of pyrrole from 2-(azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides

The modification of utilizing 2-azidobenzenesulfonyl-3,6-dihydro-1,2-thiazine 1-oxides was envisaged as a means to circumvent the difficulties mentioned above, which was blamed upon the presence of the nucleophilic amine functionality in the structure. Intriguingly, treatment of the 2-(azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400c) with a 1:1 molar equivalent mixture of triethylamine:trimethylphosphite in methanol, under an atmosphere of nitrogen at room temperature, resulted in a one-pot ring contraction, accompanied by concomitant same pot azide reduction to provide the desired amino pyrrole (455c) in 11% yield (Scheme 4.6). A second product was isolated, which was identified as the $N$-phosphoramidate (462c) which was formed in 39% yield. Recovered starting material accounted for the balance of product.
With reference to the mechanism, it is considered that this interesting one-pot dual transformation proceeds via the ring contraction, desulfurisation and aromatization process as depicted in Scheme 4.3, shown previously. This is accompanied by concomitant same pot conversion of the azide functionality into the corresponding amine via the hydrolysis of intermediate iminophosphorane (464) formed after Staudinger reaction\textsuperscript{141-142} of the azide (463) with the phosphite as shown in Scheme 4.7. The formation of the N-phosphoramidate (465) could have arisen as a result of partial basic hydrolysis of the iminophosphorane (464) via route ‘a’ in Scheme 4.7, or via reaction of the final amine product, (466), with the PO(OMe)\textsubscript{3} as per route ‘b’.

Based on these findings, we became interested in optimizing the yield of pyrrole (455c) as it could potentially provide a route through to the desired pyrrole in two fewer steps than our original plan. Having examined many potential conditions for the concomitant azide reduction/ring contraction reaction of the 2-azidobenzenesulfonyl-3,6-dihydro-1,2-thiazine 1-oxide (400c), optimal results were obtained by using a 1:2 molar equivalent mixture of triethylamine:trimethylphosphite in methanol, followed by a basic aqueous work up with 2M...
sodium hydroxide. It was found to be most important to purify the crude product by chromatography with eluent containing 10% triethylamine. These conditions produced the desired amino pyrrole (455c) in 50% yield.

Having established the efficiency of the ring contraction reaction of the 2-azidobenzensulfonyl-3,6-dihydro-1,2-thiazine 1-oxide, the value of the new optimized conditions using 1,2-thiazine 1-oxides derived from isoprene and butadiene was next examined. Accordingly, 2-azidobenzensulfonyl-3,6-dihydro-1,2-thiazine 1-oxides (400a) and (400b) were treated with a 1:2 molar equivalent mixture of triethylamine:trimethylphosphite in methanol under nitrogen. In both cases the ring contraction proceeded readily, yielding the desired amino pyrrole, which was again isolated upon work-up with 2M sodium hydroxide solution and purification by column chromatography using 10% triethylamine in the eluent mixture. The products (455a) and (455b) were isolated in good yields (50-73%) and the results are presented in Table 4.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Method</th>
<th>Yield of 455 (%)</th>
<th>Yield of 462 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>Et₃N, P(OMe)₃ (1:2), MeOH, r.t.</td>
<td>50</td>
<td>23</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Me</td>
<td>Et₃N, P(OMe)₃ (1:2), MeOH, r.t.</td>
<td>73</td>
<td>10</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>Me</td>
<td>Et₃N, P(OMe)₃ (1:2), MeOH, r.t.</td>
<td>50</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 4.1: % yields of the amino pyrroles (455a-c) and the N-phosphoramidate pyrroles (462a-c)

### 4.3 Formylation of the pyrrole

With the desired pyrroles (455) in hand, the next task of our synthetic strategy was to establish cyclisation of the amino pyrrole system to the desired seven-membered ring with the imine functionality at the N10-C11 position. Potentially, there are two key sites available in our compound where the extra carbon needed to bring about such a ring closure can be introduced, namely via the formylation of the electron-rich pyrrole or of the nucleophilic amine. Either route in effect could then afford the desired tricyclic pyrrolobenzothiadiazepine, bearing the imine bond that is so essential to the biological activity of several similar compounds in the literature. Our first approach to the synthesis of the formylated precursor involved the introduction of the formyl group on the pyrrole, an obvious choice, which is well documented in the literature.

One of the most common methods of formylating activated aromatic rings, such as pyrroles, is via the Vilsmeier-Haack reaction. The reaction proceeds with the combination of an N,N-dimethylamide and phosphorus oxychloride to form an iminium cation (467). Subsequent
reaction of the reactive carbon electrophile with pyrrole results in the formation of a stable iminium salt (468), which upon work-up with aqueous sodium bicarbonate hydrolyses to the desired formylated pyrrole (469) as illustrated in Scheme 4.8.

Initially, we decided to test the methodology using the N-phosphoramidate pyrrole (462c), in order to avoid any possible side reactions of the amine group that is present in compound (455c). Once the formylation proved to be efficient, the intention was to remove the phosphorus grouping from the nitrogen using HCl\textsubscript{203} and to then cyclise the ring in a one-pot reaction to form the desired tricyclic system (457). Accordingly, a solution of the N-phosphoramidate pyrrole (462c) in dry dichloromethane was added at 0°C to a mixture of N,N-dimethylformamide and phosphorus oxychloride in anhydrous dichloromethane. The mixture was gradually allowed to attain room temperature and was stirred for 18 h. Work-up with aqueous sodium hydroxide, followed by purification via column chromatography, resulted in the isolation of the desired product (470c) and the unexpected N-[o-(N',N'-dimethylformamidinyl)benzenesulfonyl] formylated pyrrole (471c) in 38% and 43% yields, respectively (Scheme 4.9).
The incorporation of the formyl group in the case of the desired product (470c) was confirmed with $^1$H NMR (400 MHz) which indicated the additional presence of the aldehyde proton as a singlet at $\delta_H$ 10.1 ppm (1H, s, CHO). In addition, the $^{13}$C NMR spectrum (100 MHz) also confirmed this with the CHO resonance at $\delta_C$ 179.0 ppm, diagnostic of the deshielded aldehyde carbonyl, together with the presence of a C=O stretching absorption at $\nu_{\text{max}}$ 1662 cm$^{-1}$ in the IR spectrum. Concurrently, analysis by MS (ESI+) and accurate mass determination were in full agreement with the proposed structure.

The $^1$H NMR spectrum (400 MHz) of the N,N-dimethylformamidyl product (471c) showed two pyrrole CH$_3$ groups as separate singlets at $\delta_H$ 1.99 ppm (3H, s, CH$_3$) and $\delta_H$ 2.28 ppm (3H, s, CH$_3$), indicating a non symmetrical pyrrole. Evidence of the successful formylation was provided by the presence of a peak at $\delta_H$ 9.98 (1H, s, CHO), diagnostic of the aldehyde. The disappearance of the NH group and the appearance of two extra sets of CH$_3$ groups at $\delta_H$ 3.01 ppm (3H, s, CH$_3$) and $\delta_H$ 3.02 ppm (3H, s, CH$_3$), together with a peak at $\delta_H$ 7.42 ppm (1H, s, N=CH) in the vinylic region further confirmed the structure. The $^{13}$C NMR (100 MHz) further supported the assignment by the presence of four CH$_3$ groups at $\delta_C$ 9.50, 10.9, 34.4, 40.3 ppm and the CHO group at $\delta_C$ 180.5 ppm, while the vinylic, aromatic and quaternary carbon atoms appeared more deshielded in the region of $\delta_C$ 120.6-152.8 ppm and showed the presence of the extra CH resonance attributed to the CH=N. This structural determination was verified by IR spectroscopy with the presence of a C=O stretching absorption at $\nu_{\text{max}}$ 1710 cm$^{-1}$. These data, in combination with a consistent MS [m/z (ESI+): [M+H]$^+$, 334] and accurate mass measurement of the desired molecular ion assisted towards the structural determination of the N,N-dimethylformamidyl compound (471c).

In terms of mechanism, it is proposed here that loss of the phosphoramidate functionality results in the formation of the amine in the first step, a process which is known to be affected by the presence HCl.$^{203}$ The second step involves reaction of the Vilsmeier salt with the free amine to give the N,N-dimethylformamidyl compound (471c) as illustrated in Scheme 4.10.
Attempted synthesis of the 1-(2‘aminobenzenesulfonyl)-2-formylpyrrole (472c) via the N-(arylamino) pyrrole (440) under Vilsmeier conditions resulted in a similar reaction with the desired 1-(2‘aminobenzenesulfonyl)-2-formylpyrrole (472c) obtained in 31% yield, together with the N,N-dimethylformamidinyl compound (471c) in 49% yield (Scheme 4.11).

![Scheme 4.11](image)

The observed isolation of the N,N-dimethylformamidinyl compound (471c) in this case is presumably due to the direct reaction of the Vilsmeier salt with the amine, accompanied by formylation of the pyrrole ring.

4.4 Synthesis of 1-(2-formamidobenzenesulfonyl) pyrroles

Although the Vilsmeier reaction discussed in the preceding section resulted in the isolation of the desired 1-(2‘aminobenzenesulfonyl)-2-formylpyrrole (472c) in a moderate 31% yield, in the event, it was found that this would not cyclise to the desired tricyclic pyrrolobenzothiadiazpine, probably due to the deactivation of the aldehyde by delocalisation into the pyrrole. Fortunately, Artico et al. in their pursuit of heterocycles with benzothiadiazepine moieties, reported the synthesis of pyrrolobenzothiadiazepines utilizing 1-(2-formamidobenzenesulfonyl)pyrroles. Thus, according to Artico treatment of the 1-(2-aminobenzenesulfonyl)pyrrole (455a) with acetic-formic anhydride resulted in the formylation of the amine. Subsequent treatment of the 1-(2-formamidobenzenesulfonyl)pyrrole (456a) with phosphorous oxychloride resulted in cyclisation via a Bischler-Napieralski reaction to provide the tricyclic pyrrolobenzothiadiazepine (457a) [Scheme 4.12].

![Scheme 4.12](image)
Thus, treatment of 1-(2-aminobenzenesulfonyl) pyrroles (455a-c) with a preformed mixture of acetic anhydride and formic acid gave the N-formylated products (456a-c) in high yields (77-98%) after purification via column chromatography (Scheme 4.13).

Spectroscopic analysis of the N-formylated pyrrole (456a-c) confirmed their proposed structure. In particular the presence of the formyl group was confirmed by the appearance of a CH group in the $^{13}$C NMR spectra at $\delta_{C} \sim 159$ ppm (CHO) and the presence of an extra CH resonance in the $^1$H NMR spectra at $\delta_{H} \sim 8.55$ ppm (1H, s, CHO) accompanied by loss of the NH$_2$ resonance and the appearance of a new NH resonance at $\delta_{H} \sim 9.45$ ppm (1H, s, NHCHO). The IR spectra showed the new C=O at $\nu_{max} \sim 1700$ cm$^{-1}$ in all cases and mass spectroscopic analysis confirmed the assignments with matching M$^+$ peaks.

### 4.5 Synthesis of pyrrolobenzothiadiazepines

Having established a straightforward and high yielding route for the conversion of the 1-(2-aminobenzenesulfonyl) pyrroles to the corresponding N-formylated pyrrole, as presented above, the final task was to cyclise the formyl onto the pyrrole via the Bischler-Napieralski reaction.$^{97}$

Accordingly, solutions of 1-(2-aminobenzenesulfonyl) pyrroles (456a-c) were heated at reflux in dichloroethane in the presence of phosphorus oxychloride for 3 hours (Scheme 4.14).
In all cases the reaction proceeded readily yielding the desired pyrrolobenzothiadiazepines (457a-c), which were purified by column chromatography and isolated in the yields shown in Table 4.2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Method</th>
<th>Yield of 457(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>POCl₃, DCM, Δ</td>
<td>55</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Me</td>
<td>POCl₃, DCM, Δ</td>
<td>59</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>Me</td>
<td>POCl₃, DCM, Δ</td>
<td>43</td>
</tr>
</tbody>
</table>

*Table 4.2: % yields of the pyrrolobenzothiadiazepines*

The structures of the pyrrolobenzothiadiazepines (457a-c) were, in each case, assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, and IR spectroscopic analysis, together with an accurate mass measurement for the desired ion. In all cases, evidence for successful cyclisation was provided by $^1$H NMR (400 MHz), which showed the disappearance of the deshielded aldehyde CH group and the appearance of a new CH group in the aromatic region at $\delta_H \sim 8.62$-8.66 ppm, diagnostic of the imine. Additionally, the presence of the imine carbon was demonstrated in the $^{13}$C NMR (100 MHz) spectra of the products by the appearance of a peak in the region of $\delta_C \sim 148.5$-150.0 ppm, which was also inferred by inspection of the IR spectra via the presence of a C=N stretching absorption at $\nu_{max}$ 1603 cm⁻¹. These data, along with consistent mass spectra and accurate mass measurement further supported the proposed structures.

### 4.6 Synthesis of tetracyclic systems

Whilst the synthesis and biological applications of the pyrrolobenzodiazepine and pyrrolobenzothiadiazepine pharmacore continues to attract considerable attention in the literature, current interest has turned to the synthesis of analogues having additional heterocyclic rings fused to the diazepine ring. As described in the introduction of this thesis, such tetracyclic systems are of enormous potential utility, particularly bretazenil (473)\textsuperscript{97,101b} which possesses an imidazole moiety at the N10-C11 position of the pyrrolobenzodiazepine (Figure 4.1), which has found clinical and commercial success as an anxiolytic agent.\textsuperscript{204-205}
On these grounds, we envisaged our compounds would be extremely useful in the synthesis of tetracyclic systems via the 1,3-dipolar cycloaddition reaction. In an attempt to investigate this transformation further and with a view to generating novel heterocycles comprising the five-membered 1,2,4-oxadiazoline, we chose to incorporate the nitrile oxides. The route that we investigated is shown in Scheme 4.15 and relies upon a 1,3-dipolar cycloaddition of benzonitrile oxide, which is readily available from benzohydroxyimoyl chloride (476) using Huisgen’s base-induced dehydrochlorination process to generate the desired 1,2,4-oxadiazolopyrrolobenzothiadiazepine 5,5-dioxide (477). Access to the benzohydroximoyl chloride (476) was accomplished via chlorination of the corresponding benzaldoxime (475), derived from commercially available benzaldehyde (474).

Following our proposed methodology shown in Scheme 4.15, the initial requirement was to synthesize the nitrile oxide, which would react with the N10-C11 imine bond in the pyrrolobenzothiadiazepine in a 1,3-dipolar cycloaddition to generate the desired 1,2,4-oxadiazoline. Nitrile oxides are in general highly reactive and thus unstable 1,3-dipoles, and although some aryl nitrile oxides can be quite stable, they generally undergo dimerisation in the absence of dipolarphiles to give the corresponding 1,2,5-oxadiazole-2-oxides (478). Consequently, in order to eliminate competitive dimerisation, they are commonly generated in situ in the presence of dipolarophiles. Among several methods developed for the in situ generation of nitrile oxides, the dehydration of primary nitro derivatives (Mukaiyama procedure...
for aliphatic nitrile oxides\(^{211}\) and the base-induced dehydrohalogenation of hydroximoyl chlorides (Huisgen’s methodology for aromatic nitrile oxides\(^{210}\) have been extensively used. In this thesis, generation of the nitrile oxides was performed using the base catalysed dehydrochlorination of benzohydroximoyl chlorides.

\[
\begin{align*}
R-\text{CHO} & \quad \rightarrow \quad R-C=\text{NOH} \\
R-\text{CH}_2X & \quad \rightarrow \quad R-C=\text{NO}_2
\end{align*}
\]

Scheme 4.16

4.6.1 Synthesis of benzaldoxime

The condensation of the carbonyl compounds with hydroxylamine constitutes one of the most valuable reactions in preparing oximes.\(^{212-214}\) Accordingly, benzaldehyde (474) was treated with hydroxylamine hydrochloride in ethanol in presence of sodium acetate. The oximation proved very efficient, generating the desired benzaldoxime (475) in 84% yield (Scheme 4.17).

\[
\begin{align*}
\text{NH}_2\text{OH.HCl} & \quad \text{EtOH, NaOAc, r.t.} \\
\text{474} & \quad \rightarrow \quad \text{475}
\end{align*}
\]

Scheme 4.17

The reaction mechanism\(^{214}\) begins with a nucleophilic addition of the hydroxylamine to the carbonyl moiety to form an unstable intermediate, which upon protonation and dehydration results in the corresponding oxime as illustrated in the Scheme 4.18.
4.6.2 Synthesis of benzohydroximoyl chloride

Having successfully generated the oxime via the condensation reaction of aldehyde and hydroxylamine, the next requirement was to chlorinate the oxime to make the benzohydroximoyl chloride precursor, which would subsequently dehydrohalogenate in the presence of base to give the desired benzonitrile oxide in the next step.

Hydroximoyl chlorides can be prepared via chlorination of the respective aldoximes using a wide variety of reagents including Cl$_2$,215 NCS,216 NBS,217 NaOCl,218 tert-butyl hypochlorite,219 chloramine-T,220 and benzyltrimethylammonium tetrachloroiodate (BTMA ICl$_4$).221 The ease of use and ready availability made NCS222 the first reagent to be tried.

Thus, treatment of benzaldoxime (475) with a solution of N-chlorosuccinimide in dry chloroform in the presence of pyridine, gave the desired benzohydroximoyl chloride (476), which upon purification via column chromatography was isolated in 76% yield (Scheme 4.19).

With regards to a mechanism, it is believed that the N-chlorosuccinimide initially breaks down to form a succinimidyl radical and chlorine radical.223 The reaction is, then, propagated by hydrogen atom abstraction by the chlorine radical, and finally terminated with the replacement of the methine hydrogen by chlorine as illustrated in the scheme below.
4.6.3 Synthesis of 1,2,4-oxadiazolopyrrolobenzothiadiazepine 5,5-dioxide via 1,3-dipolar cycloaddition reaction

Following the synthetic methodology shown in Scheme 4.15, the final step involved the generation of the benzonitrile oxide via dehydrochlorination of the benzohydroximoyl chloride using Huisgen's approach and subsequent in situ 1,3-dipolar cycloaddition of the corresponding benzonitrile oxide with pyrrolobenzothiadiazepines.

The transformation of the hydroximoyl chloride into nitrile oxides is an extremely rapid process and can be readily achieved in the presence of a basic reagent. Consequently, in order to avoid possible competitive dimerisation, slow addition of base such as triethylamine or pyridine to the mixture of the dipolarophiles and dipole precursor is essential.

Accordingly, the 1,3-dipolar cycloaddition precursor, benzohydroximoyl chloride (476) and the pyrrolobenzothiadiazepines (457b-c) were reacted together, with a view to synthesising the desired 1,2,4-oxadiazoline-annulated pyrrolobenzothiadiazepine (477a-b). The cycloaddition reaction conditions involved the addition of a solution of the benzohydroximoyl chloride (476) in anhydrous tetrahydrofuran to a solution of the pyrrolobenzothiadiazepines (457b-c) in anhydrous tetrahydrofuran in the presence of triethylamine (Scheme 4.21).
In all cases the \textit{in situ} cycloaddition proceeded readily, generating, after purification by column chromatography, the desired 1,2,4-oxadiazoline annulated pyrrolobenzothiadiazepines (477a-b) in 47% and 69% yields, respectively.

The incorporation of the benzonitrile oxide in both products (477a-b) was confirmed by $^1$H NMR (400 MHz) which indicated the additional presence of 5 protons in the region of $\delta_H \sim 7.20$-$7.94$ ppm. More importantly, the incorporation of the oxadiazoline moiety in the molecules was manifested by the occurrence in the $^{13}$C NMR spectra of an additional deshielded quaternary carbon atom at $\delta_C 155.6$ ppm and at $\delta_C 155.9$ ppm for compounds (477a) and (477b), respectively, together with the appearance of the extra expected aromatic carbons, and the new sp$^3$ methine carbon. The presence of an imine was also evident by IR analysis, which showed a band of medium intensity at $\nu_{\text{max}} \sim 1585$ cm$^{-1}$. These data, in combination with consistent MS [m/z (ESI)]: [M+H]$^+$, 366 and [m/z (ESI)]: [M+H]$^+$, 380 for compound (477a) and (477b), respectively, together with accurate mass measurement of the desired molecular ion assisted the structural determination of both cycloadducts.

Following the success of the above methodology for the construction of 1,2,4-oxadiazoline annulated pyrrolobenzothiadiazepines, we decided to implement this strategy with other nitrile oxides. Consequently, the preparation of 1,2,4-oxadiazoline derivatives \textit{via} the readily available ethylchloroximidoacetate was next attempted, using pyrrolobenzothiadiazepines (457b-c). In all cases the 1,3-dipolar cycloaddition proceeded smoothly, generating, after purification by column chromatography, the desired 1,2,4-oxadiazoline annulated pyrrolobenzothiadiazepines (479a-b) in 47% and 69% yields, respectively (Scheme 4.22).

The incorporation of the ethyl ester grouping was confirmed by $^1$H and $^{13}$C NMR spectroscopic analysis of the products (479a-b). Significantly, in each case, the $^1$H NMR spectrum (400 MHz) indicated the additional presence of the CH$_2$ and CH$_3$ groups, split by each other as a multiplet at $\delta_H \sim 4.25$ ppm (2H, m, CO$_2$CH$_2$CH$_3$) and a triplet at $\delta_H \sim 1.28$ ppm (3H, t, J 7.1, CO$_2$CH$_2$CH$_3$), respectively. Additionally, $^{13}$C NMR spectra (100 MHz) of the products
showed the ethyl ester CH$_2$ and CH$_3$ groups at $\delta_H$ 62.7 ppm and $\delta_H$ 13.8 ppm, respectively, together with the deshielded quarternary carbon atoms at $\delta_C$ $\sim$147.8 ppm and at $\delta_C$ 156.6 ppm, values distinctive for the resonance of the C=N and C=O groups, respectively. Further evidence of the proposed structure was provided by IR spectra of the products, which showed a band of medium intensity in the region $\nu_{\text{max}}$ $\sim$1574-1582 cm$^{-1}$, corresponding to the imine, together with a sharp carbonyl band in the region $\nu_{\text{max}}$ $\sim$1733-1736 cm$^{-1}$. These data, in combination with consistent MS [m/z (ESI+): [M+H]$^+$, 362] and [m/z (ESI+): [M+H]$^+$, 376] for compounds (479a) and (479b), respectively, together with accurate mass measurements of the desired molecular ions confirmed the structures of both cycloadducts.

With regards to the mechanism of the 1,3-dipolar cycloadditions, it is proposed that initial proton abstraction by triethylamine, and thus, removal of HCl, provides the reactive nitrile oxide, followed by a 1,3-dipolar cycloaddition, leading to the formation of a 1,2,4-oxadiazoline ring, as illustrated in Scheme 4.23.

\[
\text{Step 1} \quad \begin{array}{c}
\text{Cl} \\
\text{Et}_{3}N \quad \text{R-C=N-O} \\
\text{HCl}
\end{array} \quad \begin{array}{c}
\text{R-C=N-O} \\
\text{[M+H]$^+$, 362}
\end{array}
\]

\[
\text{Step 2} \quad \begin{array}{c}
\text{R-C=N-O} \\
\text{[M+H]$^+$, 376}
\end{array} \quad \begin{array}{c}
\text{R'= Ph or CO$_2$Et} \\
\text{R',R''=H, Me}
\end{array}
\]

\[\text{Scheme 4.23}\]

4.3 Conclusion

In conclusion, the attempt to formulate a novel synthetic approach to pyrrolobenzothiadiazepine heterocycles was fruitful. Generation of the 1,2-thiazine 1-oxides was performed routinely, starting from the commercially available 2-aminobenzenesulfonamide. Advantageously, the use the 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxides in a ring contraction reaction led to the desired arylpyrrole (455a-c) via a one-pot ring contraction, desulfurisation and aromatization process, accompanied by concomitant same pot conversion of the azide to a primary amine through a Staudinger reaction. Formylation of the arylpyrrole proved
problematic as the desired amino pyrrole was only obtained in low yields. However, N-formylation was successful and a subsequent Bischler-Napieralski reaction yielded the pyrrolobenzothiadiazepines (457a-c) in moderate yields. Access to tetracyclic systems via a 1,3-dipolar cycloaddition using nitrile oxides proved successful, and four 1,2,4-oxadiazoline-annulated pyrrolobenzothiadiazepines were obtained in good yields.
Discussion-Part IV
5.1 Synthesis of aziridinobenzothiadiazocines and pyrrolobenzothiadiazines

Following the successful synthesis of the pyrrolobenzothiadiazepine 1,1-dioxides via the ring contraction process\(^{122}\) of 1,2-thiazine 1-oxides, we embarked upon an alternative to the route described in the preceding section and sought to take advantage of the fact that the 1,2-thiazine 1-oxide nucleus (402), upon hydrolysis,\(^{109-115}\) should yield a sulfinic acid, which, after spontaneous retro-ene type loss of sulfur dioxide would furnish a homoallylic sulfonamide (480). We anticipated that a 5-endo-trig iodocyclisation\(^{224}\) would then yield the corresponding pyrrolidine system (481), which would serve as a useful precursor for the synthesis of the pyrrolobenzothiadiazepine nucleus, as shown in Scheme 5.1. Access to the tricyclic pyrrolobenzothiadiazepine (457) could be accomplished in four further steps involving loss of HI, followed by oxidation to pyrrole (455).\(^{225}\) N-formylation followed by Bischler-Napieralski ring closure\(^{97}\) using an acetic anhydride/formic acid mixture would complete the synthesis. Also possible via this route would be an exploration of the use of the precursor (481) to furnish compound (482), an interesting analogue of the usual [2,1-c] fused pyrrolobenzodiazepine systems.

![Scheme 5.1](image)

Scheme 5.1: Reagents and conditions: (i) acid hydrolysis; (ii) iodocyclisation; (iii) HI elimination/oxidation; (iv) N-formylation; (v) Bischler-Napieralski cyclisation; (vi) cyclisation.

5.1.1 Synthesis of homoallylic sulfonamides via hydrolysis of 1,2-thiazine 1-oxides

Recently, Weinreb and co-workers\(^{113-115}\) have exploited some of the known reactions of the 1,2-thiazine 1-oxides, along with new transformations, in the selective preparation of some
complex nitrogen-containing molecules. One useful transformation of these adducts is the hydrolysis/retro-ene elimination of sulfur dioxide shown in Scheme 5.2. Thus, treatment with acid of the two epimeric cycloaddition adducts of \((E,E)\) and \((E,Z)\)-tetramethylbutadiene, (483) and (486), resulted in hydrolysis to produce allylic sulfinic acids (484) and (487), which suffered a retro-ene reaction via the chair-like conformation shown to give the desired \(E\)-erythro (485) and \(E\)-threo (488) isomeric homoallylic sulfonamides,\(^{106,111,113-115}\) respectively. It is thought that this transformation arises due to the methyl group on the sulfur-bearing carbon occupying a quasi-equatorial position, which directs intramolecular protonation to one of the diastereoisotopic faces of the double bond to establish \((E)\)-geometry in the newly formed double bond.

\[
\begin{align*}
\text{Me}_2C\backslash\text{S}=\mathcal{O} & \quad \xrightarrow{1.5\% \text{ NaOH} \quad 2.5\% \text{ HCl}} \quad \text{Me}_2C\backslash\text{S}^{\text{H}}\mathcal{O} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{NHTs} & \quad \text{Me} \\
483 & \quad 484 & \quad 485 & \quad 486 & \quad 487 & \quad 488
\end{align*}
\]

\text{Scheme 5.2}

In an adaptation of this method, the 2-(2-aminobenzenesulfonyl)-1,2-thiazine 1-oxides (402a-c) were heated at reflux in tetrahydrofuran in the presence of aqueous HCl. Upon completion, the reaction was neutralized with aqueous sodium hydroxide generating the desired homoallylic sulfonamides (480a-c), presumably via the intermediate sulfinic acids (489a-c)\(^{106,111,113-115}\) (Scheme 5.3). In all cases the reaction proceeded readily yielding the homoallylic sulfonamides (480a-c) which were purified by column chromatography and isolated in the yields shown in Table 5.1.

\[
\begin{align*}
\text{O}_{\text{S}}\backslash\text{N} & \quad \xrightarrow{\text{aq. HCl} \quad \text{THF}, \Delta} \quad \text{O}_{\text{S}}\backslash\text{N} \quad \text{OH} \quad \text{R}^1 \\
\text{R}^1 & \quad \text{NH}_2 & \quad \text{R}^1 & \quad \text{NH}_2 & \quad \text{R}^1 & \quad \text{R}^1 \\
402a-c & \quad 489a-c & \quad 480a-c
\end{align*}
\]

\text{Scheme 5.3}
The structure of the homoallylic sulfonamides (480a-c) was, in each case, assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, and IR spectroscopic analysis, together with an accurate mass measurement for the desired ion. In all cases, evidence for a successful ring opening was provided by $^1$H NMR (400 MHz), which showed the presence of a broad peak at $\delta_H \sim 4.82-5.63$ ppm, corresponding to the sulfonamide NH proton. In the vinylic region, compound (480a) showed three protons around $\delta_H \sim 4.99-5.13$ ppm, as a complex multiplet, corresponding to the vinyl CH$_2$ and vinyl CH groups. This was further confirmed by $^{13}$C NMR (100 MHz) [(DEPT -135) $\delta_c 117.7$ (CH), $118.0$ (CH$_2$)]. As expected, the $^1$H NMR spectrum of compounds (480b,c) revealed two protons in the vinylic region, which showed up clearly as a CH$_2$ in the $^{13}$C NMR, together with the quaternary carbon bearing the CH$_3$ group. The presence of one methyl group at $\delta_H 1.53$ ppm for compound (480b), together with the presence of two methyl groups in compound (480c), helped to confirm the assignments. In each case IR spectra [3x NH absorption at $v_{\text{max}} \sim 3285-3479$ cm$^{-1}$], along with consistent mass spectra and accurate mass measurement further supported the proposed structures.

### 5.1.2 Attempted synthesis of pyrrolidine via 5-endo-trig iodocyclisation

With the homoallylic sulfonamides in hand, the next objective was to synthesize the corresponding pyrrolidine via an iodocyclisation. Electrophile-induced 5-endo-trig cyclisations are now well established as a viable and often highly stereoselective approach to tetrahydrofurans. In the light of these studies, Knight et al. have shown that similar cyclisations of the (E)-homoallylic sulfonamides (490) by treatment with excess iodine in the presence of anhydrous potassium carbonate or sodium bicarbonate leads to the 2,5-trans-iodopyrrolidines (491). Additionally, access to the 2,5-cis-isomers (492) was accomplished by treatment of the same sulfonamides (490) with iodine (Scheme 5.4).
This general transformation of homoallylic sulfonamides (490) into a 5-membered ring, is considered to be electrophile driven, involving a chair-like transition state (493), wherein an equatorial positioning of substituents R² is the controlling feature (Scheme 5.5).

Based upon this finding, the 5-endo-trig iodo cyclisation process was adopted for the attempted conversion of homoallylic sulfonamides (480a-c) to the corresponding aryl iodo pyrrolidines (481a-c). Accordingly, the homoallylic sulfonamides (480a-c) were treated with iodine in anhydrous acetonitrile in presence of sodium bicarbonate at ambient temperature (Scheme 5.6). In two cases [(480b) and (480c)] apparent evidence of successful 5-endo-trig iodo cyclisation was provided by the appearance of a new major product. This was in contrast to the homoallylic sulfonamide derived from 1,3-butadiene (480a), which yielded no identifiable product. Intriguingly, in both cases, the major products of the attempted 5-endo-trig iodo cyclisation were neither the desired aryl iodo pyrrolidine (481), nor the de-iodo products derived therefrom (494) and (495), nor the possible further cyclised product (482).
In both reactions the major product were assigned on the basis of their $^1$H NMR, $^{13}$C NMR, $^1$H,$^1$H-COSY, $^1$H,$^{13}$C-COSY, MS, IR spectra and accurate mass measurements. Specifically, two dimensional $^1$H NMR (400 MHz) studies of the product derived from compound (480b) showed the absence of the NH$_2$ group protons and confirmed the presence of the distinct sulfonamide NH group at $\delta _H$ 5.25 ppm (1H, t, $J$ 6.2, NH(h)) [see Figure 5.1]. The sulfonamide NH$_{(h)}$ was coupled to the methylene group (C1) at $\delta _H$ 3.80 (1H, m, br, NHCH-H(g)), which in turn in the expansion, was coupling to H$_{(b)}$ on the same carbon. Furthermore, H$_{(e)}$ was coupling to H$_{(c)}$ of a second methylene unit (C2), together with H$_{(c)}$ coupling with H$_{(b)}$. The C2 methylene unit was attached to a quaternary but sp$^3$ carbon which in turn was attached to a methyl group and also to a further methylene group. This final methylene unit had no further carbon or hydrogen coupling, and showed a clear and distinct singlet for each of its two hydrogens at $\delta _H$ 2.11 ppm and 2.31 ppm. This together with the two hydrogens being non-equivalent and unable to couple to each other led to the assignment of the structure as the aziridine fused benzothiadiazocine (496b). Such a pattern is very distinctive of aziridine CH$_2$ groups by virtue of the geometric constraints in the ring, as shown in the literature. Further evidence was given by the $^{13}$C NMR spectrum (100 MHz) of the molecule, which showed (DEPT-135) the three CH$_2$ groups at $\delta _C$ 35.8, 39.2, 40.2 ppm, and a methyl group at $\delta _C$ 20.2 ppm. The C3 quaternary carbon appeared as expected at 44.0 ppm, while the aromatic and the two aromatic quaternary carbon atoms appeared more downfield at $\delta _C$ 121.7-147.8 ppm. These data combined with IR spectroscopic analysis [NH absorption (strong) at 3101 cm$^{-1}$], MS [m/z (ESI+): [M+H]$^+$, 239] and accurate mass measurement supported the structural assignment. The stereochemistry at nitrogen was not established, but the product was one diastereoisomer.
Compound (480c) behaved in a similar fashion to give the aziridine fused benzothiadiazocine (496c) which, as well as showing all of the expected connectivities by 2D NMR, was also formed as a single diastereoisomer. NOE studies showed that the two methyl groups in compound (496c) were trans (or anti) to one another, a feature implied by a relatively strong correlation between the hydrogen on C4 of the 1,2,6-benzothiadiazocine ring and the C5 methyl substituent, indicating that the C4 hydrogen and the C5 methyl were cis (or syn) to each other. Again the stereochemistry at the aziridine nitrogen was not determined. Yields of compounds (496b) and (496c) were 49% and 30%, respectively (Scheme 5.7).
With regards to a possible mechanism, it is thought that the arylamino nitrogen and not the sulfonamido nitrogen is the participating nucleophile in the iodocycloisolation, thereby giving the thia diazocine ring (497). Formation of the aziridine (496) then follows from cyclisation onto the primary alkyl iodide (Scheme 5.8), paralleling well known methods for the synthesis of aziridines.229b-229c,230

It is of note that compounds (480) are able to adopt conformations, such as that shown in structures (498) or (499) in Scheme 5.9, that favour cyclisation via the arylamino nitrogen rather than the alternative 5-endo-trig sulfonamido nitrogen cyclisation, although the latter process whilst disfavoured by Baldwin’s rules, is known to occur.224a It is of further note that compound (480a; R1=R2= H) is able to offer less stability, having no methyl group, to the proposed iodonium intermediate than that offered by compounds (480b; R1=H, R2=Me) and (480c; R1=R2=Me) and this may explain its failure to react. Finally, it seems that a possible explanation for the trans relationship of the two methyl groups in compound (496c) is that the R1 and R2 groups in conformers (498) or (499) occupy the two pseudo equatorial positions shown in the six membered ring transition state, leading to the observed trans stereochemistry (Scheme 5.9).
Despite the failure of the 5-endo-trig iodocyclisation to generate the aryl iodopyrrolidine, the somewhat serendipitous discovery of a iodocyclisation \textsuperscript{224a} in the synthesis of an aziridine fused 1,2,6-benzothiadiazocine is of interest due to the difficulties encountered in constructing both the eight- and three-membered rings and, thus, yields of 49\% and even 30\% are, in this context, respectable. Furthermore, this transformation is of particular interest as benzodiazocines have attracted attention as analogues of the 1,4-benzodiazepines,\textsuperscript{231} as novel antibacterial compounds\textsuperscript{232} and as positive inotropic calcium sensitizing agents.\textsuperscript{233} The corresponding 1,2,6-benzothiadiazocines are attractive as sulfur analogues of this system and have also received particular interest as potential NNRTIs,\textsuperscript{98} whilst aziridine fused systems are of general and widespread utility as DNA alkylating agents and potential antitumour agents.\textsuperscript{234}

### 5.2 Synthesis of pyrrolidine via 5-endo-trig iodocyclisation

As described above, the attempt to use the (2-aminoaryl)allylic sulfonamides (480) as precursors to making the aryl iodopyrrolidine was not successful, due to the involvement of the arylamine nitrogen undergoing 8-exo-trig iodocyclisation to furnish aziridino fused 1,2,6-benzothiadiazocines. Therefore to overcome this problem, we embarked upon a modified route and investigated the use of 2-azido, 2-iminophosphoranyl and 2-nitroaryl allylic sulfonamide, each of which has a non-nucleophilic nitrogen. The idea was to convert these homoallylic systems to their corresponding pyrrolidine via iodocyclisation, and subsequent reduction of the 2-arylnitrogen functionality would then give access to the desired cyclisation precursor (481) [Scheme 5.10].
5.2.1 Acid hydrolysis of 2-(2-[iminophosphoranyl]benzenesulfonyl)- and 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxides

Following this revised synthetic strategy, the synthesis of 2-azido and 2-iminophosphoranyl homoallylic sulfonamides was explored first. Accordingly, the 2-(2-azidobenzenesulfonyl)-1,2-thiazine 1-oxide (400b) and iminophosphorane (401b) were heated at reflux in tetrahydrofuran in the presence of aqueous HCl. In both cases the reaction proceeded readily yielding the homoallylic sulfonamides (501b) and (502b), which were purified by column chromatography and isolated in 55% and 65% yield, respectively (Scheme 5.11).

![Scheme 5.11](image)

The structure of the homoallylic sulfonamides (501b) and (502b) was, in each case, assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, and IR spectroscopic analysis, together with an accurate mass measurement for the desired ion. As an example, the $^1$H NMR spectrum (400 MHz) of the homoallylic sulfonamide (501b), revealed the presence of methyl group at $\delta_H$ 1.52 ppm (3H, s, CH$_3$) and two sets of CH$_2$ in the region of $\delta_H$ 2.10-2.95 ppm, with the more downfield CH$_2$ being next to the more electronegative nitrogen atom. In the vinylic region, the vinyl CH$_2$ appeared as two sets of doublets at $\delta_H$ 4.62-4.75 ppm and further downfield a broad triplet at $\delta_H$ 5.21 (1H, t, br, J 5.9, NH) indicated the presence of the secondary sulfonamide. In the $^{13}$C NMR spectrum (100 MHz) of the same product, evidence of the allylic CH$_2$ group was given by DEPT-135 analysis, where the CH$_2$ appeared at $\delta_C$ 112.4 ppm, while the two sets of CH$_2$ and the CH$_3$ appeared at $\delta_C$ 40.5, 36.7 ppm and 21.3 ppm, respectively. Analysis by IR spectroscopy showed
the presence of a broad N-H stretch band at $\nu_{\text{max}} \sim 3308$ cm$^{-1}$ and N-H bending absorption at $\nu_{\text{max}} \sim 1575$ cm$^{-1}$, while MS [m/z (ESI+):[M+H]$^+$, 267] further supported the structure of the product.

Similarly, in the case of the homoallylic sulfonamide (502b), $^1$H NMR (400 MHz) revealed the presence of methyl group at $\delta_H$ 1.52 ppm (3H, s, $CH_3$) and two sets of $CH_2$ in the region of $\delta_H$ 2.02-2.93 ppm, with the more downfield $CH_2$ being next to the more electronegative nitrogen atom. In the vinylic region, the vinylic $CH_2$ this time appeared as a singlet at $\delta_H$ 4.40 ppm and downfield of the aromatic region, a broad singlet at $\delta_H$ 6.65 ppm indicated the presence of the secondary sulfonamide. Further enlightenment was given by the presence of additional 15 protons in the aromatic region, which is diagnostic of the triphenyl functionality. This data, together with spectroscopic analysis by $^{13}$C NMR (100 MHz) [(DEPT-135) 22.1 (CH$_3$), 37.4, 41.5 (2x CH$_2$) and 111.9 (CH$_2$)] and IR spectra [N-H absorption at $\sim 3020$ cm$^{-1}$ and a N-H bending absorption at 1585 cm$^{-1}$], along with a consistent MS [m/z (ESI+):[M+H]$^+$, 501] and accurate mass measurement supports the proposed structure.

In the event, the attempted iodocyclisation$^{22a}$ of compounds (501b) and the corresponding iminophosphorane (502b) proved unsuccessful under a number of conditions, yielding only some unchanged starting material together with significant multi-spot TLC degradation (Scheme 5.12). We reasoned that the azide or iminophosphorane functionality present in compound (501b) or (502b) might be intolerant of the iodo based methodologies. Considering this we moved onto synthesize the nitro analogue in order to attempt further iodo cyclisation.

![Scheme 5.12](image-url)
5.2.2 Synthesis of 2-nitroaryl allylic systems \textit{via} 2-(2-nitroaryl)-1,2-thiazine 1-oxide

Access to the 2-(2-nitroaryl)-1,2-thiazine 1-oxides was accomplished \textit{via} the hetero Diels-Alder cycloaddition, as established in Chapter 2 of this thesis. We initially explored this methodology starting from commercially available 2-nitrobenzenesulfonamide (505a: X=SO$_2$) and 2-nitrobenzamide (505b: X=CO) using isoprene as the diene. Accordingly, sulfinylation of the 2-nitrobenzenesulfonamide (505a) and 2-nitrobenzamide (505b) with thionyl chloride using rigorously dry conditions in the presence of pyridine proceeded rapidly at 0\(^\circ\)C to provide the desired N-sulfinyl-2-nitrobenzenesulfonamide (506a), and N-sulfinyl-2-nitrobenzamide (506b), which were used without purification in a Diels-Alder reaction with excess isoprene to furnish 2-(2-nitrobenzenesulfonamide)-1,2-thiazine 1-oxide (507a) and 2-(2-nitrobenzamide)-1,2-thiazine 1-oxide (507b) in 77\% and 67\% yields, respectively (Scheme 5.13).

![Scheme 5.13](image)

The structures of the products were confirmed by the presence of the two CH$_2$ groups in the \textsuperscript{1}H NMR spectrum (400 MHz), shown as four sets of doublet signals in the region of \(\delta_H \sim 1.86-3.70\) ppm, with the more downfield CH$_2$ being, presumably, next to the more electronegative nitrogen atom. The vinylic proton in both cases appeared more deshielded at \(\delta_H \sim 5.68-5.73\) ppm and finally the appearance of the four aromatic protons in the region of \(\delta_H \sim 7.71-8.19\) ppm designated the presence of an ortho-disubstituted benzene ring. The \textsuperscript{13}C NMR (100 MHz) further supported the assignment by revealing one CH$_3$ group at \(\delta_C \sim 24.3-25.0\) ppm, two CH$_2$ groups at \(\delta_C \sim 38.5-54.2\) ppm and finally the vinylic, aromatic and quaternary carbon atoms more downfield of the spectrum in the region of \(\delta_C \sim 117.6-148.3\) ppm. Furthermore, the structural determination was verified by IR spectroscopy, MS and accurate mass measurements.

Having successfully synthesized the 2-(2-nitrobenzenesulfonamide)-1,2-thiazine 1-oxide (507a) and 2-(2-nitrobenzamide)-1,2-thiazine 1-oxide (507b), we then moved on to transform the thiazine rings to their corresponding homoallylic system \textit{via} acid hydrolysis. Accordingly, compounds (507a-b) were heated at reflux in tetrahydrofuran in the presence of aqueous HCl.
both cases the acid hydrolysis proceeded smoothly and upon purification, yielded the (2-nitroaryl)allylic sulfonamide (508a) and (2-nitroaryl)allylic amide (508b) in 65% and 55% yield, respectively (Scheme 5.14).

Evidence of successful ring opening of the thiazine ring in both cases was provided by \(^1\)H NMR, which showed the presence of the new vinylic CH\(_2\) group as pairs of singlets in the region of \(\delta_H \sim 4.69-4.85\) ppm. As expected the CH\(_2\) next to the nitrogen now appeared as a quartet at \(\delta_H \sim 3.25-3.58\) ppm, due to coupling with the adjacent NH and neighbouring allyl CH\(_2\) group, which subsequently appeared as a triplet at \(\delta_H \sim 2.25-2.35\) ppm. Further enlightenment was the diagnostic presence of a broad signal at \(\delta_H \sim 5.35-6.00\) ppm, corresponding to the sulfonamide or amide NH proton. Analysis of both products by \(^{13}\)C NMR (100 MHz) revealed the presence of two relatively shielded CH\(_2\) groups at \(\delta_C \sim 36.9-45.1\) ppm and more importantly the new deshielded CH\(_2\) group at \(\delta_C \sim 112.5-113.4\) ppm. These data, combined with consistent IR spectra verified the structural assignment.

5.2.3 Synthesis of 1-(2'-nitroaryl)-3-iodopyrrolidine via 5-endo-trig iodocyclisation

Following the new synthetic plan as outlined in Scheme 5.10, the next task involved the generation of the iodopyrrolidines (500;\(Y=NO_2\)) via the 5-endo-trig iodocyclisation.\(^{224a}\) Encouragingly, treatment of the homoallylic benzamide (508b) with iodine and sodium hydrogen carbonate in anhydrous acetonitrile at ambient temperature resulted in a smooth cyclisation to generate the iodopyrrolidine (509b) in 91% yield. Conversely, the homoallylic benzenesulfonamide (508a) underwent a slow reaction and, after purification via column chromatography resulted in the desired iodopyrrolidine (509a) and recovered starting material in 53% and 25% yields, respectively (Scheme 5.15).
The structure of the 2-nitroaryl iodopyrrolidines (509) was assigned on the basis of $^1$H and $^{13}$C NMR spectroscopic analysis. Specifically, in each case, the $^1$H and $^{13}$C NMR spectrum (400 MHz), showed the expected three relatively shielded CH$_2$ groups, with each proton being different environmentally, hence appearing as six different CH's in the region of $\delta$H $\sim$1.81-3.86 ppm. The disappearance of both the NB and the allylic CH$_2$ group further supported the proposed structure, which was verified by mass spectrometry which confirmed the presence of the single iodine.

Unfortunately, all attempts to reduce the NO$_2$ group present in (509a-b) were unsuccessful and to date we have been unable to isolate the desired products (481a-b), or any recognizable product.

Finally, the unexpected success of the iodocyclisation in the synthesis of the aziridino-1,2,6-benzothiadiazocine discussed earlier in this section, naturally led us to attempt the transformation of the analogous 2-(aminoaryl)homoallylic amide (510), derived via reduction of (508b) using Pd/C, to the corresponding aziridine fused 8-membered ring. In the event, iodocyclisation of 2-(aminoaryl)homoallylic amide (510) led to a multi spot reaction by TLC. Nevertheless, purification of the crude mixture yielded one major identifiable product, which was assigned by NMR, MS and IR spectra as the 1-(2'-amino-4'-iodoaryl)-3-iodo-3-methylpyrrolidine (511), the product of an unexpected over-iodisation (Scheme 5.17). Attempts to cyclise compound (511) were unsuccessful.
Chapter 5 Discussion - Part IV

The unsuccessful attempts to prepare a 1-(2-aminoaryl)-3-iodopyrrolidine (481) from the corresponding 1-(2-nitroaryl)-3-iodopyrrolidine (509), together with the failure of 2-aminoaryl homoallylic amide (510) to undergo ring cyclisation to the desired aziridino fused 8-membered ring meant that possibilities for the synthesis of pyrrolobenzothiadiazepines via this route were exhausted. With a reliable, but unexpected, synthesis of the aziridino benzothiadiazocines in hand, our attention now turned to exploring alternative avenues to produce such aziridine fused 8-membered ring heterocycles with the further intention to verify this unusual structure by alternative synthesis.

5.3 Attempted alternative synthesis of aziridine fused benzothiadiazocines

Recently, Ciufolini et al.\textsuperscript{235} have demonstrated the utility of the tethered alkenic aryl azide (512) for the synthesis of N-aryl aziridine (514), by simply refluxing compound (512) in toluene, followed by dediazoniation of the corresponding triazoline (513) via irradiation in benzene at room temperature (Scheme 5.18).

In the context of our interest in the application of 1,2-thiazine 1-oxide based methodologies in heterocyclic synthesis, together with the intention to synthesis aziridine fused 8-membered ring heterocycles, we envisaged a synthetic approach utilizing a similar methodology to that above. In this respect, the plan was to heat homoallylic sulfonamido arylazide (501), derived from 2-(2-azidobenezenesulfonyl)-1,2-thiazine 1-oxides (400) via acid hydrolysis, to generate the triazoline intermediate (515) via a 1,3-dipolar cycloaddition process, which upon extrusion of
nitrogen would furnish the desired aziridine (496) [Scheme 5.19]. This would confirm the structural assignment made in section 5.1.2, above, and offer a more straightforward route to compound (496).

![Scheme 5.19](image)

5.3.1 Thermolysis of homoallylic sulfoamido arylazide

Following the synthetic plan, we attempted to transform the homoallylic sulfonamido azide (501a) into the corresponding aziridinobenzothiadiazocine (496a) using DMF. Intriguingly, heating a solution of homoallylic sulfonamido arylazide (501a) in DMF resulted in the isolation of one new product, which, was not the triazole (515a), nor the aziridine (496a), but was, in fact, the pyrrolo-1,2,4-benzothiazine 1,1-dioxide (516a) [Scheme 5.20], obtained in 18% yield.

![Scheme 5.20](image)

The structure of the product was assigned on the basis of $^1$H NMR, $^{13}$C NMR, $^1$H-$^1$H-COSY, $^1$H-$^{13}$C-COSY, MS, IR spectra and accurate mass measurements. The appearance of a broad peak at $\delta_H$ 4.28 ppm, corresponding to the aryl $NH$ group, together with the disappearance of the azide, vinylic $CH_2$ group and the $NH$ group of the sulfonamide. Two dimensional $^1$H-$^{13}$C correlation spectrum allowed a definite assignment of the resonance due to the chiral $CH$ group,
whose carbon resonance occurred at an expected position around δ_C 71.2 ppm, while the proton resonance was shifted to the region of δ_H 5.48 ppm, indicating its being next to the two electronegative nitrogen atoms. The ^1H-^1H COSY spectrum allowed all of the other proton resonances to be assigned and showed that the chiral methine was coupling to the NH and to a methylene group, which in turn was coupling to a second methylene group, which was then coupled to a third methylene, whose protons appeared more downfield at δ_H 3.20 ppm and 3.57 ppm, corresponding to being next to the more electronegative nitrogen atom. The fact that the two dimensional NMR shows a clear NHCHCH₂CH₂ linkages, rules out the alternative eight membered ring triazoline and aziridine fused system, where we would expect a CH₂-CH-CH₂-CH₂ linkage. These data combined with IR spectroscopic analysis [NH absorption (strong) at ν_max 3363 cm⁻¹], MS [m/z (ESI+): [M+H]+, 225], high resolution mass spectra and X-ray crystallographic analysis (figure 1.2) confirmed the structural assignment.

Figure 5.2: X-ray crystal structure of 1,2,7-pyrrolobenzothiazine-1,1-dioxide (516a)
With regards to mechanism it was thought, given the use of DMF at reflux as solvent, that initial nitrene formation is followed by ring closure to a nine membered ring, free radical migrations and closure to a 6,5-fused system, perhaps akin to that shown in Scheme 5.21.

![Scheme 5.21](image)

In order to verify this proposed mechanism, a further two examples of homoallylic sulfonamido azides (501b: R¹=H, R²=Me) and (501c: R¹=R²=Me), were heated at reflux in DMF. In both cases thermolysis proceeded readily, however, in each case, the major products isolated were not the expected pyrrolo-1,2,4-benzothiazine 1,1-dioxides (516b) and (516c), but were in fact the differently substituted pyrrolo-1,2,4-benzothiazine-1,1-dioxides (517b) and (517c), respectively (Scheme 5.22). This indicates a more complex mechanism to that proposed in Scheme 5.21, whereby a rearrangement of the carbon backbone must occur (see later).

![Scheme 5.22](image)

Again, the structures of the products were assigned on the basis of their \(^1\)H NMR, \(^{13}\)C NMR, \(^1\)H,\(^1\)H-COSY, \(^1\)H,\(^{13}\)C-COSY, MS, IR spectra and accurate mass measurements. In both cases these data contrasted markedly with those expected for the supposed products (516b) and...
In the case of compound (517b), the most notable feature was a clear CH$_2$-CH$_2$-CH$_2$ chain, thus ruling out structure (516b) in which the expected CH-CH(Me)-CH$_2$-CH$_2$ linkage was not present. Further enlightenment was given by the presence of the methyl group at $\delta_H$ 1.78 ppm, appearing as a singlet, giving a strong indication that the methyl group is on the bridgehead, and further ruling out structure (516b), where the methyl is expected to be split into a doublet by the neighbouring methine. A deshielded quaternary carbon at $\delta_C$ 79.0 ppm would seem to correspond to the deshielded bridgehead carbon.

Similarly, a detailed analysis of compound (517c) by $^1$H-$^{13}$C COSY, now showed the presence of two methyl groups, whose resonance occurred at $\delta_C$ 18.7 ppm and 28.3 ppm. In the $^1$H-$^1$H COSY spectrum these methyl groups appeared as a doublet at $\delta_H$ 1.07 ppm (3H, d, $J$ 6.6, CH$_3$CH), as a result of coupling to the adjacent CH group, while the other appeared as an unsplit singlet at 1.78 ppm (3H, s, CCH$_3$), indicating its position on the bridgehead, and evidently ruling out the (516c) structure. As expected, the CHMe group appeared more complex ($\delta_H$ 2.36-2.53 ppm (1H, m, CH$_2$CHMeCH$_2$), as a result of the coupling with the methyl group and with the neighbouring methylene groups, that are present on each side of the CHMe group. The CH$_2$ next to the nitrogen appeared more deshielded at $\delta_H$ 3.58 ppm (1H, dd, $J$ 9.7, 9.7 NCH-H) and $\delta_H$ 3.23 ppm (1H, dd, $J$ 10.3, 7.0, NCH-H), while the CH$_2$ between the two chiral centre appeared relatively shielded at $\delta_H$ 2.21 ppm (1H, dd, $J$ 13.0, 7.1, CMeCH-HCHMe) and 1.88 ppm (1H, dd, $J$ 12.9, 10.3, CMeCH-HCHMe). Furthermore, $^1$H-$^1$H COSY clearly showed the CH$_2$CHMeCH$_2$ linkage, together with an IR spectrum that supported the structural determination by showing the NH stretch absorption at $v_{\text{max}} \approx 3366$ cm$^{-1}$, while the mass spectrometry (ESI+) and accurate mass measurement verified the structural assignment.

As discussed above, the mechanism put forward in Scheme 5.21 for compound (516a) cannot apply here, as the products expected [516b and 516c] do not form. An alternative mechanism, which would explain the formation of (517a) as well as that of (517b) and (517c) is shown in Scheme 5.23 and involves a rearrangement of the carbon backbone.
5.4 Conclusion

A novel synthetic route to aziridino-1,2,7-benzothiadiazocines (496) was established via an homoallylic arylamino sulfonamide iodocyclisation strategy. Advantageously, the use of 2-(2-aminobenzenesulfonyl)-1,2-thiazine-1-oxides, obtained in excellent yields via a Staudinger/hydrolysis sequence of the corresponding azides, allowed access to the required homoallylic arylamino sulfonamides (480). Attempted synthesis of iodopyrrolidines via the azide or iminophosphorane, proved to be problematic. These difficulties were addressed by the use of the corresponding nitro compound where iodocyclisation yielded the 1-(2'-nitroaryl)-3-iodopyrrolidine (509), through 5-endo-trig iodocyclisation. However, these later failed to be reduced to the corresponding amine. Interestingly, in the case of the analogous homoallylic arylazido sulfonamides (501), it was found that thermolysis in DMF proved to be a good method for the synthesis of pyrrolo-1,2,4-benzothiazine 1,1-dioxides (517), a process that occurs via an unusual mechanism involving a rearrangement of the carbon backbone.
6.1 Attempted synthesis of aziridinopyrrolobenzodiazepines and pyrrolobenzodiazepines

As part of our interest in the synthesis of pyrrolobenzothiadiazepines and pyrrolobenzodiazepines, we have so far, in this thesis, explored the 1,3-dipolar cycloaddition reaction of nitrile oxides to pyrrolobenzothiadiazepines and further, in the previous section, described the intramolecular azide cycloaddition to alkenes. In a continuation of our pursuit to develop a novel synthetic strategy for the synthesis of tetracyclic pyrrolobenzothiadiazepine and pyrrolobenzodiazepine heterocycles, this final chapter is to unite these two themes by exploring 'click chemistry'\textsuperscript{236} approaches to these heterocycles. Currently, the term click chemistry has become synonymous with the Huisgen 1,3-dipolar cycloaddition between a terminal alkyne and an azide,\textsuperscript{236a} and has found many applications in organic chemistry,\textsuperscript{237} drug discovery,\textsuperscript{238} bioconjugations,\textsuperscript{239} materials science,\textsuperscript{240} and the synthesis of natural product derivatives,\textsuperscript{241} and polymers.\textsuperscript{242}

The concept of this strategy, as depicted in Scheme 6.1, relies upon the synthesis of a C-ring (the pyrrole) that is substituted with the 1,3-dipolarophile (518), which in turn, would be coupled to a pre-formed A-ring azidic component to provide access to the desired backbone containing both the azide dipole and the alkene, alkyne or nitrile dipolarophiles as shown in compound (520). Subsequent intramolecular 1,3-dipolar cycloaddition would, hopefully, furnish the novel tetracyclic heterocycles (521). This chapter will describe the synthesis and uses of alkene, alkyne and nitrile in the synthesis of target compounds (521).

![Scheme 6.1]

The route that we investigated first is shown in Scheme 6.2 and relies upon the generation of 2-ethylene pyrrolidine (526), which is readily available from Fmoc protected ethylene pyrrolidine (525). Access to the Fmoc protected ethylene pyrrolidine (525) would be accomplished via a Wittig reaction\textsuperscript{243} of the corresponding aldehyde (524), derived from N-protection of the commercially available (S)-prolinol (522), followed by oxidation of the Fmoc
protected prolinol (523). Deprotection of the Fmoc protected ethylene pyrrolidine (525) and *in situ* condensation reaction of the resulting free amine (526) to 2-azidobenzoyl chloride, derived from a diazotization and chlorination sequence from anthranilic acid, would generate the desired cyclisation precursor (527).

![Diagram of synthetic process](image)

**Scheme 6.2**

### 6.1.1 Synthesis of N-Fmoc protected (S)-prolinol

Following the proposed methodology in Scheme 6.2, the initial requirement was to protect the nitrogen of (S)-prolinol with Fmoc. Accordingly, a solution of (S)-prolinol (522) was treated with 9-fluorenylmethyl chloroformate and sodium hydrogen carbonate in anhydrous dichloromethane at ambient temperature under nitrogen (Scheme 6.3). The reaction was found to proceed readily and the purification of the crude mixture yielded the Fmoc-protected (S)-prolinol (523) in 82% yield.

![Diagram of synthetic process](image)

**Scheme 6.3**

The incorporation of the Fmoc group was confirmed by $^1$H and $^{13}$C NMR spectroscopic analysis of the products. Significantly, the $^1$H NMR spectrum (400 MHz) indicated the additional presence of the 9-fluorenylmethoxycarbonyl CH and CH$_2$ groups, split by each other as a triplet at
\( \delta_H \sim 4.30 \text{ ppm} \) and a doublet at \( \delta_H \sim 4.50 \text{ ppm} \), respectively. In the aromatic region, the fluorenyl CH groups appeared in the region of \( \delta_H \sim 7.25-7.45 \text{ ppm} \) and \( \delta_H \sim 7.55-7.80 \text{ ppm} \), together with the expected fluorenyl carbons in the aromatic region of the \(^{13}\text{C}\) spectrum and the deshielded carbamate \( \text{C}=\text{O} \) group at \( \delta_C 156.3 \text{ ppm} \). Further evidence of the carbamate group was provided by the occurrence in the IR spectrum of a \( \text{C}=\text{O} \) stretching absorption at \( \nu_{\text{max}} 1681 \text{ cm}^{-1} \).

### 6.1.2 Synthesis of N-Fmoc protected (S)-prolinol via oxidation

Having successfully protected the nitrogen of the (S)-prolinol, the next objective was to synthesise the corresponding aldehyde via an oxidation. The use of Dess-Martin periodinane was examined first due to its mild conditions and ease of use.\(^\text{180}\) Accordingly, the N-Fmoc prolinol (523) was treated with Dess-Martin periodinane in anhydrous dichloromethane at ambient temperature under nitrogen (Scheme 6.4). The oxidation proceeded smoothly yielding the desired aldehyde (524) in 96% yield, after purification by column chromatography (Scheme 6.4).

![Scheme 6.4](image)

The successful oxidation of the alcohol was confirmed with \(^1\text{H}\) NMR (400 MHz) which indicated the additional presence of the aldehyde proton as a singlet at \( \delta_H 9.57 \text{ ppm} \) (1H, s, \( \text{CHO} \)). Additionally, the presence of the carbonyl moiety was demonstrated in the \(^{13}\text{C}\) NMR spectra (100 MHz) of the products by the appearance of a deshielded aldehyde \( \text{CHO} \) peak at \( \delta_C 199.8 \text{ ppm} \), together with the disappearance of the \( \text{CH}_2\text{OH} \) group. Further confirmation of the desired structure was obtained from the IR spectrum, which showed the presence of a carbonyl \( \text{C}=\text{O} \) stretch in the range of \( \nu_{\text{max}} 1732 \text{ cm}^{-1} \).
6.1.3 Synthesis of the (2S)-N-(9′-fluorenymethoxycarbonyl)-pyrrolidine-2-ethene via a Wittig reaction

The Wittig reaction, a process by which phosphorus ylides convert aldehydes and ketones to alkenes, is one of the most important reactions in organic chemistry and is widely used as a key step in many natural product syntheses as well as in industrial processes. The phosphorus ylides (Wittig reagent) are usually prepared in two step process involving an $S_N2$ reaction between an alkyl halide and triphenylphosphine, followed by deprotonation of the corresponding alkyltriphenylphosphonium salt with a strong base such as $n$-BuLi, NaH, or $t$-BuOK. Although, the ylides can be isolated, they are usually produced and used as reagents immediately, and consequently, exposure to aldehydes or ketones, results in a nucleophilic addition of the phosphorus ylide to the carbonyl compound to form an unstable oxaphosphetane ring, which promptly fragments to give the desired alkene and triphenylphosphine oxide as side product.

Accordingly, the synthesis of the desired alkene was attempted via the Wittig reaction of the Fmoc protected carbonylpyrrolidine (Scheme 6.6), where the latter was generated from the readily available methyltriphenylphosphonium bromide by deprotonation using butyllithium in anhydrous tetrahydrofuran.

Scheme 6.5

Scheme 6.6
However, it was found that the Wittig reaction afforded the desired alkene (525) only in low yields (20%). The structure of the product was confirmed by $^1$H NMR (400 MHz) which indicated the disappearance of the aldehyde proton and the appearance of three vinylic protons in the region of $\delta_H 4.90-5.90$ ppm [$4.90-5.15$ ppm (2H, m, $=\text{CH}_2$) and 5.77 ppm (1H, m, br, $=\text{CH}$)]. Additionally, the presence of the vinylic CH and CH$_2$ groups was demonstrated in the $^{13}$C NMR spectra (100 MHz) of the products by the appearance of peaks at $\delta_C 137.9$ and 114.2 ppm, respectively, together with the disappearance of the CHO group.

### 6.1.4 Attempted synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene

The low yield of the alkene was attributed to competitive base induced cleavage of the Fmoc protecting group in both the product and starting material. In the event, the attempted coupling of the C-ring component via deprotection of N-Fmoc alkene (525) and subsequent addition of the 2-azidobenzoyl chloride to the reaction mixture resulted in a multi-spot TLC (Scheme 6.7). Purification of the crude product yielded only the unchanged 2-azidobenzoyl chloride. Consequently, we moved on to explore alternative means to bring about the synthesis of the desired compound (527).

![Scheme 6.7](image)

Fortunately, work by Ikeda$^{248}$ on the construction of optically active pyrrolizidinone ring systems (536) via the $\alpha$-chlorosulfides (535), involved the use of (S)-prolinol (522) for the generation of the (S)-(−)-2-ethenyl-1-ethoxycarbonylpyrrolidine (533). Thus, in Ikeda’s$^{248}$ work $N$-protection of (S)-prolinol (522), followed by oxidation of the corresponding (S)-N-ethoxycarbonylprolinol (531) with sulfur trioxide (SO$_3$)-pyridine in dimethyl sulfoxide gave the aldehyde (532) in 74% yield. Access to the alkene (526) was accomplished by means of the Wittig reaction of the aldehyde (532) using triphenylphosphonium methylide, followed by hydrolysis of the corresponding $N$-protected alkene (533) with potassium hydroxide/hydrazine hydrate in refluxing ethylene glycol. Treatment of the resultant amine (526) with phenylthio- or
methylthio-acetyl, followed by chlorination of the resultant acetamides \((\text{534})\) with \(N\)-chlorosuccinimide furnished the \(\alpha\)-chlorosulfides \((\text{535})\).

Based on this finding, the above method was utilized as an approach to access the desired C-ring component \((\text{526})\) as discussed below.

### 6.2 Synthesis of aziridinopyrrolobenzodiazepines and pyrrolobenzodiazepines via \(N\)-ethyl ester

#### 6.2.1 Synthesis of \((S)-(-)\)-1-ethoxycarbonylpyrrolidine-2-methanol

Following the method outlined in Scheme 6.8, the initial requirement was to protect the prolinol nitrogen. Accordingly, \((S)\)-prolinol \((\text{522})\) was treated with ethyl chloroformate in 4M sodium hydroxide at 0°C. The reaction was found to have proceeded smoothly and upon purification of the crude mixture yielded the desired \(N\)-protected prolinol \((\text{531})\) in 93% yield (Scheme 6.9).
6.2.2 Synthesis of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde

With the success of the N-protection, the next objective was to synthesize the corresponding aldehyde via an oxidation. Amongst the various oxidizing agents available, the use of pyridinium chlorochromate was examined first.

Pyridinium chlorochromate (PCC) is a useful reagent for the facile and efficient oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones, respectively. The reagent is usually prepared easily and safely by adding one equivalent of pyridine to a solution of one equivalent of chromium(VI) oxide and concentrated hydrochloric acid.

![Scheme 6.10]

The mechanism by which the pyridinium chlorochromate oxidation takes place engages two steps. The first step involves the formation of a chromate ester. Once the chromate ester is formed, it undergoes an elimination reaction to generate the carbonyl group as outlined in Scheme 6.11.

![Scheme 6.11]

Accordingly, a solution of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-methanol (531) in dichloromethane was treated with pyridinium chlorochromate at ambient temperature and monitored by TLC. The reaction was found to be slow but was complete in three hours, with TLC indicating one new product. Workup with ether, followed by purification via column chromatography, resulted in the isolation of the desired aldehyde (532) in 56% yield. Although the necessary oxidation had occurred, isolation of the product from the sticky tar deposit of the chromium byproduct proved problematical on many occasions, and for this reason we turned attention to the use of Swern conditions and sulfur trioxide pyridine complex as alternative oxidants, with the hope to improve the yield and to find an oxidizing reagent which was...
easy to use and handle. In the event, it was found that the use of sulfur trioxide pyridine complex turned out to be the best oxidant, as its use led to the desired product in high yields as shown in Table 6.1. It is also notable that Ikeda reports that this oxidant leads to no racemisation, in contrast, for example, to Swern oxidation.

\[
\begin{array}{c}
\text{[O]} \\
\text{531} \\
\text{532}
\end{array}
\]

\text{Scheme 6.12}

<table>
<thead>
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<th>Entry</th>
<th>Method</th>
<th>Yield of 532 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>PCC, DCM, r.t., 3 hrs</td>
<td>56</td>
</tr>
<tr>
<td>b</td>
<td>Et\textsubscript{3}N, DMSO, SO\textsubscript{3}-pyridine complex, 0°C, 2 hrs</td>
<td>83</td>
</tr>
<tr>
<td>c</td>
<td>(COCl\textsubscript{2}, DMSO, DCM, DIEA</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 6.1: % yields of the aldehyde

6.2.3 Synthesis of (S)-(−)-2-ethenyl-1-ethoxycarbonylpolyrrolidine

Having established an efficient route through to the aldehyde (532), the next objective was to convert the aldehyde to the corresponding alkene moiety via the Wittig reaction. Initially, we decided to implement the Wittig conditions as described by Ikeda et al.\textsuperscript{248} using sodium hydride in DMSO to generate the phosphorus ylide from the readily available methyltriphenylphosphonium bromide. Accordingly, a preformed mixture of methyltriphenylphosphonium bromide in DMSO in the presence of NaH was treated with a solution of aldehyde (532) in DMSO at room temperature and stirred for 1 hour (Method A). Work-up with a mixture of water and hexane, followed by purification of the crude mixture via column chromatography, resulted in the isolation of the desired product (533) in 50% yield as a mixture of rotamers. It was also found that treating the methyltriphenylphosphonium bromide using n-butyllithium as base (Method B) generated the phosphorus ylide, and subsequent reaction with the aldehyde (532) afforded the alkene (533) in 49% yield.
The structure of product (533) was assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, IR spectroscopic analyses and accurate mass measurement. Specifically, $^1$H NMR showed evidence of the incorporation of an alkene by the occurrence of the vinylic methine and methylene peaks at $\delta_{H}$ 5.74 ppm (1H, s, br, $=CH$) and 5.09 ppm (2H, m, $=CH_2$), respectively. The three pyrrolidine CH$_2$ groups appeared as broad multiplets in the region of $\delta_{H}$ 1.70-3.50 ppm. As expected the chiral methine appeared more deshielded at $\delta_{H}$ 4.32-4.39 ppm (1H, m, br, NCH), due to the neighbouring electronegative nitrogen. Lastly, the presence of a methyl group at $\delta_{H}$ 1.24 ppm (3H, m, br, CH$_3$) together with the relatively deshielded peak at $\delta_{H}$ 4.13 ppm, indicated the ethyl ester still intact. These data combined with spectroscopic analysis by $^{13}$C NMR (100 MHz) [(DEPT-135) $\delta_{C}$ 22.4/23.3, 31.1/31.8, 46.1/46.3 (3x CH$_2$) and 113.7/114.0, 138.1/138.4 (vinylic CH$_2$ and CH, respectively) as mixture of rotamers], IR spectroscopic [alkene absorption at $\nu_{\text{max}}$ 1698 cm$^{-1}$], MS [m/z (ESI+): [M+H]$^+$, 170] and correct accurate mass measurement supported the structure assignment.

### 6.2.4 Synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene

With the alkene in hand, attention turned to the use of potassium hydroxide and hydrazine in refluxing ethylene glycol as the literature conditions to generate the free amine (526), which would be reacted in situ with 2-azidobenzoyl chloride, derived from chlorination of 2-azidobenzoic acid with thionyl chloride, to gain access to the desired cyclisation precursor (527). Accordingly, a solution of carbamate (533) in ethylene glycol was heated at reflux in the presence of potassium hydroxide and hydrazine hydrate. Upon completion, the reaction mixture was cooled, quenched with aqueous sodium hydroxide and extracted with diethyl ether. Subsequent treatment of the ethereal solution with triethylamine and a solution of 2-azidobenzoyl chloride in diethylether, afforded the desired coupled precursor (527) as a rotameric mixture in 49% yield after work up and purification by column chromatography (Scheme 6.14).
The structural assignment of the coupled precursor (527) was performed in the view of the $^1H$ NMR, $^{13}C$ NMR, MS, IR and accurate mass measurement. The $^1H$ NMR spectrum (400 MHz) established a rotameric mixture, with the doubling of the desired peaks. Evidence of successful coupling reaction was confirmed by the appearance of four aromatic protons in the region of δ$_H$ 6.90-7.50 ppm [6.94-7.23 (3H, m, ArH); 7.21-7.34 (1H, m, ArH)] corresponding to the ortho-disubstituted benzene ring, the presence of the distinctive pyrrolidine signals, together with the disappearance of the methyl and methylene groups that were diagnostic of the ethyl ester in the protected pyrrolidine. The structure of the product was further confirmed by $^{13}C$ NMR (100 MHz) [(DEPT-135), which showed the presence of three CH$_2$ groups in the region of δ$_C$ 20.5-49.5 ppm, a CH resonance at 57.9 and 60.6 ppm (rotamers) and the vinylic, aromatic and quaternary carbon atoms more downfield at δ$_C$ 113.9-166.9 ppm. These data combined with IR spectroscopic analysis [$N_3$ absorption (strong) at $\nu_{max}$ 2128 cm$^{-1}$ and C=O absorption at $\nu_{max}$ 1718 cm$^{-1}$], MS [m/z (ESI+): [M+H]$^+$, 243] and accurate mass measurement supported the structural assignment.

### 6.2.5 Synthesis of the pyrrolobenzodiazepine targets

With precursor (527) in hand, the final requirement was to explore the synthesis of tetracyclic pyrrolobenzodiazepines via intramolecular 1,3-dipolar cycloaddition. Thus, a solution of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene (527) in DMF was heated at reflux, whilst being monitored carefully by TLC. Purification by column chromatography of the crude reaction mixture gave one major product. The structure of the compound was assigned by spectroscopic analysis as the hydroxypyrrolobenzodiazepine (539) formed in 38% yield (Scheme 6.15).
The structure of the hydroxypyrrolobenzodiazepine (539) was assigned on the basis of $^1$H NMR (400 MHz) spectrum, where the OH group was evident as a broad singlet at $\delta_{H}$ 5.24 ppm, a feature confirmed by infra-red analysis, while the methyl group on the adjacent carbon was present at $\delta_{H}$ 1.52 ppm as a singlet. Significantly, one of the C-3 protons of the pyrrolidine ring appeared at $\delta_{H}$ 3.18 ppm (1H, td, $J$ 14.5, 3.0, CH-H), while the other resonated at 4.68 ppm (1H, dt, $J$ 10.4, 3.7, CH-H), being shifted more downfield due to the presence of the electronegative OH group at C-4. The pyrrolidine C-1 and C-2 protons appeared in the region of $\delta_{H}$ 1.90-2.72 ppm [1H, m, CH-H), 2.08-2.19 (1H, m, CH-H) and 2.70 (2H, q, $J$ 8.6, 5.0, CH$_2$)], with the more downfield CH$_2$ being next to the more electronegative nitrogen atom. Further support for the proposed structure was provided by $^{13}$C NMR (100 MHz) (DEPT-135), which revealed the presence of three relatively shielded CH$_2$ groups at $\delta_{C}$ 22.2, 35.6 and 37.5 ppm, and a deshielded quaternary carbon at $\delta_{C}$ 75.1 ppm, indicative of the C-4 attached to OH. IR analysis also confirmed the presence of alcohol by the occurrence of a relatively broad OH absorption at $\nu_{max}$ 3315 cm$^{-1}$. These data combined with a consistent MS spectrum [m/z (ESI+): [M+H]$^+$, 231] and accurate mass measurement, verified the structural assignment, and beyond doubt confirmed that the molecule contained an unexpected extra oxygen atom.

Mechanistically, this transformation might proceed via the mechanism shown in Scheme 6.16, whereby high temperature free radical formation from the triazoline leads to loss of nitrogen and rearrangement of the resultant methylene radical to a tertiary carbon radical. Oxygen insertion (the reaction was not done under an inert atmosphere or in degassed solvent) followed by cleavage of the O-O bond in the peroxide would then give the proposed product. Similar mechanisms involving initial nitrene formation can also be written and cannot be discounted at this temperature.
Although, the thermolysis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene (527) proved interesting in generating a tricyclic pyrrolobenzodiazepine analogue (539), it was clear that the high temperature associated with DMF was problematic. Subsequently our attention next turned to the use of acetonitrile, as it was envisaged that the use of a solvent with a lower boiling point to that of DMF may reduce the chance of free radical formation and thus, (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene (527) could cyclise to achieve the desired tetracyclic pyrrolobenzodiazepine (537). In the event, heating (2S)-N-(2-azidoaroyl)-pyrrolidine-2-ethene (527) in acetonitrile at reflux, resulted in the isolation of an inseparable mixture of two new products. The structure of the products were confirmed by spectroscopic analysis and were found to be the aziridinopyrrolobenzodiazepine (538) and pyrrolobenzodiazepine (540) in a 3:1 ratio, respectively. Interestingly, heating the precursor (527) in dichloromethane afforded the same products, however this time in a 1:1 ratio.
Diagnostic signals in the $^1$H NMR were the methyl group of (540) together with a doublet for each of the aziridine methylene protons where these protons coupled to the neighbouring methine but not to each other (typical of such aziridines).\textsuperscript{229} Mass spectroscopic analysis confirmed the loss of N$_2$, i.e. the triazoline (537) was not isolated.

With regards to mechanism, it is believed that the initial 1,3-dipolar cycloaddition does take place (nitrene being unlikely at the lower temperature) to form the triazoline, which then undergoes extrusion of nitrogen by two different routes to yield the two products (538) and (540) as shown in Scheme 6.18.

Interestingly and concurrent with the work in this thesis, Broggini\textsuperscript{251} has recently shown that compound (527) [which he constructed by a different route] gives the triazoline (537) as the only product in refluxing carbon tetrachloride. A personal communication from Broggini indicated that the formation of aziridine (538) or imine (540) was not observed.

Finally in this section, it is worth mentioning that attempts to convert the prolinol coupled product (541) into the alkene (527) \textit{via} oxidation followed by Wittig olefination (Scheme 6.19), failed at the Wittig stage, possibly due to nucleophilic attack of the ylide at the azide.
6.3 Synthesis of triazolopyrrolobenzodiazepines via alkyne

Having established the validity of an intermolecular 1,3-dipolar cycloaddition between an azide and a terminal alkene within this system, we next explored the feasibility of the process using an alkyne as the dipolarophile, a process considered to be the classic "click" reaction. This process was anticipated to be easier than the alkene, in that cycloaddition leads to 1,2,3-triazoles which are stable and are isolated as the single products. In this respect, the idea was to convert the aldehyde (532) to the corresponding alkyne (544), via the Corey-Fuchs approach, and in turn couple it to 2-azidobenzoyl chloride after deprotection. This would generate the key cyclisation precursor (546), containing the azidic dipole and terminal alkyne. Ring closure would then give the triazole (547) which, besides being a tetracyclic pyrrolobenzodiazepine analogue, is an interesting analogue of the anxiolytic drug bretazenil, as discussed before. As discussed above, Wittig type reactions on the aldehyde (542) derived from 2-azidoaroyl prolinol (541) are not successful (Scheme 6.19), and hence routes from aldehyde (542) were not investigated further. The focus in this section is therefore on the synthesis and coupling of alkyne (545) as the route to cyclisation precursor (546).

![Scheme 6.20](image)

6.3.1 Corey-Fuchs approach to the alkyne

The conversion of aldehydes into alkynes is a key challenge. One solution, and the one used here, is the so called Corey-Fuchs approach whereby an aldehyde is transformed into the corresponding alkyne in two steps. The first step is comparable to a Wittig reaction and leads to a dibromoalkene (549) via the ylide (548).
Chapter 6 Discussion-Part V

In the second step a lithium base (BuLi, LDA) generates a bromoalkyne (550) intermediate via dehydrohalogenation, which undergoes metal-halogen exchange under the reaction conditions and yields the terminal alkyne (551) upon work-up (Scheme 6.22).

Based on this finding, the initial requirement was to generate dibromomethyltriphenylphosphonium bromide. Accordingly, a solution of triphenylphosphine in anhydrous dichloromethane was treated with carbon tetrabromide at ambient temperature and monitored by TLC. The reaction was very fast and was complete in 30 minutes, after which workup with aqueous dichloromethane, followed by precipitation using acetonitrile, resulted in the isolation of the desired salt in excellent yield (Scheme 6.24).
The following step involved an in situ generation of the ylide and its concomitant reaction with the aldehyde (532) to form the 1,1-dibromoalkene (543). Therefore, treatment of the dibromomethyltriphenylphosphonium bromide with t-BuOK in anhydrous tetrahydrofuran at ambient temperature resulted in a yellow-brown reaction mixture, indicating the formation of the ylide. The aldehyde (532) was added to the mixture at ambient temperature and stirred for 2 hours. The reaction was found to have proceeded smoothly, and the desired 1,1-bromoalkene (543) was isolated as a mixture of rotamers in 65% yield after workup and purification by column chromatography (Scheme 6.25).

The structure of the product (543) was confirmed by spectroscopic analysis. Specifically, the $^1$H NMR spectrum (400 MHz) showed the disappearance of the aldehyde proton and the appearance of one vinylic proton in the region of $\delta_H \approx 6.15$ ppm. The three CH$_2$ groups of the pyrrolidine ring resonated in the region of $\delta_H \approx 1.50$-3.30 ppm, with the more downfield CH$_2$ being, presumably, next to the more electronegative nitrogen atom. The chiral CH group appeared more deshielded at $\delta_H 4.22$ ppm, while the methyl and methylene groups of the ethyl ester were also present and appeared at $\delta_H 1.03$ ppm (3H, t, $J 5.7$, CH$_2$CH$_3$) and 3.88 ppm (2H, q, $J 7.1$, CH$_2$CH$_3$), respectively. The $^{13}$C NMR (100 MHz) further supported the assignment by the presence of four CH$_2$ groups at $\delta_C 21.9/22.8$, 29.4/30.1, 43.9/45.0, 57.5/58.5 ppm and two CH groups at $\delta_C 54.4/55.0$, 137.7/137.9 ppm. These data, in combination with consistent MS [m/z (ESI+): [M+H]$^+$, 328] confirmed the structure of the 1,1-dibromoalkene (543).

Following the Rassat et al. approach, the 1,1-dibromoalkene (543) was next treated with t-BuOK in anhydrous tetrahydrofuran (Scheme 6.26). It was observed that the dehalogenation reaction proceeded readily at ambient temperature to provide the desired alkyne (544) in 100% yield, again as a rotameric mixture.
6.3.2 Synthesis of (2S)-N-(2-azidoaroyl)-2-ethynylpyrrolidine

With the alkyne (544) in hand, the next objective was to cleave the carbamate and couple the corresponding free amine (545) in situ to 2-azidobenzoyl chloride to generate the key cyclisation precursor (546). Accordingly, alkyne (544) in ethylene glycol was heated at reflux in the presence of potassium hydroxide and hydrazine hydrate. Upon completion, the reaction mixture was cooled, quenched with aqueous sodium hydroxide solution and extracted with diethyl ether. Subsequent treatment of the ethereal solution with triethylamine and a solution of 2-azidobenzoyl chloride in diethyl ether afforded the desired compound (546) as a rotameric mixture in only 11% yield, after workup and purification by column chromatography.

Evidence of a successful deprotection/coupling sequence of the (S)-(−)-1-ethoxycarbonylpyrrolidine-2-prop-1-yne (546) was provided by $^1$H NMR, which showed the expected pyrrolidine methylene and methine protons together with the additional presence of the four aromatic protons in the region of $\delta_H$ 7.00-7.50 ppm, while more downfield in the spectrum, the presence of a signal at $\delta_H$ 4.63 ppm (1H, s, alkyne-CH) verified the presence of the alkyne. Additionally, $^{13}$C NMR spectra (100 MHz) of the product showed the alkyne quaternary carbon and CH resonances at $\delta_C$ 114.6 ppm and 118.5/119.6 ppm, respectively, together with the expected aromatic carbons in the region of $\delta_C$ ~124.0-134.0 ppm and the deshielded carbonyl C=O group at $\delta_C$ 167.8 ppm. The IR spectrum of the product showed a C=O stretching absorption at $v_{max}$ 1717 cm$^{-1}$, and the diagnostic presence of absorptions at 3394 cm$^{-1}$, 2435 cm$^{-1}$ and 2127 cm$^{-1}$,
corresponding to the alkyne C-H and carbon-carbon triple bond stretch and \( \text{N}_3 \) stretch, respectively.

6.3.3 Synthesis of \((S)-(-)-1\text{-t-butoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene)}\)

Although the necessary deprotection/coupling sequence of the alkyne (544) with 2-azidobenzoyl chloride in refluxing ethylene glycol proved successful, the yields of the desired cyclisation precursor were low. The reason for this is uncertain; however the instability of the intermediate (545), together with the use of high temperature during the deprotection of the carbamate might be contributing factors. In considering alternative strategies, we turned to the use of a Boc protecting group and hoped that it would behave differently. Accordingly, a solution of dibromomethylenetriphenylphosphorane in anhydrous tetrahydrofuran, generated \emph{in situ} from dibromomethyltriphenylphosphonium bromide and \( t\)-BuOK, was treated with the readily available \( N\)-Boc-prolinal (552) at ambient temperature whilst being monitored by TLC (Scheme 6.28).

\[
\begin{align*}
\text{N-Boc-prolinal (552)} & \quad \xrightarrow{\text{Ph}_3\text{P}=\text{CBr}_2} \quad \xrightarrow{\text{THF}} \\
\text{552} & \quad \text{553}
\end{align*}
\]

Scheme 6.28

In the event, purification by column chromatography of the crude reaction mixture resulted in the isolation of one major product. The structure of the product was confirmed by spectroscopic analysis and was found to be the desired \( N\)-Boc 1,1-dibromoalkene (553) formed in 69% yield as a mixture of rotamers. Specifically, the \( ^1\text{H} \) NMR spectrum of the product showed evidence of successful Wittig reaction by the occurrence of the vinylic proton at \( \delta_{\text{H}} 6.37 \text{ ppm} \) and the disappearance of the aldehyde proton. The three \( \text{CH}_2 \) groups of the pyrrolidine ring resonated in the region of \( \delta_{\text{H}} \sim 1.70-3.50 \text{ ppm} \), with the more downfield \( \text{CH}_2 \) being, presumably, next to the more electronegative nitrogen atom. The chiral \( \text{CH} \) group appeared more deshielded at \( \delta_{\text{H}} \sim 4.35 \text{ ppm} \), while the tert-butyl group appeared as a singlet at \( \delta_{\text{H}} 1.47 \text{ ppm} \) (6H, s, \((\text{CH}_3)_3\)). Further enlightenment was given by the \( ^13\text{C} \) NMR (100 MHz), which showed as expected three \( \text{CH}_2 \) groups at \( \delta_{\text{C}} 22.8, 31.2, 46.2 \) and two \( \text{CH} \) groups at 60.4, and 140.2 ppm, while the \text{tert}-butyl methyls appeared more shielded at \( \delta_{\text{C}} 29.3 \text{ ppm} \).
6.3.4 Synthesis of (S)-(−)-1-t-butoxycarbonylpyrrolidine-2-prop-1-yn

We next examined the efficacy of t-BuOK in the conversion the N-Boc 1,1-dibromoalkene (553) to the corresponding alkyne (554). Thus, a solution of N-Boc 1,1-dibromoalkene (553) in anhydrous tetrahydrofuran was treated with t-BuOK at ambient temperature under an atmosphere of dry nitrogen. The reaction proceeded smoothly and the t-BuOK successfully dehalogenated the N-Boc 1,1-dibromoalkene (553) to give the desired N-Boc protected alkyne (554) in quantitative yield (Scheme 6.29).

The structure of the product (554) was confirmed by spectroscopic analysis, specifically, the $^1$H NMR spectrum of the molecule showed the disappearance of the vinylic proton and the appearance of a characteristic signal for the alkyne proton at $\delta_H$ 5.34 ppm. The resonance of the tert-butyl group appeared as a singlet at $\delta_H$ 1.27 ppm, while the three methylene groups and one methine group appeared as expected in the region of ~1.50-3.30 ppm. Furthermore, the $^{13}$C NMR spectrum of the product showed three sets of $\text{CH}_2$ groups at $\delta_C$ 22.8/23.6, 32.2/32.9, 44.7/45.1 and two $\text{CH}$ groups at $\delta_C$ 80.9, 119.3 with the more upfield being the alkyne $\text{CH}$. These data combined with IR spectroscopy [alkyne CH absorption at 3292 cm$^{-1}$ and alkyne carbon carbon triple bond absorption at 2202 cm$^{-1}$] and MS [m/z (ESI)$^+$: [M+H]$^+$, 196] supported the structure assignment.

6.3.5 Synthesis of (2S)-N-(2-azidoaroyl)-2-ethynylpyrrolidine

With the new protecting group in place, attention turned to the deprotection/coupling of the N-Boc alkyne (554) to the 2-azidobenzoyl chloride. Accordingly, a solution of N-Boc alkyne (554) was treated with trifluoroacetic acid in dichloromethane.$^{194}$ Upon completion, the reaction mixture was quenched with aqueous sodium hydroxide solution, neutralised with hydrochloric acid and extracted with dichloromethane. Subsequent treatment of the dichloromethane extract with triethylamine and a solution of 2-azidobenzoyl chloride in dichloromethane afforded the
required cyclisation precursor (546) as a rotameric mixture in 37% yield over two steps (Scheme 6.30).

![Scheme 6.30]

The incorporation of the 2-azidobenzoyl group was confirmed by $^1$H and $^{13}$C NMR spectroscopic analysis of the product. Significantly, the $^1$H NMR spectrum (400 MHz) indicated the additional presence of the four aromatic protons in the region of $\delta_H \approx 7.00-7.60$ ppm. The three $CH_2$ groups were present and appeared in the region of $\delta_H \approx 1.60-3.90$ ppm as complex signals, together with the $CH$ group at 4.35 ppm. More importantly, the alkyne $CH$ remained intact and appeared at $\delta_H 4.65$ ppm. In the $^{13}$C NMR spectrum (100 MHz) of the same product, evidence of the alkyne CH group was given by DEPT-135 analysis, where the CH appeared at $\delta_C 118.5/119.6$ ppm, whilst the three $CH_2$ groups appeared at $\delta_C 22.2/24.3, 28.0/29.6, 45.8/48.8$ and one CH appeared at $\delta_C 56.3/58.4$ ppm. These data combined with a consistent IR spectrum [alkyne CH absorption at $\nu_{max} 3394$ cm$^{-1}$, alkyne carbon carbon triple bond at 2435 cm$^{-1}$, azide absorption at 2127 cm$^{-1}$ and C=O stretch at 1717 cm$^{-1}$] further verified the structural assignment.

### 6.3.6 Synthesis of 1,2,3-triazolopyrrolo[2,1-c][1,4]benzodiazepine

Having established an efficient route through to the cyclisation precursor, the final requirement was to cyclise the azide onto the terminal alkyne. Subsequently, a solution of the cyclisation precursor (546) was heated at reflux in toluene whilst being carefully monitored by TLC (Scheme 6.31).
Gratifyingly, the cycloaddition reaction was very clean and yielded the desired tetracycle (547) as the only product in 16% yield. The structure of the product (547) was confirmed by $^1$H NMR, $^{13}$C NMR, $^1$H-$^1$H COSY, $^1$H-$^{13}$C COSY, IR, MS and accurate mass measurements. This time, the non-occurrence of a rotameric mixture, together with the presence of a characteristic singlet at $\delta_H 7.64$ ppm, diagnostic of the triazole $CH$, were significant evidence of the proposed structure. The chiral $CH$ appeared as doublet of doublets at $\delta_H 4.76$ ppm, whilst the three $CH_2$ groups appeared in the region of $\delta_H \sim 2.10$-4.00 ppm, with the more downfield $CH_2$ being next to the more electronegative nitrogen atom. Lastly, four aromatic protons were present, as expected, in the region of $\delta_H \sim 7.50$-8.30 ppm. Furthermore, the $^{13}$C NMR spectrum of the molecule showed three $CH_2$ group at $\delta_C 23.7$, 29.4, 47.6 ppm and a $CH$ group at $\delta_C 49.6$ ppm, while the five aromatic protons and four quaternary carbons appeared more downfield at $\delta_C 122.9$-164.0 ppm. These data combined with IR spectroscopy, MS [m/z (ESI+): [M+H]$^+$, 241] and correct accurate mass measurement supported the structural assignment.

6.4 Synthesis of tetrazolopyrrolobenzodiazepines via the nitrile

Having made the tetracyclic triazolopyrrolobenzodiazepine from the intramolecular 1,3-dipolar cycloaddition reaction of an azide with a terminal alkyne, it seemed sensible to attempt the corresponding nitrile-azide cycloaddition in order to access tetrazolopyrrolobenzodiazepines, again useful analogues of bretazenil.\textsuperscript{97,101b} Nitriles are very useful intermediates in synthetic organic chemistry\textsuperscript{255} and can be obtained readily from primary amines,\textsuperscript{256} aldehydes,\textsuperscript{257} or from dehydration of amides\textsuperscript{258} and aldoximes.\textsuperscript{259}

Recently, Togo \textit{et al.}\textsuperscript{260} reported a direct oxidative conversion of primary alcohols to the corresponding nitriles in a one-pot procedure, using molecular iodine in ammonia water. Thus, in Togo’s\textsuperscript{260} work heating a mixture of 3-phenypropanol (555) and ammonia water in the presence of iodine at 60°C afforded the 3-phenylpropionitrile (556) in 91% yield (Scheme 6.32).

![Scheme 6.32](image)

The mechanism suggested for this transformation is given in Scheme 6.33.
Based on this finding, we envisaged a synthetic approach utilizing the above method to access the nitrile. In this respect, the plan was to treat (S)-(−)-1-ethoxycarbonylpyrrolidine-2-methanol (531) with iodine in ammonia to generate the nitrile (557). Subsequent deprotection of the carbamate, followed by an \textit{in situ} coupling of the free amine (558) with 2-azidobenzoyl chloride would furnish the desired cyclisation precursor (559), and thus a straightforward route to compound (560) as outlined in Scheme 6.34.

**Scheme 6.33**

6.4.1 Oxidative conversion of alcohol to nitrile

Following the synthetic methodology shown in Scheme 6.34, the initial requirement was to oxidise the alcohol (531) to the corresponding nitrile (557). Accordingly, a solution of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-methanol (531) in aqueous ammonia was heated at 70°C in presence of finely powdered iodine for 20 hours (Scheme 6.35). The reaction was found to be very clean and the desired nitrile (557) was isolated in good yield, after work up and purification by column chromatography.
6.4.2 Synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile

With the nitrile (557) in place, attention next turned to the deprotection of the carbamate and in situ coupling reaction of the corresponding free amine (558) with 2-azidobenzoyl chloride. Thus, a solution of nitrile (557) in ethylene glycol was heated at reflux in the presence of potassium hydroxide. Upon disappearance of the starting material, the mixture was cooled and extracted with dichloromethane. The free amine (558) was immediately alkylated with 2-azidobenzoyl chloride to give the required cyclisation precursor (559) in a disappointingly low yield (<10%), which could not be improved upon (Scheme 6.36).

In an alternative approach for the synthesis of the cyclisation precursor (559) containing the nitrile dipolarophile, it was envisaged that the nitrile could be synthesized by a direct oxidation of (2S)-N-(2-azidoaroyl)-2-hydroxymethylpyrrolidine (541), derived from the reaction of the readily available (S)-prolinol (522) with 2-azidobenzoyl chloride. Accordingly, (2S)-N-(2-azidoaroyl)-2-hydroxymethylpyrrolidine (541) was treated with finely ground iodine in aqueous ammonia and the mixture was heated at 70°C. Upon completion the reaction mixture was cooled, quenched with an aqueous solution of sodium sulphite and extracted with diethyl ether. Gratifyingly, purification of the crude product via column chromatography resulted in the isolation of the desired cyclisation precursor (559) in 36% yield, as a mixture of rotamers (Scheme 6.37).
Evidence of successful transformation of the alcohol to nitrile was provided by $^1$H NMR, which showed the appearance of only three CH$_2$ groups in the region of $\delta_H \sim 2.00$-$3.90$ ppm, together with the disappearance of the OH group and the remaining CH$_2$ group. The chiral methine was present and appeared at $\delta_H$ 4.86 ppm, while the four aromatic protons appeared in the region of $\delta_H \sim 7.00$-$7.50$ ppm. Analysis of the same product by $^{13}$C NMR (100 MHz) revealed the presence of the three CH$_2$ groups at $\delta_C$ 23.0/24.8, 30.2/32.0, 45.6/47.7 ppm, one CH group at $\delta_C$ 46.0/48.6 ppm, and more importantly a new deshielded quaternary carbon at $\delta_C$ 118.1 ppm, diagnostic of the nitrile carbon. These data, combined with IR spectroscopy [nitrile absorption at $\nu_{max}$ 2242 cm$^{-1}$, azide absorption at $\nu_{max}$ 2131 cm$^{-1}$ and C=O stretch at $\nu_{max}$ 1645 cm$^{-1}$] and consistent MS [m/z (ESI+): [-N$_2$+Na$^+$], 236] further verified the structural assignment.

6.4.3 An alternative synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile

During the course of our studies in the design and synthesis of the (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile (559), it occurred to us to explore further efficient and convenient methodologies for the preparation of the nitrile. Recently, tosyl chloride with pyridine has been used by Ley and co-workers$^{261}$ for the conversion of a prolinamide (562) to the corresponding nitrile (563) [Scheme 6.38].
Scheme 6.38

Based on this development, we envisioned a synthetic approach utilizing the above method to access the nitrile. In this respect, the plan was to couple the readily available (L)-prolinamide (567) to 2-azidobenzoyl chloride to generate the coupled product (568) containing the amide. Subsequent dehydration of the amide (568) moiety using tosyl chloride and pyridine would then give access to the desired cyclisation precursor (559).

![Scheme 6.39](image)

However, in the event, the treatment of L-prolinamide (567) with an aqueous solution of potassium carbonate in dichloromethane, followed by reaction with 2-azidobenzoyl chloride, resulted in the isolation of the one new product, which was not the amide (568), but was, in fact, the desired (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbonitrile (559), obtained in 48% yield (Scheme 6.40).

![Scheme 6.40](image)

The structure of the product (559) was assigned on the basis of $^1$H NMR, $^{13}$C NMR, MS, and IR spectra. The appearance of the pyrrolidine protons together with the presence of four additional protons in the in the region of $\delta_1$H ~7.10-7.70 ppm, confirmed the successful coupling of the 2-azidobenzoyl chloride. More importantly, the incorporation of the nitrile moiety in the molecule was manifested by the occurrence in the IR spectra of a characteristic nitrile absorption at $v_{max}$ 2242 cm$^{-1}$, together with the non existence of the two amide protons in the $^1$H NMR and the loss of one of the amide carbonyls in the $^{13}$C NMR spectrum.
Mechanistically it is thought that the initial coupled product, the amide (568) reacts with the aroyl chloride to afford the intermediate (569) shown in Scheme 6.41 below. Dehydration then occurs to give the nitrile (559) together with 2-azidobenzoic acid (570), the presence of which was confirmed by chromatography. In fact, this is just a variation on the tosyl chloride assisted dehydration, with 2-azidobenzoyl chloride in place of tosyl chloride.

![Scheme 6.41](image)

### 6.4.4 Synthesis of 1,2,3,4-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine

With reliable syntheses of the cyclisation precursor (559) in hand, the final requirement was to cyclise the azide onto the nitrile. Gratifyingly, heating a solution of the precursor (559) in toluene at reflux resulted in a successful cyclisation and the desired tetrazolopyrrolobenzodiazepine (560) was obtained in almost quantitative yield (99%) as seen in Scheme 6.42.

![Scheme 6.42](image)

Evidence of successful cycloaddition was provided by IR spectroscopy, which showed the disappearance of an azide and the nitrile absorption peak, which were present in the cyclisation precursor at $\nu_{max} = 2130$ cm$^{-1}$ and 2245 cm$^{-1}$, respectively, together with the appearance of an imine absorption at 1606 cm$^{-1}$. The $^1$H NMR spectrum (400 MHz) of the [1,2,3,4]-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine (560) showed the three $CH_2$ groups in the region of $\delta_H = 2.10-4.00$ ppm, with the more downfield $CH_2$ being next to the more electronegative nitrogen atom. The chiral $CH$ appeared as a doublet of doublets at $\delta_H = 4.83$ ppm, while the four aromatic protons were present
in the region of $\delta_H \sim 7.59-8.25$ ppm. In addition, the $^{13}$C NMR spectrum of the molecule showed as expected three CH$_2$ groups at $\delta_C$ 23.5, 28.2, 48.2 ppm and a CH group at $\delta_C$ 49.7 ppm, while the four aromatic protons and four quaternary carbons appeared more downfield at $\delta_C$ 122.5-163.4 ppm. These data combined, MS [m/z (ESI+): [M+H]$^+$, 242] and correct accurate mass measurement supported the structural assignment.

6.5 Conclusion

This section has described work that demonstrates that intermolecular 1,3-dipolar cycloaddition of azides to nitriles and alkynes offers an efficient route to access triazolo- and tetrazolo- fused pyrrolobenzodiazepines. Intramolecular ring closure onto an alkene was less clear cut, giving either a hydroxy pyrrolobenzodiazepine (i.e. no fourth ring) at high temperature or pyrrolobenzodiazepines and aziridinopyrrolobenzodiazepines as inseparable mixtures at lower reaction temperatures.
Experimental
Chapter 7

Experimental Section

General Information

Unless otherwise stated, all reactions were conducted using oven-dried glassware under nitrogen, dried through 4Å molecular sieves and silica gel and delivered to the reaction through a gas manifold. Workup procedures were done in air. All solvents were purchased from either BDH or Fisher chemicals and were of analytical grade. Petroleum ether used for chromatography was of the 40-60°C boiling point range. All anhydrous grade solvents, commercially available starting materials and reagents were purchased from Sigma-Aldrich and used without additional drying or further purification.

All reactions were monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm Merck silica gel-60 F254 precoated plates and visualisation of the plates was achieved using ultraviolet light and/ or vanillin stain. Flash column chromatography was performed on flash grade silica gel (70-230 mesh; 60Å) using eluents described in the experimental protocol.

The NMR spectra were recorded either on a Bruker DPX-400 instrument, operating at 400 MHz for $^1$H and 100 MHz for $^{13}$C channels, respectively, or on a Bruker Avance 500 with multinuclear probe, operating at 500 MHz for $^1$H and 125 MHz for $^{13}$C, respectively. All NMR spectra were obtained at 25°C using TMS as internal reference and the chemical shift are expressed in parts per million (ppm). The list of coupling constants ($J$) are reported to the nearest 0.1 Hertz (Hz) and the splitting patterns were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a suitable combination. Assignment of signals in $^{13}$C NMR was based on the H-decoupled experiments and, in most cases, on DEPT-135 and DEPT-90 experiments.

IR spectra were recorded on a Perkin Elmer paragon 1000 FT-IR instrument as thin film between NaCl plates (oil) or as KBr disks (solids) and are reported using the following abbreviations: s (strong), m (medium), w (weak) or br (broad).

Low resolution mass spectra were recorded on a Micromass Quattro II Triple Quadrupole mass spectrometer operating at a positive ion mode under electron impact (EI), chemical ionisation (CI), or electrospray ionisation (ESI) methods. Molecular ions are reported as their mass, with the percentage abundance quoted in brackets. High resolution mass spectra were recorded on a Finnegan MAT 900 XTL instrument operated by the EPSRC National Mass Spectrometry service at the University of Swansea.
Experimental Part I

7.1.1 Synthesis of 2-azidobenzenesulfonamide

\[
\text{SO}_2\text{NH}_2 \quad \xrightarrow{\text{NaNO}_2, 0^\circ\text{C}} \quad \xrightarrow{\text{HCl (aq)}} \quad \text{N} = \text{N} \quad \xrightarrow{\text{NaN}_3, 0^\circ\text{C}} \quad \text{SO}_2\text{NH}_2
\]

To a suspension of 2-aminobenzenesulfonamide (409; 0.800 g, 4.65 mmol, 1.0 eq) in concentrated hydrochloric acid (10 ml) and water (10 ml) at 0°C was added, with vigorous stirring, a solution of sodium nitrite (0.380 g, 5.57 mmol, 1.2 eq) in water (10 ml), dropwise over 20 minutes. The resulting mixture was further stirred for 1 hr at 0°C and was added dropwise to an ice-cooled mixture of sodium azide (0.360 g, 5.57 mmol, 1.2 eq) and sodium acetate (15.0 g, 185.83 mmol, 40 eq) in water (50 ml). The white precipitate so-formed was filtered, washed thoroughly with water (3x 25 ml) and dried in the oven (~100°C) overnight to give 2-azidobenzenesulfonamide (398; 0.73 g, 79% yield) as a beige solid, m.p: 189-190°C (lit. m.p: 191°C).²⁶²

\[\delta_H (400 \text{ MHz, CDCl}_3): 3.35 (2H, s, br, \text{NH}_2), 7.32 (1H, t, J 7.7, \text{ArH}), 7.52 (1H, d, J 8.0, \text{ArH}), 7.66 (1H, t, J 7.3, \text{ArH}), 7.84 (1H, d, J 7.4, \text{ArH}). \delta_C (100 \text{ MHz, CDCl}_3): 120.6 (\text{CH}), 124.6 (\text{CH}), 128.0 (\text{CH}), 133.4 (\text{CH}), 133.8 (q), 136.9 (q). \nu_{\text{max}} (\text{thin film cm}^{-1}): 3357 (s), 3255 (s), 3096 (m), 2137 (s), 1578 (s), 1472 (s), 1337 (s), 1285 (s), 1157 (s), 770 (s), 657 (s). \text{EI}^+ \text{ mass spectrum (m/z, \%): 199 ([M+H]^+, 2\%), 198 ([M]^+, 7\%), 172 (10\%), 155 (15\%), 105 (40\%), 91 (15\%), 77 (100\%), 64 (25\%), 52 (25\%), 39 (30\%), 28 (40\%).} \]
7.1.2 Synthesis of 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides

To a solution of 2-azidobenzenesulfonylamide (398; 1.0 eq) and thionyl chloride (0.46-0.55 ml, 1.0 eq) in anhydrous tetrahydrofuran (15-30 ml) at 0°C, under an atmosphere of dry nitrogen, was added a solution of anhydrous pyridine (0.51-0.61 ml, 2.0 eq) in anhydrous tetrahydrofuran (5-10 ml) over a period of 3 hr. Maintaining the temperature at 0°C, the stirring was continued for a further 1 hr, followed by dropwise addition of the appropriate 1,3-diene (1.6 eq), and the whole was allowed to warm up to ambient temperature over 20 hours. In the case of the 1,3-butadiene adduct (400a), the diene was condensed at low temperature (-20°C) and subsequently added to the mixture, maintaining the low temperature of the reaction for 4-6 hr. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash column silica chromatography (eluent PE:EtOAc/ 3:2). The 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides were obtained as follows:

2-(2-Azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a) was obtained as a yellow solid (1.150 g, 61% yield) from 2-azidobenzenesulfonylamide (398; 1.250 g, 6.31 mmol) and 1,3-butadiene (large excess, ~10eq).

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 3.45 (1H, ddd, J 16.5, 6.2, 2.3, CH$_2$S=O), 3.61 (1H, dddd, J 16.5, 10.0, 4.8, 2.5, CH$_2$S=O), 3.83 (1H, dddd, J 17.4, 9.5, 4.7, 2.3, CH$_2$N), 4.11-4.17 (1H, m, CH$_2$N), 5.73-5.79 (1H, m, HC=CH), 5.96-6.01 (1H, m, HC=CH), 7.28 (1H, dd, J 7.8, 0.9, ArH), 7.34 (1H, dd, J 8.0, 0.8, ArH), 7.66 (1H, td, J 7.8, 1.5, ArH), 8.01 (1H, dd, J 8.0, 1.5, ArH). $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 39.0 (CH$_3$), 50.6 (CH$_2$), 114.6 (CH), 120.3 (CH), 124.3 (CH), 124.6 (CH), 127.7 (q), 131.6 (CH), 135.1 (CH), 139.1 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3010 (w), 2919 (w), 2133 (s), 1575 (m), 1470 (s), 1433 (m), 1352 (s), 1282 (s), 1170 (s), 1103 (s), 1060 (s), 1003 (m), 868 (m), 771 (s), 653 (m). EI+ mass spectrum (m/z, %): 298 ([M$^+$]+, 4%), 282 (1%), 270 (2%), 250 (3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). CI+ mass spectrum (m/z, %): 316 ([M+NH$_4^+$], 100%), 299 ([M+H$^+$]+, 6%). HRMS (ESI+): found [M+NH$_4^+$]+ 316.0534, C$_{10}$H$_{10}$N$_4$O$_3$S$_2$ requires 316.0538.
2-(2-Azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (400b) was obtained as a yellow solid (1.980 g, 84% yield) from 2-azidobenzenesulfonamide (398; 1.500 g, 7.57 mmol) and isoprene (1.51 ml, 15.14 mmol).

$$\delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.85 \text{ (3H, s, CH}_3\text{), 3.24 \text{ (1H, dd, J 16.2, 1.8, CH}_2\text{S=O), 3.56-3.67 \text{ (1H, dt, J 16.2, 1.1, CH}_2\text{S=O), 3.75-3.85 \text{ (1H, dm, J 16.8, CH}_2\text{N), 4.05-4.15 \text{ (1H, dm, J 17.1, CH}_2\text{N), 5.65 \text{ (1H, d, J 1.9, MeC=CH), 7.28 \text{ (1H, t, J 7.4, ArH), 7.34 \text{ (1H, d, J 8.0, ArH), 7.65 \text{ (1H, td, J 7.9, 1.3, ArH), 8.01 \text{ (1H, dd, J 8.0, 1.3, ArH).}}}}
$$

$$\delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 24.4 \text{ (CH), 39.3 \text{ (CH}_2\text{), 54.4 \text{ (CH}_2\text{), 117.7 \text{ (CH), 120.3 \text{ (CH), 122.7 \text{ (q), 124.6 \text{ (CH), 127.8 \text{ (q), 131.6 \text{ (CH), 135.1 \text{ (CH), 139.1 \text{ (q). \nu}_{\text{max}} \text{ (thin film cm}^{-1}: 2135 \text{ (s), 1575 \text{ (m), 1473 \text{ (s), 1444 \text{ (m), 1349 \text{ (s), 1293 \text{ (m), 1172 \text{ (s), 1103 \text{ (s), 832 \text{ (s), 763 \text{ (m), 735 \text{ (m), 655 \text{ (m), 626 \text{ (s). \text{EI+ mass spectrum (m/z, %): 312 ([M]^{+}, 2\%), 296 \text{ (1\%), 284 \text{ (3\%), 264 \text{ (1\%), 183 (5\%), 171 (10\%), 156 (15\%), 130 (10\%), 108 (15\%), 104 (15\%), 90 (55\%), 84 (45\%), 76 (35\%), 68 (100\%). \text{Cl+ mass spectrum (m/z, %): 330 ([M+NH}_4]^{+}, 97\%), 313 ([M+H]^{+}, 15\%), 284 \text{ (M-N}_2]^{+}, 90\%). HRMS (ESI+): found [M+H]^{+} 313.0416, C_{11}H_{12}N_4O_3S_2 requires 313.0424.}}}$$

2-(2-Azidobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (400c) was obtained as a yellow solid (1.890 g, 77% yield) from 2-azidobenzenesulfonamide (398; 1.500 g, 7.57 mmol) and 2,3-dimethyl-1,3-butadiene (1.71 ml, 15.15 mmol).

$$\delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.71 \text{ (3H, s, CH}_3\text{), 1.79 \text{ (3H, s, CH}_3\text{), 3.23 \text{ (1H, d, J 15.9, CH}_2\text{), 3.63 \text{ (1H, d, J 14.2, CH}_2\text{), 3.68 \text{ (1H, d, J 14.2, CH}_2\text{), 3.86 \text{ (1H, d, J 16.2, CH}_2\text{), 7.28 \text{ (1H, t, J 7.8, ArH), 7.34 \text{ (1H, d, J 8.0, ArH), 7.66 \text{ (1H, dt, J 7.8, 1.1, ArH) 8.01 \text{ (1H, dd, J 8.0, 0.9, ArH). \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 16.9 \text{ (CH}_3\text{), 19.7 \text{ (CH}_3\text{), 42.9 \text{ (CH}_2\text{), 55.5 \text{ (CH}_2\text{), 115.0 (q), 120.3 (CH), 123.5 (q), 124.6 (CH), 127.5 (q), 131.6 (CH), 135.1 (CH), 139.0 (q). \nu}_{\text{max}} \text{ (chloroform cm}^{-1}: 3006 \text{ (w), 2918 (w), 2134 (s), 1585 (m), 1575(m), 1472 (s), 1444 (m), 1351 (s), 1291 (m), 1171 (s), 1102 (s), 885 (m), 758 (s), 614 (m). \text{EI+ mass spectrum (m/z, %): 326 ([M+H]^{+}, 9\%), 298 (12\%), 278 (10\%), 156 (10\%), 116 (25\%), 104 (20\%), 90 (40\%), 76 (35\%), 64 (50\%), 54 (30\%), 39 (100\%). HRMS (ESI+): found [M+H]^{+} 327.0587, C_{12}H_{14}N_4O_3S_2 requires 327.0585.}}$$
7.1.3 Synthesis of 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides

![Chemical Structure](image)

General Procedure:

A solution of triphenylphosphine (1.0 eq) in anhydrous tetrahydrofuran (10-20 ml) was added dropwise over a period of 1 hr to a stirring solution of the 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a-c; ~3-6 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10-20 ml) under an atmosphere of dry nitrogen. The reaction mixture was stirred for 4 hr at ambient temperature and water (~16 eq) was added to the mixture and the whole was heated at reflux for 15-18 hours. The reaction mixture was allowed to cool to ambient temperature and the solvent was removed in vacuo. The crude product was purified by column chromatography (eluent: PE:EtOAc/ 3:2) to yield the 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (402a-c), as follows:

2-(2-Aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (402a) was obtained as a yellow oil (1.190 g, 87% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a; 1.500 g, 5.03 mmol, 1.0 eq).

$\delta_H$ (400 MHz, CDCl₃): 3.33 (1H, ddd, $J$ 16.5, 6.4, 2.2, $CH_2S=O$), 3.55 (1H, d, $J$ 16.5, 2.7, $CH_2S=O$), 3.80 (1H, d, $J$ 8.5, 2.1, $HC=CH$), 3.94-4.02 (1H, dm, $J$ 17.2, $CH_2N$), 5.33 (2H, s, br, $NH_2$), 5.65 (1H, t, $J$ 8.5, 2.1, $HC=CH$), 6.67-6.75 (2H, m, 2$ArH$), 7.25 (1H, td, $J$ 7.7, 1.4, $ArH$), 7.41-7.43 (1H, m, $ArH$). $\delta_C$ (100 MHz, CDCl₃): 38.8 ($CH_2$), 50.3 ($CH_2$), 114.3 ($CH$), 117.0 ($CH$), 117.1 (q), 117.9 ($CH$), 124.1 ($CH$), 129.8 ($CH$), 132.7 (q), 135.2 ($CH$). $\nu_{max}$ (thin film cm⁻¹): 3470 (m), 3372 (m), 2983 (m), 2892 (m), 1622 (s), 1600 (s), 1567 (m), 1484 (s), 1455 (s), 1438 (s), 1389 (m), 1319 (s), 1144 (s), 1120 (s), 1016 (s), 1002 (m), 881 (s), 753 (s), 723 (s), 696 (s). EI+ mass spectrum (m/z, %): 273 ([M+H]+, 3%), 272 ([M]+, 15%), 224 (15%), 218 (30%), 172 (5%), 156 (40%), 140 (10%), 116 (10%), 108 (30%), 92 (100%), 65 (80%), 54 (10%). CI+ mass spectrum (m/z, %): 290 ([M+NH₄]+, 100%), 273 ([M+H]+, 60%). HRMS (ESI+): found [M+H]+ 273.0367, C_{10}H_{12}N_{2}O_{3}S_{2} requires 273.0367.
2-(2-Aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (402b) was obtained as a yellow oil (0.810 g, 88% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (400b; 1.000 g, 3.21 mmol, 1.0 eq).

δH (400 MHz, CDCl₃): 1.83 (3H, s, CH₃), 3.22 (1H, dd, J 16.2, 2.1, CH₂S=O), 4.00 (1H, dt, J 16.6, 2.1, CH₂N), 5.14 (2H, s, br, NH₂), 5.67 (1H, s, MeC=CH), 6.75 (1H, dd, J 8.1, 0.6, ArH), 6.80 (1H, dt, J 7.6, 0.8, ArH), 7.35 (1H, td, J 7.7, 1.4, ArH), 7.70 (1H, dd, J 8.1, 1.4, ArH). δC (100 MHz, CDCl₃): 24.3 (CH₃), 39.3 (CH₂), 54.3 (CH₂), 117.6 (CH), 117.8 (CH), 117.9 (q), 118.0 (CH), 122.6 (q), 130.2 (CH), 135.4 (CH), 146.1 (q). v max (thin film cm⁻¹): 3462 (m), 3338 (m), 2961 (m), 2928 (s), 1625 (m), 1598 (m), 1483 (s), 1438 (s), 1343 (s), 1158 (s), 1093 (s), 1027 (w), 927 (m), 758 (s), 668 (s).

EI+ mass spectrum (m/z, %): 286 ([M]+, 4%), 238 (8%), 218 (15%), 172 (10%), 156 (30%), 140 (10%), 108 (35%), 92 (100%), 65 (25%). ESI+ mass spectrum (m/z, %): 309 ([M+Na]+, 8%), 287 ([M+H]+, 20%). HRMS (ESI+): found [M+H]+ 287.0524, C11H14N2O3S2 requires 287.0524.

2-(2-Aminobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (402c) was obtained as a yellow oil (1.000 g, 83% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (400c; 1.000 g, 3.06 mmol, 1.0 eq).

δH (400 MHz, CDCl₃): 1.59 (3H, s, CH₂), 1.67 (3H, s, CH₃), 3.14 (1H, d, J 16.1, CH₂S=O), 3.55 (1H, d, J 16.3, CH₂S=O), 3.67 (2H, s, CH₂N), 5.25 (2H, s, br, NH₂), 6.65-6.71 (2H, m, 2xArH), 7.24 (1H, t, J 7.6, ArH), 7.69 (1H, d, J 8.4, ArH). δC (100 MHz, CDCl₃): 16.7 (CH₃), 19.2 (CH₃), 42.9 (CH₂), 55.2 (CH₂), 114.8 (q), 116.7 (CH), 116.8 (q), 117.7 (CH), 123.5 (q), 129.6 (CH), 134.9 (CH), 146.2 (q). v max (thin film cm⁻¹): 3473 (s), 3347 (s), 2916 (m), 1624 (s), 1601 (s), 1564 (m), 1485 (s), 1454 (s), 1345 (s), 1157 (s), 1095 (s), 962 (m), 913 (m), 881 (m), 835 (s), 731 (m), 617 (s). EI+ mass spectrum (m/z, %): 300 ([M]+, 3%), 252 (5%), 218 (15%), 108 (25%), 92 (100%), 77 (35%). HRMS (EI+): found [M+H]+ 301.0675, C₁₂H₁₆N₂O₃S₂ requires 301.0680.
7.1.4 Synthesis of (2-aminobenzenesulfonamidyl)alkenols via phenyl allylic sulfoxides

To a stirring solution of 2-(2-aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (402a-b; 1.450 g, 5.06 mmol, 1.0 eq) in anhydrous tetrahydrofuran (25 ml) was added dropwise a solution of phenylmagnesium bromide (3M in ether; 3.4 ml, 21.26 mmol, 2.0 eq) at -78°C, under an atmosphere of dry nitrogen. The resulting mixture was further stirred for 3 hr at -50°C, quenched at -20°C with saturated ammonium chloride solution (25 ml) and allowed to warm to ambient temperature. The mixture was extracted with ethyl acetate (3x 15 ml) and washed with brine (10 ml). The organic phase was collected, dried (MgSO₄), filtered and the solvent was removed in vacuo to yield the crude phenyl allylic sulfoxide (403). To a solution of the crude allylic sulfoxide (403) in anhydrous methanol (25 ml) was added trimethyl phosphite (2.2 ml, 18.65 mmol, 2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for 18 hr. The solvent was removed in vacuo and the crude product was purified by flash column chromatography (eluent: PE:EtOAcl 3:2) to yield 4-(2-aminobenzenesulfonylamidyl)-2-methyl-buten-3-ol (405b; 1.170 g, 90% yield) as a yellow oil.

δH (400 MHz, CDCl₃): 1.61 (3H, s, CH₃), 2.84 (1H, ddd, J 13.0, 8.5, 4.3, CH₂NH), 3.02 (1H, s, br, OH), 3.09 (1H, ddd, J 13.1, 6.9, 3.8, CH₂NH), 4.02 (1H, dd, J 8.1, 3.0, CHO), 4.86 (1H, s, MeC=CH₂), 4.95 (1H, s, MeC=CH₂), 4.97 (2H, s, br, NH₂), 5.59 (1H, quartet, J 4.1, SO₂NH), 6.78 (1H, d, J 7.7, ArH), 6.79 (1H, t, J 7.8, ArH), 7.31 (1H, td, J 7.7, 1.4, ArH), 7.69 (1H, dd, J 7.9, 1.4, ArH). δC (100 MHz, CDCl₃): 18.3 (CH₃), 47.0 (CH₂), 73.3 (CH), 112.2 (CH₂), 117.7 (CH), 117.8 (CH), 121.3 (q), 129.4 (CH), 134.2 (CH), 144.0 (q), 145.0 (q). v_max (thin film cm⁻¹): 3477 (br, m), 3376 (br, m), 2986 (m), 1622 (m), 1600 (m), 1573 (m), 1483 (s), 1455 (s), 1319 (s), 1143 (s), 1024 (m), 754 (s). El⁺ mass spectrum (m/z, %): 256 ([M⁺]⁺, 12%), 185 (15%), 168 (10%), 156 (41%), 108 (31%), 92 (100%), 84 (20%), 65 (40%). CI⁺ mass spectrum (m/z, %): 274 ([M+NH₄]⁺, 30%), 257 ([M+H]⁺, 100%). HRMS (ESI⁺): found [M+H]⁺ 257.0953, C₁₁H₁₆N₂O₃S requires 257.0954.
4-(2-Aminobenzenesulfonylamidyl)-but-1-en-3-ol (405a) was obtained in the same fashion as a yellow oil (0.612 g, 86% yield) from 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (402a; 0.800 g, 2.937 mmol, 1.0 eq).

$\delta_H$ (400 MHz, CDCl$_3$): 2.85 (1H, ddd, $J$ 13.1, 8.0, 5.2, CH$_2$NH), 4.15-4.17 (1H, m, CHOH), 4.75 (2H, s, br, NH$_2$H), 5.17 (1H, dt, $J$ 10.5, 1.0, HC=CH$_2$), 5.28 (1H, dt, $J$ 17.2, 1.2, HC=CH$_2$), 5.44 (1H, t, br, $J$ 5.9, SO$_2$NH), 5.73 (1H, ddd, $J$ 17.1, 10.6, 5.7, H$_2$C=CH), 6.78-6.84 (2H, m, 2xArH), 7.34 (1H, td, $J$ 7.7, 1.5, ArH), 7.71 (1H, dd, $J$ 8.0, 1.4, ArH). $\delta_C$ (100 MHz, CDCl$_3$): 48.2 (CH$_2$), 71.1 (CH), 117.0 (CH$_2$), 117.8 (CH), 117.9 (CH), 121.5 (q), 129.6 (CH), 134.3 (CH), 137.0 (CH), 145.0 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3476 (br, m), 3377 (br, m), 2987 (m), 2928 (m), 1620 (m), 1600 (m), 1573 (w), 1483 (s), 1456 (s), 1332 (s), 1156 (s), 1073 (m), 896 (m), 747 (s). Ei$^+$ mass spectrum (m/z, %): 242 ([M$^+$, 5%], 224 ([M−H$_2$O]$^+$, 2%), 185 ([M−(CH$_2$=CH−CHOH)]$^+$, 35%), 168 ([C$_6$H$_4$SO$_2$NHCH]$^+$, 15%), 156 ([C$_6$H$_4$SO$_2$NH$_2$]$^+$, 50%), 108 ([C$_6$H$_4$S]$^+$, 35%), 92 ([C$_6$H$_4$NH$_2$]$^+$, 100%), 65 ([C$_6$H$_3$]$^+$, 100%), 57 ([CH$_2$=CH−CHOH])$^+$, 90%). CI$^+$ mass spectrum (m/z, %): 260 ([M+NH$_4$]$^+$, 95%), 243 ([M+H]$^+$, 100%). HRMS (ESI$^+$): found [M+H]$^+$ 243.0804, C$_{10}$H$_{14}$N$_2$O$_3$S requires 243.0803.

7.1.5 Synthesis of {o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl} alkenols

![Diagram of synthesis](image_url)

To a solution of the 4-(2-aminobenzenesulfonylamidyl)-2-methyl-but-1-en-3-ol (405a-b; 0.330 g, 1.28 mmol, 1.0 eq) in anhydrous dichloromethane (10 ml) was added sodium hydrogen carbonate (0.230 g, 2.69 mmol, 2.1 eq) and 9-fluorenylmethyl chloroformate (0.701 g, 2.69 mmol, 2.1 eq) under an atmosphere of dry nitrogen. The reaction mixture was stirred at ambient temperature for 18 hr, and distributed between dichloromethane/water (1:1; 10 ml) and extracted with dichloromethane (3x 5 ml), dried over MgSO$_4$, and filtered under gravity. Evaporation of the solvent gave the crude product as a orange oil, which was purified by flash chromatography.
Chapter 7

Experimental Part I

(ELuent: PE:EtOAc/3:2) to yield 4-{o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyL}-2-methyl-but-1-en-3-ol (406b; 0.440 g, 71% yield) as a colourless oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.58 (3H, s, CH_3), 2.28 (1H, d, J 2.9, OH), 2.91 (1H, ddd, J 12.7, 8.5, 4.2, CH_2NH), 3.16 (1H, ddd, J 12.3, 8.4, 4.2, CH_2NH), 3.94 (1H, t, J 3.9, CHOH), 4.31 (1H, t, J 7.2, CHCH_2OCNHH), 4.50 (2H, d, J 7.2, CHCH_2OCNHH), 4.86 (1H, s, HC=CH_2), 4.92 (1H, s, HC=CH_2), 5.30 (1H, t, J 4.2, SO_2NH), 7.20 (1H, td, J 8.0, 0.8, ArH), 7.35 (2H, td, J 7.4, 1.0, 2xArH), 7.44 (2H, t, J 7.4, 2xArH), 7.56 (1H, t, J 7.5, ArH), 7.65 (2H, d, J 7.4, 2xArH), 7.80 (2H, d, J 7.5, 2xArH), 7.90 (1H, dd, J 8.0, 1.4, ArH), 8.13 (1H, s, ArH), 8.75 (1H, s, CO_2NH). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 18.2 (CH_3), 46.7 (CH_2), 46.8 (CH), 67.7 (CH_2), 73.1 (CH), 112.5 (CH_2), 120.0 (CH), 122.1 (CH), 123.4 (CH), 125.0 (CH), 127.2 (CH), 127.8 (CH), 129.3 (CH), 134.2 (CH), 136.0 (q), 141.3 (q), 143.5 (q), 143.8 (q), 153.3 (q). \]

\[ \nu_{max} (\text{thin film ern}:^1): 3502 \text{ (br, w), 3349 \text{ (br, m), 2949 \text{ (m), 1737 \text{ (m), 1588 \text{ (s), 1531 \text{ (s), 1444 \text{ (s), 1291 \text{ (m), 1249 \text{ (m), 1216 \text{ (s), 1152 \text{ (s), 1083 \text{ (m), 1048 \text{ (m), 910 \text{ (s), 755 \text{ (s), 740 \text{ (m).}} \]

4-\{(9'-fluorenylmethoxycarbonyl)amino\}benzenesulfonylamidyL\}-but-1-en-3-ol (406a) was obtained as a colourless oil (0.120 g, 63% yield) from 4-(2-aminobenzenesulfonamidyL)-but-1-en-3-ol (405a; 0.101 g, 0.413 mmol, 1.0 eq).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.90 (1H, ddd, J 12.8, 8.0, 4.7, CH_2NH), 3.15 (1H, ddd, J 11.7, 8.0, 3.7, CH_2NH), 3.57 (1H, s, br, OH), 4.05-4.12 (1H, m, CHOH), 4.33 (1H, t, J 7.1, CHCH_2OCNHH), 4.52 (2H, d, J 7.2, CHCH_2OCNHH), 5.02 (1H, quart, J 5.7, SO_2NH), 5.18 (1H, d, J 10.5, HC=CH_2), 5.25 (1H, d, J 17.3, HC=CH_2), 5.71 (1H, ddd, J 17.1, 10.8, 5.7, H_2C=CH), 7.22 (1H, t, J 7.7, ArH), 7.36 (2H, t, J 7.5, 2xArH), 7.45 (2H, t, J 7.5, 2xArH), 7.59 (1H, t, J 7.8, ArH), 7.65 (2H, d, J 7.4, 2xArH), 7.81 (2H, d, J 7.5, 2xArH), 7.90 (1H, dd, J 8.0, 1.0, ArH), 8.15 (1H, d, br, J 7.8, ArH), 8.69 (1H, s, br, CO_2NH). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 46.9 (CH), 47.9 (CH_2), 67.7 (CH_2), 70.9 (CH), 111.3 (CH_2), 117.5 (q), 118.0 (q), 120.1 (CH), 122.3 (CH), 123.5 (CH), 125.1 (CH), 127.2 (CH), 127.9 (CH), 129.4 (CH), 134.3 (CH), 136.8 (CH), 141.4 (q), 143.6 (q), 153.3 (q). \]

\[ \nu_{max} (\text{thin film ern}:^1): 3512 \text{ (br, w), 3355 \text{ (br, m), 2925 \text{ (m), 2853 \text{ (m), 1735 \text{ (s), 1588 \text{ (s), 1469 \text{ (m), 1458 \text{ (s), 1329 \text{ (s), 1291 \text{ (m), 1250 \text{ (m), 1154 \text{ (s), 1132 \text{ (m), 1082 \text{ (m), 1047 \text{ (m), 933 \text{ (w), 757 \text{ (s), 668 \text{ (m).}} \]

ESI+ mass spectrum (m/z, %): 979 ([2M+Na]^+, 5%), 957 ([2M]^+, 15%), 501 ([M+Na]^+, 20%), 479 ([M]^+, 70%). C,H,N(%): found C 65.5, H 5.4, N 5.9; C_{26}H_{26}N_{2}O_{2}S requires C 65.2, H 5.5, N 5.9.

4-\{(9'-fluorenylmethoxycarbonyl)amino\}benzenesulfonylamidyL\}-but-1-en-3-ol (405a; 0.101 g, 0.413 mmol, 1.0 eq).
7.1.6 Synthesis of \{\text{o-}\{[9'-fluorenylmethoxycarbonyl]amino\}benzenesulfonamidyl\} alkenones

To a stirring solution of 4-{\text{o-}\{[9'-fluorenylmethoxycarbonyl]amino\}benzenesulfonamidyl}-2-methyl-but-1-en-3-ol (406b; 0.340 g, 0.710 mmol, 1.0 eq), in anhydrous dichloromethane (10 ml) was added finely powdered Dess-Martin periodinane (0.331 g, 0.782 mmol, 1.1 eq) under an atmosphere of dry nitrogen. The mixture was stirred at ambient temperature for 1/2 hr and the solvent was removed \textit{in vacuo} to give the crude product as a yellow suspension, which was purified by flash column chromatography (eluent: PE:EtOAc 3:1) to yield 4-{\text{o-}\{[9'-fluorenylmethoxycarbonyl]amino\}benzenesulfonamidyl}-2-methyl-but-1-en-3-one (407b; 0.280 g, 80% yield) as a pale yellow solid.

$\delta_H$ (400 MHz, CDCl$_3$): 1.84 (3H, s, CH$_3$), 4.17 (2H, d, $J$ 4.6, CH$_2$NH), 4.36 (1H, t, $J$ 7.4, CHCH$_2$OCONH), 4.50 (2H, d, $J$ 7.4, CHCH$_2$OCONH), 5.79 (1H, t, $J$ 4.5, SO$_2$NH), 5.83 (2H, dd, $J$ 6.1, 1.6, MeC=CH$_2$), 7.19 (1H, t, $J$ 8.1, ArH), 7.37 (2H, td, $J$ 7.5, 0.8, 2xArH), 7.45 (2H, t, $J$ 7.4, 2xArH), 7.58 (1H, t, $J$ 8.5, ArH), 7.68 (2H, d, $J$ 7.4, 2xArH), 7.81 (2H, d, $J$ 7.5, 2xArH), 7.90 (1H, dd, $J$ 8.0, 1.4, ArH), 8.24 (1H, d, $J$ 7.9, ArH), 8.86 (1H, s, br, CO$_2$NH). $\delta_C$ (100 MHz, CDCl$_3$): 17.2 (CH$_3$), 46.8 (CH), 47.5 (CH$_2$), 67.8 (CH$_2$), 120.0 (CH), 121.8 (CH), 123.1 (CH), 125.1 (CH), 125.8 (q), 126.3 (q), 127.2 (CH), 127.8 (CH), 129.2 (CH), 134.4 (CH), 136.4 (q), 141.2 (q), 141.8 (q), 143.5 (q), 153.0 (q, CO$_2$NH), 193.3 (q, C=O). $\nu_{max}$ (thin film cm$^{-1}$): 3348 (br, m), 2925 (s), 2853 (m), 1739 (br, s), 1687 (s), 1587 (s), 1531 (s), 1470 (m), 1444 (s), 1329 (s), 1291 (m), 1216 (m), 1154 (s), 1134 (m), 1083 (m), 1059 (m), 910 (s), 759 (s), 738 (m). ESI$^+$ mass spectrum (m/z, %): 499 ([M+Na]$^+$, 65%), 478 ([M+H]$^+$, 6%). C,H,N (%): found C 65.7, H 5.0, N 6.0; C$_{26}$H$_{24}$N$_2$O$_5$S requires C 65.5, H 5.1, N 5.9.

4-\{\text{o-}\{[9'-fluorenylmethoxycarbonyl]amino\}benzenesulfonamidyl\}-but-1-en-3-one (407a) was obtained as a pale yellow oil (0.047 g, 78% yield) from 4-\{\text{o-}\{[9'-fluorenylmethoxycarbonyl]amino\}benzenesulfonamidyl\}-but-1-en-3-ol (406a; 0.060 g, 0.1292 mmol, 1.0 eq).
\( \delta_H (400 \text{ MHz, CDCl}_3): 4.05 (2H, d, J 4.7, \text{CH}_2\text{NH}), 4.36 (1H, t, J 7.3, \text{CHCH}_2\text{OCONH}), 4.52 (2H, d, J 7.4, \text{CHCH}_2\text{OCONH}), 5.73 (1H, t, br, J 4.5, \text{SO}_2\text{NH}), 5.93 (1H, dd, J 9.8, 1.5, \text{H}_2\text{C}=\text{CH}), 6.21-6.34 (2H, m, \text{HC}=\text{CH}_2), 7.19 (1H, t, J 7.6, \text{ArH}), 7.37 (2H, t, J 7.4, 2x\text{ArH}), 7.45 (2H, t, J 7.4, 2x\text{ArH}), 7.58 (1H, t, J 7.8, \text{ArH}), 7.77 (2H, d, J 7.4, 2x\text{ArH}), 7.81 (2H, d, J 7.5, 2x\text{ArH}), 7.89 (1H, dd, J 8.0, 1.3, \text{ArH}), 8.23 (1H, d, br, J 8.1, \text{ArH}), 8.82 (1H, s, br, \text{CO}_2\text{NH}). \) 
\( \delta_C (100 \text{ MHz, CDCl}_3): 46.9 (\text{CH}), 49.2 (\text{CH}_2), 67.7 (\text{CH}_2), 120.0 (\text{CH}), 121.9 (\text{CH}), 123.1 (\text{CH}), 125.1 (\text{CH}), 125.9 (q), 127.2 (\text{CH}), 127.8 (\text{CH}), 129.2 (\text{CH}), 130.8 (\text{CH}_2), 132.7 (\text{CH}), 134.5 (\text{CH}), 136.4 (q), 141.3 (q), 143.6 (q), 153.1 (q), 192.1 (q). \) 
\( \nu_{\text{max}} (\text{thin film cm}^{-1}): 3355 (\text{br, m}), 2920 (s), 2850 (s), 1735 (s), 1589 (s), 1529 (s), 1470 (m), 1459 (s), 1330 (s), 1291 (m), 1240 (m), 1155 (s), 1133 (m), 1079 (m), 1048 (m), 756 (s), 667 (m). \) 
ESI+ mass spectrum (m/z, %): 485 ([M+Na]+, 40%), 480 ([M+NH_4]+, 50%).

7.1.7 Synthesis of 2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxides

**Route A**

To a solution of the 4-\{o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl\}-2-methyl-but-1-en-1-one (407b; 0.230 g, 0.483 mmol, 1.0 eq) in anhydrous dichloromethane (5 ml), was added \( N,N \)-diisopropylethylamine (0.17 ml, 0.965 mmol, 2.0 eq) and the mixture was heated at reflux in an atmosphere of dry nitrogen for a total of 21 hrs, whilst being monitored by TLC. Upon completion of the reaction the solvent was evaporated off and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc 1:1) to yield the 2,3-dihydro-3-hydroxy-4-(i-propyl)-1,2,5-benzothiadiazepine 1,1-dioxide (435b; 0.032 g, 26%) as a yellow oil.

\( \delta_H (400 \text{ MHz, CDCl}_3): 0.80 (3H, d, J 6.8, \text{CH}_3), 1.01 (3H, d, J 6.9, \text{CH}_3), 2.25 (1H, quart quart, J 6.8, 3.4, \text{Me}_2\text{CH}), 4.14 (1H, m, br, \text{CHOH}), 4.28 (1H, d, J 3.2, \text{CHOH}), 7.23 (1H, d, J 8.2, \text{ArH}), 7.39 (1H, t, J 7.7, \text{ArH}), 7.52 (1H, td, J 8.4, 1.2, \text{ArH}), 7.87 (1H, d, J 7.9, \text{ArH}), 9.78 (1H, s, \text{SO}_2\text{NH}). \) 
\( \delta_C (100 \text{ MHz, CDCl}_3): 15.3 (\text{CH}_3), 19.0 (\text{CH}_3), 32.8 (\text{CH}), 75.1 (\text{CH}), 117.2 (\text{CH}), 121.6 (q), 124.5 (\text{CH}), 127.1 (\text{CH}), 133.0 (\text{CH}), 133.6 (q), 160.8 (q). \) 
\( \nu_{\text{max}} (\text{thin film cm}^{-1}): \)
3477 (br, m), 3261 (br, m), 2965 (m), 2930 (m), 1602 (m), 1560 (w), 1523 (m), 1482 (m), 1442 (w), 1297 (s), 1260 (s), 1161 (s), 1082 (s), 1028 (s), 800 (s), 756 (m). EI+ mass spectrum (m/z, %): 254 ([M]+, 2%), 237 (4%), 212 (25%), 196 (20%), 147 (70%), 119 (50%), 108 (15%), 91 (45%), 77 (15%), 64 (25%). ESI+ mass spectrum (m/z, %): 785 ([3M+Na]+, 4%), 763 ([3M+H]+, 2%), 531 ([2M+Na]+, 35%), 509 ([2M+H]+, 10%), 277 ([M+Na]+, 35%), 255 ([M+H]+, 100%). HRMS (ESI+): found [M+H]⁺ 255.0803, C₁₁H₁₄N₂O₃S requires 255.0803.

Epoxybenzothiadiazine (436b) was similarly obtained as a yellow oil (0.033 g, 24% yield) from the same reaction.

δH (400 MHz, CDCl₃): 1.82 (3H, s, CH₃), 1.84 (3H, s, CH₃), 5.32 (1H, s, br, NH), 6.23 (1H, s, NCH), 7.22 (1H, t, J 7.7, ArH), 7.48 (1H, t, J 7.9, ArH), 7.74 (1H, d, J 8.0, ArH), 7.95 (1H, d, J 8.4, ArH). δC (100 MHz, CDCl₃): 17.3 (CH₃), 67.4 (CH), 115.8 (q), 120.6 (CH), 124.5 (CH), 125.3 (CH), 127.2 (q), 131.9 (q), 132.7 (q), 133.5 (CH), 150.7 (q). v_max (thin film cm⁻¹): 3252 (br, m), 2923 (m), 1767 (s), 1724 (s), 1595 (m), 1575 (m), 1482 (m), 1450 (m), 1395 (s), 1374 (s), 1346 (s), 1299 (s), 1262 (m), 1213 (s), 1178 (s), 1150 (s), 1054 (m), 1001 (m), 955 (m), 909 (s), 839 (s), 810 (s), 760 (s). EI+ mass spectrum (m/z, %): 280 ([M]+, 4%), 182 (5%), 134 (5%), 118 (10%), 106 (3%), 98 (40%), 90 (100%), 70 (42%), 64 (40%). HRMS (ESI+): found [M+NH₄]+ 298.0862, C₁₂H₁₆N₃O₄S requires 298.0856.

Route B

A solution of the {o-{(9'-fluorenylmethoxycarbonylamino]benzenesulfonamidy}alkenone (407; 0.151 g, 0.322 mmol, 1.0 eq) in a mixture of triethylamine (0.23 ml, 1.58 mmol, 5.0 eq) and anhydrous dichloromethane (10 ml) was heated at reflux in an atmosphere of dry nitrogen whilst being monitored by TLC. Upon completion (approx. 15 hours) of the reaction, the solvent was evaporated off and the crude residue was purified by flash column chromatography (eluuent: PE:EtOAc/ 1:1) to yield the 1,2,5-benzothiadiazepine 1,1-dioxides (435) as follows:

4-Ethyl-2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxide (435b) was obtained as a light yellow oil which solidified on standing (0.053 g, 69% yield), mp: 89-92 °C.

δH (400 MHz, CDCl₃): 1.06 (3H, t, J 7.4, CH₃), 1.87 (1H, dq, J 7.4, 3.8, MeCH₂), 2.08 (1H, m, MeCH₂), 3.6-3.8 (1H, s, br, OH), 4.49 (1H, d, J 3.8, CHOH), 7.12 (1H, d, J 8.2, ArH), 7.45 (1H, t, J 7.7, ArH), 7.57 (1H, t, J 7.7, ArH), 7.96 (1H, d, J 8.0, ArH). δC (100 MHz, CDCl₃): 9.1 (CH₃), 28.5 (CH₂), 72.3 (CHOH), 117.0 (CH), 121.6 (q), 124.7 (CH), 127.2 (CH), 132.9 (CH), 133.6 (q), 160.4 (q). v_max (thin film cm⁻¹): 3475 (br, m), 3277 (br, m), 2963 (m), 2927 (m), 1604 (m), 1560 (w), 1525 (m), 1481 (m), 1440 (w), 1297 (m), 1261 (s), 1158 (s), 1079 (s), 1020 (s), 801
(s), 759 (s). ESI+ mass spectrum (m/z, %): 743 ([3M+Na]+, 5%), 503 ([2M+Na]+, 30%), 481 ([2M+H]+, 6%), 263 ([M+Na]+, 70%), 241 ([M+H]+, 100%). HRMS (ESI+): found [M+H]+ 241.0642, C_{10}H_{12}N_{2}O_{3}S requires 241.0647. C, H, N (%): found C 49.9, H 5.1, N 11.9; C_{10}H_{12}N_{2}O_{3}S requires C 50.0, H 5.0, N 11.7.

2,3-Dihydro-3-hydroxy-4-(i-propyl)-1,2,5-benzothiazepine 1,1-dioxide (435a) was obtained as a yellow solid (0.0129 g, 62% yield), mp: 117-119 °C from 4-{o-[(9'-fluorenylmethoxycarbonyl)aminobenzenesulfonamidyl]-but-1-en-3-one (407a; 0.391 g, 0.82 mmol).

δH (400 MHz, CDCl3): 0.87 (3H, d, J 6.9, CH3), 1.07 (3H, d, J 6.9, CH3), 2.34 (1H, qq, J 6.8, 6.7, Me2CH), 3.4-3.5 (1H, s, br, OH), 4.33 (1H, d, J 3.3, CHO)H), 7.13 (1H, d, J 8.2, ArH), 7.43 (1H, t, J 7.6, ArH), 7.54 (1H, t, J 7.8, ArH), 7.92 (1H, d, J 7.9, ArH), 9.40 (1H, s, br SO2NH).

δC (100 MHz, CDCl3): 15.3 (CH3), 19.0 (CH3), 32.8 (CH), 75.1 (CH), 117.2 (CH), 121.6 (q), 124.5 (CH), 127.1 (CH), 133.0 (CH), 133.6 (q), 160.8 (q). νmax (thin film cm⁻¹): 3477 (br, m), 3261 (br, m), 2965 (m), 2930 (m), 1602 (m), 1560 (w), 1523 (m), 1482 (m), 1442 (w), 1297 (s), 1260 (s), 1161 (s), 1082 (s), 1028 (s), 800 (s), 756 (m). EI+ mass spectrum (m/z, %): 254 ([M]+, 2%), 237 ([M-OH]+, 4%), 212 ([M-CHMe2]+H)+, 25%), 196 (20%), 147 (70%), 119 (50%), 108 (15%), 91 (45%), 77 (15%), 64 (25%). ESI+ mass spectrum (m/z, %): 785 ([3M+Na]+, 4%), 763 ([3M+H]+, 2%), 531 ([2M+Na]+, 35%), 509 ([2M+H]+, 10%), 277 ([M+Na]+, 35%), 255 ([M+H]+, 100%). HRMS (ESI+): found [M+H]+ 255.0803, C_{11}H_{14}N_{2}O_{3}S requires 255.0803. C, H, N (%): found C 51.8, H 5.6, N 10.8; C_{11}H_{14}N_{2}O_{3}S requires C 52.0, H 5.5, N 11.0.
7.1.8 Synthesis of 4-[(o-tert-butoxycarbamylamino)benzenesulfonylamidyl]-2-methyl-but-1-en-3-ol

To a solution of 4-(2-aminobenzenesulfonamidyl)-2-methyl-but-1-en-3-ol (405b; 0.041 g, 0.159 mmole, 1.0 eq) in anhydrous acetonitrile (2 ml) was added 4-dimethylaminopyridine (0.002 g, 0.0159 mmol, 0.1 eq), followed by di-tert-butyldicarbonate (0.16 ml, 0.159 mmol, 1.0 eq) at 0°C under an atmosphere of dry nitrogen. The mixture was further stirred for 20 minutes at 0°C and the solvent was removed in vacuo to give the crude product as a brown oil, which was purified by flash column chromatography (eluent: PE:EtOAcl 3:1) to yield 4-[(o-tert-butoxycarbamylamino)benzenesulfonylamidyl]-2-methyl-but-1-en-3-ol (431b; 0.028 g, 50% yield) as yellow oil.

H (400 MHz, CDCl₃): 1.35 (9H, s, 3xCH₃), 1.83 (3H, s, CH₃), 4.97 (1H, s, BoeNH), 7.20 (1H, td, J 8.0, 0.8, ArH), 7.35 (2H, td, J 7.4, 1.0, 2xArH), 7.44 (2H, t, J 7.4, 2xArH), 7.56 (1H, t, J 7.5, ArH), 7.65 (2H, d, J 7.4, 2xArH), 7.80 (2H, d, J 7.5, 2xArH), 7.90 (1H, dd, J 8.0, 1.4, ArH), 8.13 (1H, s, ArH), 8.75 (1H, s, CO₂NH). δC (100 MHz, CDCl₃): 18.2 (CH₃), 46.7 (CH₂), 46.8 (CH), 67.7 (CH₂), 73.1 (CH), 112.5 (CH₂), 120.0 (CH), 122.1 (CH), 123.4 (CH), 125.0 (CH), 127.2 (CH), 127.8 (CH), 129.3 (CH), 134.2 (CH), 136.0 (q), 141.3 (q), 143.5 (q), 143.8 (q), 153.3 (q, CO₂NH). νₘₐₓ (thin film cm⁻¹): 3502 (br, w), 3349 (br, m), 2949 (m), 1737 (s), 1588 (s), 1531 (s), 1444 (s), 1326 (s), 1291 (m), 1249 (m), 1216 (s), 1152 (s), 1132 (m), 1083 (m), 1048 (m), 910 (s), 755 (s), 740 (m). ES+ mass spectrum (m/z, %): 713 (45%), 603 (21%), 358 (16%), 357 (90%), 301 (100%), 283 (20%), 174 (31%). HRMS (ESI+): Found [M+H]+ 357.1483, C₁₆H₂₅O₅N₂S requires 357.1479.

The O-Boc derivative (432b) was similarly obtained as yellow oil (0.028 g, 50% yield) from the same reaction.

H (400 MHz, CDCl₃): 1.38 (9H, s, 3xCH₃), 1.49 (9H, s, 3xCH₃), 1.84 (3H, s, CH₃), 3.98 (1H, dd, J 14.7, 4.8, NHCH₂), 4.16 (1H, dd, J 14.7, 8.4, NHCH₂), 5.03 (1H, s, CH₂CH₂), 5.04 (2H, s, br, 2xNH), 5.14 (1H, s, CH₂CH₂), 5.32 (1H, q, J 6.6, CH₂CHOBoc), 6.69 (1H, d, J 8.3, ArH), 6.73 (1H, t, J 7.7, ArH), 7.30 (1H, t, J 7.7, ArH), 7.67 (1H, d, J 8.1, ArH). δC (100 MHz,
CDCl$_3$): 18.3 (CH$_3$), 27.7 (2x(CH$_3$)$_3$), 48.4 (CH$_2$), 77.6 (CH), 82.1 (q), 84.4 (q), 114.4 (CH$_2$), 116.8 (CH), 117.5 (CH), 120.8 (q), 130.8 (CH), 134.5 (CH), 140.7 (q), 146.3 (q), 151.0 (q), 152.7 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3493 (br, s), 3386 (s), 2981 (s), 1738 (s), 1623 (s), 1567 (m), 1486 (s), 1456 (s), 1254 (m), 1157 (s), 991 (m), 913 (s), 843 (s), 731 (s). ES$^+$ mass spectrum (m/z, %): 457 (22%), 401 (14%), 397 (21%), 379 (22%), 357 (87%), 301 (100%), 283 (15%), 239 (16%), 232 (14%), 174 (34%), 150 (6%), 128 (11%), 102 (10%), 84 (5%). HRMS (ESI$^+$): Found [M+H]$^+$ 457.2002, C$_{21}$H$_{33}$O$_7$N$_2$S requires 457.2003.

7.1.9 Synthesis of 4-[(o-tert-butoxycarbonylamino)benzenesulfonamidyl]-2-methylbut-1-en-3-one

To a solution of 4-[(o-tert-butoxycarbonylamino)benzenesulfonamidyl]-2-methyl-but-1-en-3-ol (431b; 0.061 g, 0.172 mmol, 1.0 eq) in anhydrous dichloromethane (5 ml) was added finely powdered Dess-Martin periodinane (0.150 g, 0.350 mmol, 2.1 eq) at ambient temperature under an atmosphere of dry nitrogen for 1 h. Evaporation of the solvent gave a residue, which was purified by flash column chromatography (eluent PE:EtOAc/ 3:2). The 4-[(o-tert-butoxycarbonylamino)benzenesulfonamidyl]-2-methyl-but-1-en-3-one (434b) was obtained as yellow oil (0.055 g, 92% yield).

$\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 1.33 (9H, s, 3xCH$_3$), 1.95 (3H, s, CH$_3$), 5.03 (2H, s, CH$_2$CO), 5.24 (2H, s, br, 2xNH$_2$), 5.90 (1H, s, C=CH$_2$), 6.03 (1H, s, C=CH$_2$), 6.71 (1H, d, J 8.3, ArH), 6.78 (1H, t, J 7.5, ArH), 7.32 (1H, t, J 8.4, ArH), 7.81 (1H, dd, J 8.2, 1.1, ArH). $\delta_{\text{C}}$ (100 MHz, CDCl$_3$): 17.7 (CH$_3$), 27.7 ((CH$_3$)$_3$), 51.3 (CH$_2$), 84.6 (q), 116.8 (CH), 117.5 (CH), 120.2 (q), 125.4 (CH$_2$), 131.0 (CH), 134.7 (CH), 141.5 (q), 146.5 (q), 150.8 (q), 193.9 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3470 (s), 3381 (s), 2928 (m), 1724 (s), 1692 (s), 1632 (s), 1485 (m), 1456 (m), 1348 (s), 1156 (m), 1066 (m), 908 (s), 735 (s). EI$^+$ mass spectrum (m/z, %): 355 (18%), 354 (100%), 156 (12%), 92 (35%), 84 (30%), 69 (39%), 57 (100%), 41 (37%). HRMS (EI$^+$): Found [M+]$^+$ 354.1242, C$_{16}$H$_{22}$O$_5$N$_2$S requires 354.1244.
7.1.10 Synthesis of 2-aminobenzenesulfonamidyl-2-methyl-but-1-en-3-one

To a stirring solution of 4-[(o-tert-butoxycarbonylamino)benzenesulfonyl]amino]-2-methyl-but-1-en-3-one (434b; 0.018 g, 0.050 mmol) in anhydrous dichloromethane (2 ml) was added trifluoroacetic acid (0.071 ml, 0.599 mmol) at 0°C under an atmosphere of dry nitrogen. The stirring was continued for 7 hrs, during which time the reaction mixture was allowed to warm up to ambient temperature. The reaction mixture was washed with aqueous NaOH (2 ml) and extracted with ethyl acetate (3 x 5 ml). The organic phase was dried over anhydrous MgSO₄, filtered under gravity and the volatiles were removed in vacuo. The crude product was purified by flash chromatography (eluent PE:EtOAc/3:2) to yield the 2-aminobenzenesulfonamidyl-2-methyl-but-1-en-3-one (408; 0.0083 g, 68%) as a yellow oil.

δ_H (400 MHz, CDCl₃): 1.84 (3H, s, CH₃), 4.15 (2H, d, J 4.7, NHCH₂), 4.94 (2H, s, br, NH₂), 5.78 (1H, m, br, NH), 5.85 (1H, s, C=CH-H), 5.90 (1H, s, C=CH-H), 6.76 (1H, d, J 8.1, ArH), 6.80 (1H, t, J 7.3, ArH), 7.33 (1H, t, J 7.0, ArH), 7.70 (1H, d, J 8.1, ArH). δ_C (100 MHz, CDCl₃): 17.5 (CH₃), 50.3 (CH₂), 83.5 (q), 115.2 (CH), 116.8 (CH), 124.2 (CH₂), 121.5 (q), 129.6 (CH), 133.5 (CH), 140.2 (q), 191.8 (q). ν_max (thin film cm⁻¹): 3421 (br, m), 3377 (br, m), 2924 (s), 2889 (s), 1730 (s), 1686 (s), 1620 (s), 1484 (s), 1456 (s), 1319 (m), 1145 (s), 1060 (s), 809 (m), 735 (m). EI+ mass spectrum (m/z, %): 255 ([M+H]+, 70%), 219 (8%), 205 (8%), 183 (6%), 157 (3%), 129 (10%), 96 (4%). HRMS (EI+): Found [M+H]^+ 255.0796, C₁₁H₁₅O₃N₂S requires 255.0798.
Experimental Part II

7.2.1 Synthesis of hex-2,4-dien-1-ol

To a stirring suspension of sodium methoxide (2.36 g, 43.69 mmol, 2.8 eq) and sodium borohydride (4.72 g, 124.83 mmol, 8.0 eq) in methanol (15 ml) at 0°C was added dropwise a solution of 2,4-hexadienal (449; 1.49 g, 15.50 mmol, 1.0 eq) over 20 minutes. The resulting mixture was further stirred for 30 minutes and allowed to warm up to ambient temperature and was added portion wise to an ice-water (15 ml) mixture. The reaction was acidified with 2M HCl to pH 2 and extracted with ethyl acetate (3x 15 ml). The organic phase was dried (MgSO₄), filtered and the solvent was removed in vacuo. The crude was purified by flash column chromatography (eluent: PE:EtOAc 2:3) to yield the hex-2,4-dien-1-ol (450; 1.125 g, 74% yield) as a thick yellow oil.

7.2.2 Synthesis of 1-bromo-2,4-hexadiene

To a stirring solution of hex-2,4-dien-1-ol (450, 1.82 g, 21.85 mmol, 1.0 eq), in anhydrous dichloromethane (10 ml) was added dropwise a solution of phosphorus tribromide (7.26 ml, 76.49 mmol, 3.5 eq) at 0°C, under an atmosphere of dry nitrogen. The resulting mixture was further stirred for 1 hr at 0°C, quenched at 0°C with ice-water (15 ml) and allowed to warm to ambient temperature. The mixture was extracted with dichloromethane (3x 10 ml) and the organic phase was dried (MgSO₄), filtered and the solvent was removed in vacuo. The crude 1-bromo-2,4-hexadiene (451; 1.54 g, 44% yield), was used without purification at the next stage.
7.2.3 Synthesis of cyclisation precursor (386)

To a stirring suspension of 2-aminobenzamide (0.540 g, 3.966 mmol, 1.0 eq), in anhydrous DMF (8 ml) was added triethylamine (0.72 ml, 5.156 mmol, 1.3 eq) dropwise at ambient temperature. Stirring of the reaction mixture was continued for a further 30 minutes at ambient temperature, followed by dropwise addition of a solution 1-bromo-2,4-hexadiene (451; 0.70 g, 4.362 mmol, 1.1 eq) in anhydrous dichloromethane (5 ml) and the whole reaction was stirred at ambient temperature for 3 hr. The reaction was quenched with saturated ammonium chloride solution (10 ml) and extracted with dichloromethane (2x 10 ml). The organic phase were combined, dried (MgSO4), filtered and the solvent was removed in vacuo and the crude was purified by flash column chromatography (eluent PE:EtOAc/ 3:2) to yield the cyclisation precursor (386, 0.279 g, 32% yield) as a yellow oil.

\[
\delta_\text{H} (400 \text{ MHz, CDCl}_3): 1.76 (3\text{H, d, } J = 6.7, \text{ CH}_3), 3.86 (2\text{H, d, } J = 5.5, \text{ NHCH}_2), 5.60-5.71 (2\text{H, m, } 2\text{x } =\text{CH}), 5.97 (2\text{H, s, br, } \text{NH}_2), 6.00-6.14 (1\text{H, m, } =\text{CH}), 6.23 (1\text{H, dd, } J = 15.0, 10.3, =\text{CH}), 6.59 (1\text{H, t, } J = 7.3, \text{ ArH}), 6.69 (1\text{H, d, } J = 8.6, \text{ ArH}), 7.32 (1\text{H, td, } J = 8.4, 1.2, \text{ ArH}), 7.40 (1\text{H, dd, } J = 7.7, 1.1, \text{ ArH}). \delta_\text{C} (100 \text{ MHz, CDCl}_3): 18.0 (\text{CH}_3), 44.6 (\text{CH}_2), 112.1 (\text{CH}), 113.1 (\text{q}), 114.5 (\text{CH}), 127.2 (\text{CH}), 128.2 (\text{CH}), 129.1 (\text{CH}), 130.8 (\text{CH}), 131.7 (\text{CH}), 133.3 (\text{CH}), 150.1 (\text{q}), 172.3 (\text{q}).
\]

\[\nu_{\text{max}}\ (\text{thin film } \text{cm}^{-1}): 3397 \text{ (br, s), 3333 (br, s), 3163 (br, s), 2932 (m), 2877 (m), 1663 (s), 1615 (s), 1586 (s), 1514 (s), 1489 (m), 1437 (m), 1411 (s), 1328 (m), 1296 (s), 1216 (s), 1166 (s), 1128 (s), 1048 (s), 986 (s), 909 (s), 846 (m), 747 (s). \text{ES}^+ \text{ mass spectrum (m/z, %): 271 ([M+H]^+, 16%), 226 ([M]^+, 85%), 198 (31%), 184 (75%), 172 (33%), 170 (100%), 156 (68%), 130 (48%), 119 (84%), 92 (48%), 81 (77%), 77 (81%), 65 (59%), 53 (64%), 41 (67%). HRMS (EI+): found [M+H]^+ 271.1328, C_{13}H_{17}N_2O requires 271.1326.\]
Experimental-Part III

7.3.1 Synthesis of 1-(2-aminobenzenesulfonyl)pyrroles

To a rapidly stirring solution of triethylamine (0.15-0.40 ml, 1.0 eq) and trimethylphosphite (0.25-0.68 ml, 2.0 eq) in anhydrous methanol (10 ml) was added the 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a-c; 0.30-0.50 g, 1.0 eq) in one portion and the mixture was stirred at room temperature under an atmosphere of dry nitrogen for 2 hrs. The volatiles were removed in vacuo and the crude mixture was purified by flash column chromatography (eluent PE:EtOAc/ 40:60 + 10% triethylamine). The 1-(2-aminobenzenesulfonyl)pyrroles (455a-c) were obtained as follows:

1-(2-aminobenzenesulfonyl)pyrrole (455a) was obtained as pale yellow oil (0.277 g, 50% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a; 0.660 g, 2.21 mmol)

δ_H (400 MHz, CDCl_3): 5.21 (2H, br s, NH_2), 6.29 (2H, t, J 2.3, pyrrole-H), 6.67 (1H, d, J 8.2, ArH), 6.74 (1H, t, J 7.4, ArH), 7.20 (2H, t, J 2.3, pyrrole-H), 7.29 (1H, td, J 8.5, 1.4, ArH), 7.70 (1H, dd, J 8.3, 1.4, ArH). δ_C (100 MHz, CDCl_3): 112.8 (2 x pyrrole-CH), 117.5 (CH), 117.9 (CH), 119.2 (q), 120.2 (2 x pyrrole-CH), 129.1 (CH), 135.4 (CH), 145.8 (q). v_max (thin film cm⁻¹): 3456 (s), 3347 (s), 2954 (s), 2851 (m), 1590 (s), 1486 (s), 1458 (s), 1373 (s), 1282 (m), 1186 (s), 1161 (s), 1106 (s), 1029 (s), 815 (s), 734 (s), 677 (m). EI+ mass spectrum (m/z, %): 222 ([M]^+, 22%), 156 (17%), 130 (4%), 108 (25%), 92 (100%), 65 (97%). HRMS (ESI+): Found [M+H]^+ 223.0537, C_{10}H_{11}N_{2}O_{2}S requires 223.0536. Identical to that in the literature.

1-(2-aminobenzenesulfonyl)-3-methylpyrrole (455b) was obtained as a pale yellow oil (0.495 g, 73% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (400b; 0.901 g, 2.88 mmol).

δ_H (400 MHz, CDCl_3): 2.03 (3H, s, CH_3), 6.05 (2H, dd, J 1.6, 1.3, NH_2), 6.75 (1H, t, J 8.0, ArH), 6.89 (1H, d, J 8.2, ArH), 6.93 (1H, s, pyrrole-H), 7.13 (1H, t, J 2.6, pyrrole-H), 7.26 (1H, td,
Chapter 7 Experimental Part III

$J$ 8.5, 1.5, $\text{ArH}$, 7.41 (1H, quartet, $J$ 4.7, 1.6, $\text{ArH}$). $\delta_{C}$ (100 MHz, CDCl$_3$): 11.7 (CH$_3$), 113.1 (CH), 117.8 (CH), 118.5 (CH), 121.6 (CH), 121.8 (q), 124.5 (CH), 128.7 (CH), 129.8 (q), 134.2 (CH), 147.5 (q). $v_{\text{max}}$ (thin film cm$^{-1}$): 3477 (m), 3342 (m), 2999 (m), 2954 (s), 2850 (s), 1591 (s), 1487 (s), 1356 (s), 1291 (m), 1263 (s), 1172 (s), 1031 (s), 914 (m), 816 (s), 760 (s), 732 (s), 677 (s), 607 (s). EI$^+$ mass spectrum (m/z, %): 236 ([M$^+$], 15%), 156 (19%), 108 (37%), 93 (100%), 65 (84%). HRMS (ESI$^+$): Found [M+H$^+$] $^{237.0734}$, $\text{C}_{11}\text{H}_{13}\text{N}_{2}\text{O}_{2}\text{S}$ requires 237.0732.

1-(2-aminobenzenesulfonyl)-3,4-dimethylpyrrole (455c) was obtained as a pale yellow oil (0.135 g, 50% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (400c; 0.350 g, 1.07 mmol).

$\delta_{H}$ (400 MHz, CDCl$_3$): 1.91 (6H, s, 2 x CH$_3$), 4.50-4.70 (2H, br s, NH$_2$), 6.63 (1H, d, $J$ 8.2, $\text{ArH}$) 6.71 (1H, t, $J$ 7.6, $\text{ArH}$), 6.84 (2H, s, 2 x pyrrole-H), 7.25 (1H, t, $J$ 7.4, $\text{ArH}$), 7.61 (1H, d, $J$ 8.1, $\text{ArH}$). $\delta_{C}$ (100 MHz, CDCl$_3$): 9.6 (CH$_3$), 10.1 (CH$_3$), 117.4 (CH), 117.6 (CH), 117.8 (CH), 120.0 (q), 124.2 (q), 129.2 (CH), 135.0 (CH), 145.6 (q). $v_{\text{max}}$ (thin film cm$^{-1}$): 3457 (s), 3377 (s), 2966 (m), 2919 (m), 1599 (m), 1484 (s), 1455 (m), 1348 (m), 1296 (m), 1068 (s), 1034 (s), 829 (s), 744 (m), 699 (m), 610 (m), 588 (m). EI$^+$ mass spectrum (m/z, %): 250 ([M$^+$], 70%), 185 (25%), 156 (20%), 108 (35%), 94 (100%), 65 (80%), 39 (50%). HRMS (ESI$^+$): Found [M+H$^+$] $^{251.0845}$, $\text{C}_{12}\text{H}_{14}\text{N}_{2}\text{O}_{2}\text{S}$ requires 251.0849.

7.3.2 Synthesis of 1-(2-formamidobenzenesulfonyl)pyrroles

Formic acid (0.036-0.193 g, 2.25 eq) was added to acetic anhydride (0.070-0.381 g, 2.0 eq) at 0°C and the solution was stirred at room temperature for 2 hrs. This solution was added to a solution of the 1-(2-aminobenzenesulfonyl)pyrrole (455a-c; 1.0 eq) in anhydrous tetrahydrofuran (5 ml) and the reaction mixture was stirred at room temperature for 20 h. The volatiles were removed in vacuo and the crude mixture was purified by flash column chromatography (eluent PE:EtOAc/ 40:60). The 1-(2-formamidobenzenesulfonyl)pyrroles (456a-c) were obtained as follows:
1-(2-formamidobenzenesulfonyl)pyrrole (455a) was obtained as pale yellow oil (0.083 g, 98% yield) from 1-(2-aminobenzenesulfonyl)pyrrole (456a; 0.076 g, 0.343 mmol), and was identical to that reported by Artico in all respects.97

1-(2-formamidobenzenesulfonyl)-3-methylpyrrole (455b) was obtained as pale yellow oil (0.383 g, 77% yield) from 1-(2-aminobenzenesulfonyl)-3-methylpyrrole (456b; 0.440 g, 1.864 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.05 (3H, s, \text{CH}_3), 6.16 (1H, s, \text{pyrrole-H}), 6.85 (1H, s, \text{pyrrole-H}), 7.05 (1H, t, J 2.6, \text{pyrrole-H}), 7.23 (1H, t, J 7.7, ArH), 7.31 (1H, d, J 7.4, ArH), 7.59 (1H, t, J 7.7, ArH), 7.79 (1H, d, J 8.0, ArH), 8.54 (1H, s, CHO), 9.40 (1H, br s, NH). \]
\[ \delta_C (100 \text{ MHz, CDCl}_3): 11.8 (\text{CH}_3), 116.5 (\text{CH}), 117.4 (\text{CH}), 120.5 (\text{CH}), 123.2 (\text{CH}), 124.6 (\text{CH}), 125.4 (q), 126.0 (q), 128.8 (\text{CH}), 129.9 (\text{CH}), 135.3 (\text{CH}), 158.9 (\text{CHO}). \]
\[ v_{\text{max}} \text{ (thin film ern)}: 3299 (s), 2953 (s), 1705 (s), 1677 (s), 1580 (s), 1517 (s), 1467 (s), 1433 (s), 1406 (s), 1361 (s), 1291 (m), 1261 (s), 1174 (s), 1096 (s), 1038 (s), 913 (s), 829 (s), 735 (s), 692 (s), 608 (s). \]
\[ \text{EI+ mass spectrum (m/z, %): 264 ([M]+, 50%), 184 (77%), 156 (45%), 120 (59%), 92 (81%), 81 (100%), 65 (95%), 53 (83%).} \]

HRMS (Cl+NH₃): Found [M+NH₄]⁺ 282.0905, C₁₂H₁₆N₃O₃S requires 282.0907.

1-(2-formamidobenzenesulfonyl)-3,4-dimethylpyrrole (455c) was obtained as pale yellow oil (0.120 g, 83% yield) from 1-(2-aminobenzenesulfonyl)-3,4-dimethylpyrrole (456c; 0.130 g, 0.523 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.97 (6H, s, 2 x \text{CH}_3), 6.85 (2H, s, 2 x \text{pyrrole-H}), 7.23 (1H, t, J 7.7, ArH), 7.61 (1H, t, J 7.7, ArH), 7.77 (1H, d, J 8.0, ArH), 8.52 (1H, d, J 7.9, ArH), 8.56 (1H, s, CHO), 9.45 (1H, br s, NH). \]
\[ \delta_C (100 \text{ MHz, CDCl}_3): 10.1 (\text{CH}_3), 117.5 (\text{CH}), 123.0 (\text{CH}), 124.2 (\text{CH}), 125.7 (q), 125.8 (q), 126.1 (q), 128.8 (\text{CH}), 135.1 (\text{CH}), 158.8 (\text{CHO}). \]
\[ v_{\text{max}} \text{ (thin film ern)}: 3290 (m), 3020 (w), 2921 (w), 1706 (s), 1674 (s), 1579 (m), 1514 (m), 1403 (m), 1358 (m), 1290 (m), 1216 (s), 1160 (s), 1071 (m), 669 (m), 611 (m). \]
\[ \text{EI+ mass spectrum (m/z, %): 278 ([M]+, 60%), 250 (10%), 228 (60%), 184 (85%), 156 (20%), 120 (50%), 95 (100%), 65 (85%).} \]

7.3.3 Synthesis of pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides

A solution of the 1-(2-formamidobenzenesulfonyl)pyrrole (456a-c; 1.0 eq) and phosphorus oxychloride (0.67-0.93 ml, 21.6 eq) in dichloroethane (2 ml) was heated at reflux temperature for 3 hrs. Saturated sodium hydrogen carbonate solution (4 ml) and ethyl acetate (4 ml) was added and the organic layer was separated and dried over NaSO₄. Evaporation of the solvent gave a residue, which was purified by flash column chromatography (eluent PE:EtOAc/ 40:60). The pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides (457a-c) were obtained as follows:

Pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457a) was obtained as pale yellow oil (0.043 g, 55% yield) from 1-(2-formamidobenzenesulfonyl)pyrrole (456a; 0.083 g, 0.331 mmol).

\[
\delta_H (400 MHz, CDCl_3): 6.45 (1H, t, J 3.3, pyrrole-H), 6.86 (1H, dd, J 3.6, 1.2, pyrrole-H), 7.43 (1H, t, J 7.6, ArH), 7.48 (1H, dm, J 8.1 pyrrole-H), 7.63 (1H, d, J 8.0, ArH), 7.66 (1H, t, J 7.7, ArH). \delta_C (100 MHz, CDCl_3): 112.6 (CH), 120.3 (CH), 123.2 (CH), 125.6 (CH), 126.6 (CH), 128.2 (q), 130.0 (q), 130.3 (CH), 134.7 (CH), 144.4 (q), 150.0 (N=CH).
\]

\[
\nu_{max} (\text{thin film em}^{-1}): 2926 (s), 1605 (s), 1583 (s), 1463 (s), 1406 (s), 1366 (s), 1289 (m), 1236 (m), 1191 (s), 1145 (s), 1125 (m), 1069 (s), 1051 (s), 909 (s), 823 (m), 765 (m), 732 (s), 696 (s), 594 (s). \text{EI}^+ \text{mass spectrum (m/z, %): 233 ([M+H]^+, 10%), 102 (100%), 74 (6%). HRMS (ESI+): Found [M+H]^+ 233.0381, C_{11}H_{10}N_{2}O_{2}S requires 233.0379.}
\]

1-methyl-pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457b) was obtained as pale yellow oil (0.067 g, 59% yield) from 1-(2-formamidobenzenesulfonyl)-3-methylpyrrole (456b; 0.121 g, 0.462 mmol).

\[
\delta_H (400 MHz, CDCl_3): 2.37 (3H, s, CH₃), 6.36 (1H, d, J 2.9, pyrrole-H), 7.44 (1H, t, J 7.4, ArH), 7.51 (1H, d, J 2.9, pyrrole-H), 7.66-7.75 (2H, m, 2 x ArH), 8.07 (1H, d, J 7.9, ArH), 8.66 (1H, s, N=CH). \delta_C (100 MHz, CDCl_3): 11.5 (CH₃), 114.8 (CH), 123.0 (q), 123.1 (CH), 124.6 (q), 125.5 (CH), 126.5 (CH), 129.9 (CH), 133.0 (q), 134.6 (CH), 143.9 (q), 148.6 (N=CH). \nu_{max} (\text{thin film em}^{-1}): 2927 (w), 1603 (s), 1580 (s), 1466 (m), 1365 (s), 1259 (m), 1187 (s), 1149 (m), 1069
(m), 910 (s), 829 (m), 765 (m), 733 (m). ES+ mass spectrum (m/z, %): 247 ([M+H]+, 100%), 172 (54%), 130 (45%), 112 (33%), 88 (15%), 58 (15%). HRMS (ES+): Found [M+H]+ 247.0532, C12H11N2O2S requires 247.0536.

1,2-dimethyl-pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457c) was obtained as pale yellow oil (0.040 g, 43% yield) from 1-(2-formamidobenzenesulfonyl)-3,4-dimethylpyrrole (456c; 0.100 g, 0.360 mmol).

δH (400 MHz, CDCl3): 2.06 (3H, s, CH3), 2.26 (3H, s, CH3), 7.33 (1H, s, pyrrole-H), 7.42 (1H, dt, J 8.0, 1.0, ArH), 7.60-7.73 (2H, m, 2 x ArH), 8.04 (1H, dd, J 7.9, 1.2, ArH), 8.62 (1H, s, N=CH) δC (100 MHz, CDCl3): 9.6 (CH3), 9.9 (CH3), 120.8 (CH), 123.6 (q), 124.9 (q), 125.3 (CH3), 126.2 (CH), 129.9 (CH), 130.1 (q), 132.5 (q), 134.4 (CH), 144.1 (q), 148.6 (N=CH). νmax (thin film ern“): 2924 (w), 1603 (s), 1582 (s), 1458 (m), 1365 (s), 1294 (m), 1181 (s), 1137 (m), 1107 (m), 910 (s), 832 (m), 767 (m), 733 (m). ES+ mass spectrum (m/z, %): 261 ([M+H]+, 100%), 86 (4%), 58 (25%). HRMS (ESI+): Found [M+H]+ 261.0691, C13H12N2O2S requires 261.0692.

7.3.4 Synthesis of 11-phenyl-[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides

A solution of benzohydroximoyl chloride (0.181 g, 1.163 mmol, 2.4 eq) in tetrahydrofuran (10 ml) was added dropwise over (10-12 h) with stirring to a mixture of 1-methylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457b; 0.121 g, 0.491 mmol, 1.0 eq) and triethylamine (16 ml, 1.171 mmol, 2.4 eq) in anhydrous tetrahydrofuran (10 ml) at ambient temperature, under an atmosphere of dry nitrogen for a total of 15-22 h. Upon completion, the volatiles were removed in vacuo and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc / 1:2) to yield the 11-phenyl-[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxides (477b-e) as follows:
11-phenyl-[1,2,4-oxadiazolo]-1-methylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (477a) was obtained as pale yellow oil (0.085 g, 47% yield).

$\delta_H$ (400 MHz, CDCl$_3$): 2.21 (3H, s, CH$_3$), 6.14 (1H, d, J 3.2, pyrrole-H), 6.85 (1H, d, J 7.6, pyrrole-H), 7.10 (1H, s, CH), 7.20-7.30 (2H, m, 2 x ArH), 7.30-7.50 (4H, m, 4 x ArH), 7.57 (2H, d, J 7.7, 2 x ArH), 7.94 (1H, dd, J 7.9, 1.4, ArH). $\delta_C$ (100 MHz, CDCl$_3$): 11.8 (CH$_3$), 91.9 (CH), 115.5 (CH), 119.5 (q), 122.3 (CH), 124.4 (q), 125.5 (CH), 127.4 (CH), 127.7 (CH), 127.8 (q), 128.5 (2 x CH), 128.8 (2 x CH), 131.1 (CH), 132.8 (q), 134.4 (CH), 135.9 (q), 155.6 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3145 (w), 3087 (w), 3066 (w), 2927 (m), 1721 (m), 1660 (m), 1585 (s), 1477 (s), 1444 (m), 1408 (m), 1358 (s), 1258 (s), 1179 (s), 1156 (s), 1089 (m), 908 (s), 836 (s), 730 (s), 694 (s), 648 (s). ES+ mass spectrum (m/z, %): 366 ([M+H]$^+$, 27%), 191 (21%), 132 (35%), 117 (26%), 85 (100%). HRMS (ESI+): Found [M+H]$^+$ 366.0905, C$_{19}$H$_{16}$N$_3$O$_3$S requires 366.0907.

11-Phenyl-[1,2,4-oxadiazolo]-1,2-dimethylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (477b) was obtained as pale yellow oil (0.201 g, 69% yield) in the same way from 1,2-dimethyl-pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457c; 0.202 g, 0.776 mmol).

$\delta_H$ (400 MHz, CDCl$_3$): 1.93 (3H, s, CH$_3$), 2.10 (3H, s, CH$_3$), 6.81 (1H, d, J 8.0, CH), 7.07 (1H, s, pyrrole-H), 7.23 (1H, t, J 7.23, ArH), 7.30-7.40 (3H, m, 3 x ArH), 7.45 (1H, t, J 7.5, ArH), 7.56 (2H, d, J 7.9, 2 x ArH), 7.90 (1H, d, J 7.9, ArH). $\delta_C$ (100 MHz, CDCl$_3$): 9.5 (CH$_3$), 10.0 (CH$_3$), 92.0 (CH), 119.6 (q), 119.8 (CH), 124.2 (q), 124.5 (q), 125.3 (CH), 127.3 (CH), 127.5 (CH), 128.2 (q), 128.4 (2 x CH), 128.7 (q), 128.8 (2 x CH), 131.1 (CH), 132.6 (q), 134.2 (CH), 135.9 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3145 (w), 3090 (w), 3070 (w), 1610 (w), 1584 (m), 1573 (m), 1500 (m), 1446 (m), 1409 (s), 1365 (s), 1308 (m), 1269 (s), 1197 (s), 1185 (s), 1174 (s), 1130 (m), 1085 (s), 905 (s), 842 (s), 774 (s), 699 (s). ES+ mass spectrum (m/z, %): 380 ([M+H]$^+$, 100%), 303 (10%), 277 (13%), 261 (35%), 249 (18%), 175 (10%), 141 (12%), 105 (18%), 89 (11%). HRMS (ESI+): Found [M+H]$^+$ 380.1063, C$_{20}$H$_{18}$N$_3$O$_3$S requires 380.1067.
7.3.5 Synthesis of ethyl[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide carboxylates

A solution of ethylchloroximidoacetate (0.291 g, 1.920 mmol, 2.4 eq) in tetrahydrofuran (10 ml) was added dropwise over (10-12 h) with stirring to a mixture of 1-methylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457b; 0.203 g, 0.824 mmol, 1.0 eq) and triethylamine (0.27 ml, 1.951 mmol, 2.4 eq) in anhydrous tetrahydrofuran (10 ml) at ambient temperature, under an atmosphere of dry nitrogen for a total of 15-22 h. Upon completion, the volatiles were removed in vacuo and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc / 1:2) to yield the ethyl[1,2,4-oxadiazolo]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide carboxylates (479a-b) as follows:

Ethyl[1,2,4-oxadiazolo]-1-methylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide 11-carboxylate (479a) was obtained as pale yellow oil (0.190 g, 66% yield).

\[
\delta_{H} (400 \text{ MHz, CDCl}_3): 1.28 (3H, t, J=7.1, \text{CO}_2\text{CH}_2\text{CH}_3), 2.12 (3H, s, \text{CH}_3), 4.25 (2H, m, \text{CO}_2\text{CH}_2\text{CH}_3), 6.13 (1H, s, \text{CH}), 7.11 (1H, s, \text{pyrrole-H}), 7.33 (1H, d, J=3.0, \text{pyrrole-H}), 7.54 (1H, t, J=7.6, \text{ArH}), 7.63 (1H, d, J=7.7, \text{ArH}), 7.70 (1H, t, J=7.6, \text{ArH}), 7.95 (1H, d, J=7.8, \text{ArH}).
\]

\[
\delta_{C} (100 \text{ MHz, CDCl}_3): 11.2 (\text{CH}_3), 13.8 (\text{CH}_3), 62.7 (\text{CH}_2), 91.3 (\text{CH}), 114.0 (\text{CH}), 121.1 (q), 123.9 (\text{CH}), 127.1 (\text{CH}), 129.0 (\text{CH}), 130.2 (q), 133.6 (\text{CH}), 134.5 (\text{CH}), 137.8 (q), 147.8 (q), 156.6 (q).
\]

\[v_{\text{max}} (\text{thin film cm}^{-1}): 3159 (m), 3100 (m), 3020 (m), 2926 (s), 1736 (s), 1574 (s), 1485 (s), 1444 (m), 1416 (m), 1362 (s), 1287 (m), 1259 (m), 1214 (s), 1193 (s), 1153 (s), 1094 (s), 1020 (m), 913 (m), 763 (s).
\]

ES+ mass spectrum (m/z, %): 362 ([M+H]+, 100%), 316 (10%), 282 (16%), 247 (15%), 89 (24%), 59 (16%). HRMS (ESI+): Found [M+H]+ 362.0804, C\text{16}H\text{16}N\text{3}O\text{5}S requires 362.0805.

Ethyl[1,2,4-oxadiazolo]-1,2-dimethylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide 11-carboxylate (479b) was obtained as pale yellow oil (0.101 g, 58% yield) from 3,5-dimethylpyrrolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (457c; 0.120 g, 0.461 mmol).

\[
\delta_{H} (400 \text{ MHz, CDCl}_3): 1.30 (3H, t, J=7.1, \text{CO}_2\text{CH}_2\text{CH}_3), 1.93 (3H, s, \text{CH}_3), 2.01 (3H, s, \text{CH}_3), 4.23-4.31 (2H, m, \text{CO}_2\text{CH}_2\text{CH}_3), 7.10 (1H, s, \text{pyrrole-H}), 7.14 (1H, s, \text{CH}), 7.52 (1H, td, J
7.3.6 Synthesis of 1-(2-phosphoramidobenzenesulfonyl) pyrroles

7.7, 1.2, ArH), 7.60 (1H, dd, J 7.9, 1.0, ArH), 7.68 (1H, td, J 7.7, 1.5, ArH), 7.95 (1H, dd, J 7.8, 1.4, ArH). δC (100 MHz, CDCl₃): 9.3 (CH₃), 9.9 (CH₃), 13.8 (CH₃), 62.7 (CH₂), 91.6 (CH), 121.0 (q), 121.5 (CH), 122.7 (q), 127.0 (CH), 128.9 (CH), 130.5 (q), 133.5 (CH), 134.2 (CH), 138.0 (q), 147.9 (q), 156.6 (q). νmax (thin film cm⁻¹): 1733 (s), 1582 (s), 1362 (s), 1310 (m), 1275 (m), 1205 (s), 1186 (s), 1130 (m), 1080 (s), 1018 (m), 903 (m), 818 (m), 786 (m), 764 (s). ES⁺ mass spectrum (m/z, %): 376 ([M+H]⁺, 41%), 262 (17%), 261 (100%), 74 (14%). HRMS (ESI⁺): Found [M+H]⁺ 376.0962, C₁₇H₁₈N₃O₆S requires 376.0966.

To a rapidly stirring solution of triethylamine (0.061-0.070 g, ½ eq) and trimethylphosphite (0.28-0.33 ml, 2.0 eq) in anhydrous methanol (10 ml) was added the 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a-c; 0.30-0.50 g, 1.0 eq) in one portion and the mixture was stirred at room temperature under an atmosphere of dry nitrogen for 2 h. Upon completion of the reaction (TLC), the mixture was washed with aqueous hydrochloric acid (10 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO₄, filtered under gravity and the volatiles were removed in vacuo. The crude product was purified by flash column chromatography (eluent: PE:EtOAc 3:2). The 1-(2-phosphoramidobenzenesulfonyl)pyrroles were obtained as follows:

1-(2-phosphoramidobenzenesulfonyl)pyrrole (462a) was obtained as pale yellow oil (0.291 g, 64% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a; 0.411 g, 1.378 mmol)

δH (400 MHz, CDCl₃): 3.72 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 6.31 (2H, t, J 2.3, pyrrole-H), 7.08 (1H, td, J 8.1, 1.0, ArH), 7.17 (2H, t, J 2.2, pyrrole-H), 7.38 (1H, s, br, NH), 7.42 (1H, d, J 8.5, ArH), 7.50 (1H, td, J 8.0, 1.3, ArH), 7.85 (1H, d, J 8.1, ArH). δC (100 MHz, CDCl₃): 53.5 (OCH₃), 53.6 (OCH₃), 113.6 (2x pyrrole-CH), 119.4 (CH), 120.5 (2x pyrrole-CH), 121.9 (CH),
124.2 (q), 129.4 (CH), 135.8 (CH), 138.8 (q).  $v_{\text{max}}$ (thin film cm$^{-1}$): 3338 (s), 3017 (s), 2956 (m), 2854 (m), 1600 (s), 1578 (s), 1492 (s), 1456 (s), 1412 (m), 1362 (s), 1310 (m), 1281 (s), 1216 (s), 1187 (s), 1162 (s), 1135 (m), 1057 (s), 1033 (s), 950 (s), 843 (m), 831 (m), 752 (s), 668 (s), 617 (s).  ES+ mass spectrum (m/z, %): 331 ([M+H]$^+$, 83%), 265 (11%), 264 (100%), 130 (10%), 102 (85%), 59 (13%).  HRMS (ESI+): Found [M+H]$^+$ 331.0512, CI$_2$H$_{16}$N$_2$O$_5$PS requires 331.0512.

1-(2-phosphoramidobenzenesulfonyl)-3-methylpyrrole (462b) was obtained as pale yellow oil (0.285 g, 69% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (400b; 0.375 g, 1.200 mmol).

$\delta_H$ (500 MHz, CDCl$_3$): 1.97 (3H, s, CH$_3$), 3.66 (3H, s, OCH$_3$), 3.69 (3H, s, OCH$_3$), 6.06 (1H, dd, $J$ 3.1, 1.5, NH), 6.82 (1H, s, pyrrole-H), 6.96-7.03 (2H, m, ArH + pyrrole-H), 7.31-7.38 (2H, m, ArH + pyrrole-H), 7.41 (1H, td, $J$ 8.0, 1.6, ArH), 7.73 (1H, dt, $J$ 8.1, 1.5, ArH).  $\delta_C$ (100 MHz, CDCl$_3$): 11.7 (CH$_3$), 53.6 (OCH$_3$), 53.6 (OCH$_3$), 116.0 (CH), 117.5 (CH), 119.3 (CH), 120.6 (CH), 121.8 (CH), 124.5 (q), 124.7 (q), 129.3 (CH), 135.5 (CH), 138.7 (q).  $v_{\text{max}}$ (thin film cm$^{-1}$): 3346 (s), 2957 (m), 1599 (s), 1577 (s), 1490 (s), 1463 (s), 1411 (m), 1357 (s), 1279 (m), 1257 (m), 1162 (s), 1094 (s), 1060 (s), 1018 (s), 944 (s), 830 (s), 765 (s), 730 (s).  EI+ mass spectrum (m/z, %): 367 ([M+Na]$^+$, 9%), 296 (2%), 242 (16%), 192 (3%), 158 (4%).  HRMS (ESI+): Found [M+Na]$^+$ 367.0488 C$_{13}$H$_{17}$N$_2$NaO$_5$PS.

1-(2-phosphoramidobenzenesulfonyl)-3,4-dimethylpyrrole (462c) was obtained as pale yellow oil (0.347 g, 75% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (400c; 0.421 g, 1.290 mmol).

$\delta_H$ (400 MHz, CDCl$_3$): 1.88 (6H, s, 2 x CH$_3$), 3.71 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 6.57 (1H, s, br, NH), 6.83 (2H, s, 2x pyrrole-H), 7.01 (1H, t, $J$ 7.6, ArH), 7.36 (1H, d, $J$ 8.3, ArH), 7.43 (1H, t, $J$ 8.6, ArH), 7.73 (1H, d, $J$ 8.1, ArH).  $\delta_C$ (100 MHz, CDCl$_3$): 9.8 (2x CH$_3$), 53.3 (2x OCH$_3$), 117.4 (2x pyrrole-CH), 119.0 (CH), 121.6 (CH), 124.4 (q), 125.0 (2x q), 129.0 (CH), 135.2 (CH), 138.3 (q).  $v_{\text{max}}$ (thin film cm$^{-1}$): 3332 (s), 2954 (s), 2926 (s), 2855 (s), 1599 (s), 1578 (s), 1492 (s), 1461 (s), 1412 (m), 1357 (s), 1280 (m), 1224 (m), 1164 (s), 1135 (s), 1059 (s), 1032 (s), 951 (s), 911 (s), 843 (s), 733 (s), 706 (m), 611 (s), 587 (s).  EI+ mass spectrum (m/z, %): 359 ([M+H]$^+$, 65%), 264 (100%), 192 (15%), 130 (10%), 102 (45%), 59 (10%).  HRMS (ESI+): Found [M+H]$^+$ 359.0843 C$_{14}$H$_{20}$N$_2$O$_5$PS requires 359.0842.
7.3.7 Synthesis of \( N-[o-(N',N'-\text{dimethylformamidinyl})\text{benzenesulfonyl}] \) formylpyrrole

To a stirring solution of \( N,N\text{-dimethylformamide} \) (0.09 ml, 1.127 mmol, 2.0 eq) in anhydrous dichloromethane (2 ml) was added phosphorus oxychloride (0.11 ml, 1.127 mmol, 2.0 eq) dropwise over the course of 2 mins at 0°C under an atmosphere of dry nitrogen. The stirring was continued for 15 mins, followed by dropwise addition of 1-(2-phosphoramidobenzenesulfonyl)-3,4-dimethylpyrrole (462c; 0.202 g, 0.564 mmol, 1.0 eq) in dichloromethane (2 ml) over an additional 5 mins. Stirring was continued for 18 hrs, during which time the reaction mixture was allowed to warm up to ambient temperature. The reaction mixture was washed with aqueous NaOH (5 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO\(_4\), filtered under gravity and the volatiles were removed in vacuo.

The crude product was purified by flash column chromatography (eluent: PE:EtOAc 3:2) to provide two products as follows:

1-(2-phosphoramidobenzenesulfonyl) formylpyrrole (470; 0.081 g, 38% yield) was obtained as a yellow oil.

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 2.00 (3\text{H, s, CH}_3), 2.27 (3\text{H, s, CH}_3), 3.77 (3\text{H, s, OCH}_3), 3.80 (3\text{H, s, OCH}_3), 7.04 (1\text{H, t, J 7.5, ArH}), 7.38-7.57 (3\text{H, m, 2xArH + pyrrole-H}), 7.68 (1\text{H, d, J 8.1, ArH}), 10.1 (1\text{H, s, CHO}). \]

\[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 9.9 (\text{CH}_3), 10.8 (\text{CH}_3), 54.1 (\text{(OCH}_3)_2), 120.0 (\text{CH}), 122.2 (\text{CH}), 123.8 (\text{q}), 124.5 (\text{q}), 127.3 (\text{CH}), 129.5 (\text{q}), 130.0 (\text{CH}), 136.2 (\text{CH}), 139.8 (\text{q}), 139.9 (\text{q}), 179.0 (\text{CHO}). \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1}) : 3348 (\text{s}), 3105 (\text{s}), 3018 (\text{s}), 2957 (\text{m}), 2928 (\text{m}), 2854 (\text{m}), 1662 (\text{s}), 1600 (\text{s}), 1578 (\text{s}), 1497 (\text{s}), 1468 (\text{s}), 1418 (\text{m}), 1378 (\text{m}), 1361 (\text{s}), 1318 (\text{m}), 1281 (\text{s}), 1263 (\text{s}), 1232 (\text{m}), 1216 (\text{m}), 1164 (\text{s}), 1130 (\text{s}), 1111 (\text{m}), 1051 (\text{s}), 1033 (\text{s}), 970 (\text{s}), 858 (\text{m}), 850 (\text{s}), 830 (\text{m}), 757 (\text{s}), 728 (\text{m}), 704 (\text{s}), 668 (\text{s}), 613 (\text{m}), 587 (\text{m}). \]

ES+ mass spectrum (m/z, %): 387 ([M+H]^+, 100%), 369 (30%), 359 (10%), 264 (25%), 124 (5%), 117 (18%), 96 (23%). HRMS (ESI+): Found [M+H]^+ 387.0768, \( C_{15}H_{20}N_2O_6PS \) requires 387.0774.

\( N-[o-(N',N'-\text{dimethylformamidinyl})\text{benzenesulfonyl}] \) formylpyrrole (471; 0.101 g, 54 % yield) was obtained as a pale yellow oil.
Chapter 7  Experimental Part III

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.99 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.01 (3H, s, NCH_3), 3.02 (3H, s, NCH_3), 6.76 (1H, dd, J = 8.0, 0.7, ArH), 7.10 (1H, td, J = 8.2, 1.1, ArH), 7.29 (1H, s, pyrrole-H), 7.42 (1H, s, N=CH), 7.46 (1H, td, J = 8.4, 1.5, ArH), 8.03 (1H, dd, J = 8.0, 1.5, ArH), 9.98 (1H, s, CHO). \delta_C (100 \text{ MHz, CDCl}_3): 9.5 (CH_3), 10.9 (CH_3), 34.4 (CH_3), 40.3 (CH_3), 120.6 (q), 121.6 (CH), 121.9 (CH), 128.2 (CH), 128.7 (q), 129.9 (CH), 130.2 (q), 135.5 (CH), 135.9 (q), 151.7 (q), 152.8 (CH), 180.5 (CHO). \]

\[ \nu_{max} (\text{thin film cm}^{-1}): 2924 (m), 1660 (m), 1631 (s), 1581 (s), 1558 (m), 1489 (m), 1469 (s), 1432 (m), 1414 (m), 1370 (s), 1280 (s), 1160 (s), 1132 (m), 1102 (s), 1061 (m), 1003 (s), 857 (s), 760 (m), 726 (s). \]

EI+ mass spectrum (m/z, %): 335 (20%), 334 (100%), 311 (8%), 102 (8%). HRMS (ESI+): [M+H]^+ 334.1224, C_{16}H_{20}N_3O_3PS requires 334.1220.

7.3.8  Synthesis of 1-(2'-aminobenzenesulfonyl)-2-formylpyrrole (472)

To a stirring solution of N,N-dimethylformamide (0.05 ml, 0.628 mmol, 1.2 eq) in anhydrous dichloromethane (1 ml) was added phosphorus oxychloride (0.06 ml, 0.628 mmol, 1.2 eq) dropwise over the course of 2 mins at 0°C under an atmosphere of dry nitrogen. The stirring was continued for 15 mins, followed by dropwise addition of the pyrrole (455c; 0.131 g, 0.523 mmol) in dichloromethane (2 ml) over additional 5 mins. The reaction mixture was allowed to warm up to ambient temperature and was stirred for 3 hrs. Upon completion the reaction mixture was washed with aqueous NaOH (5 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO_4, filtered under gravity and the volatiles were removed in vacuo. The crude residual product was purified by flash column chromatography (eluent: PE:EtOAc/ 3:2) to provide two products as follows:

1-(2'-aminobenzenesulfonyl)-2-formylpyrrole (472; 0.082 g, 57% yield) was obtained as a yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.02 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.79 (2H, br s, NH_2), 6.83 (1H, d, J = 8.0, ArH), 6.97 (1H, t, J = 7.8, ArH), 7.41 (1H, s, pyrrole-H), 7.75 (1H, t, J = 7.6, ArH), 7.97 (1H, d, J = 8.1, ArH), 10.5 (1H, s, CHO). \delta_C (100 \text{ MHz, CDCl}_3): 9.7 (CH_3), 10.8 (CH_3), 122.1 (CH), 178.5 (CHO). \]
123.4 (CH), 124.5 (q), 125.6 (q), 128.8 (CH), 130.1 (q), 131.3 (CH), 137.1 (CH), 140.5 (q), 140.9 (q), 180.3 (CHO). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3454 (s), 3380 (s), 2967 (m), 2928 (m), 1680 (s), 1600 (s), 1488 (s), 1461 (s), 1357 (m), 1318 (m), 1232 (m), 1216 (m), 1165 (s), 1130 (s), 1049 (s), 1033 (s), 839 (m), 755 (s), 710 (m), 668 (s), 587 (m). ES+ mass spectrum (m/z, %): 279 ([M+H]$^+$, 30%), 250 (10%), 185 (5%), 156 (35%), 122 (5%), 108 (25%), 94 (83%). HRMS (ESI+): Found [M+H]$^+$ 279.0821, C$_{13}$H$_{15}$N$_2$O$_3$S requires 279.0819.

$N$-$o$-($N'$,$N'$-dimethylformamidinyl)benzenesulfonyl] formylpyrrole (471; 0.074 g, 43% yield) was obtained as pale yellow oil.
7.4.1  Synthesis of 2-amino-N-(but-3-enyl)benzenesulfonamide

A stirring solution the of 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (402a-c; 1.0 eq) in aqueous hydrochloric acid/ tetrahydrofuran (1:1; ~10-20 ml) was heated under reflux for 3 hrs. On cooling the mixture was washed with brine (10 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO₄, filtered under gravity and the volatiles were removed in vacuo. The crude residual product was purified by flash silica column chromatography (eluent: PE:EtOAc/ 3:2). The 2-amino-N-(but-3-enyl)benzenesulfonamides were obtained as follows:

2-Amino-N-(but-3-enyl)benzenesulfonamide (480a) was obtained as a pale yellow oil (0.470 g, 47% yield) from 2-(2-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (402a; 1.050 g, 3.855 mmol).

δH (400 MHz, CDCl₃): 2.13 (2H, q, J 6.5, CH₂), 2.92 (2H, q, J 6.5, NCH₂), 4.67 (2H, s, br, NH₂), 5.01 (2H, d, J 10.9, =CH₂), 5.18 (1H, t, J 6.1, =CH), 5.60 (1H, ddd, J 17.0, 9.9, 3.3, NH), 6.75 (2H, m, 2x ArH), 7.28 (1H, t, J 7.8, ArH), 7.67 (1H, d, J 7.8, ArH). δC (100 MHz, CDCl₃): 31.9 (CH₂), 42.0 (CH₂), 117.7 (CH), 117.8 (CH), 117.9 (CH₂), 123.0 (q), 129.0 (CH), 132.7 (CH), 133.1 (CH), 144.5 (q). νmax (thin film cm⁻¹): 3479 (s), 3378 (s), 3298 (s, br), 2978 (m), 2939 (m), 1621 (s), 1600 (s), 1568 (s), 1484 (s), 1455 (s), 1318 (s), 1154 (s), 1076 (s, br), 1028 (m), 992 (m), 920 (s), 755 (s), 696 (s), 657 (s). ES+ mass spectrum (m/z, %): 226 ([M⁺], 35%), 214 (15%), 187 (4%), 157 (9%), 108 (24%), 92 (7%), 80 (10%). HRMS (ESI+): found [M+H]+ 227.0825, C₁₀H₁₅N₂O₂S requires 227.0824.

2-Amino-N-(3-methylbut-3-enyl)benzenesulfonamide (480b) was obtained as pale yellow oil (0.270 g, 51% yield) from 2-(2-aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (402b; 0.630 g, 2.201 mmol).
\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.52 (3H, s, CH_3), 2.05 (2H, t, J 6.9, NHCH_2CH_2), 2.93 (2H, quartet, J 6.6, NHCH_2), 4.60 (1H, s, =CH-H), 4.71 (1H, s, =CH-H), 5.00 (2H, s, br, NH_2), 5.22 (1H, t, br, J 6.1, NH), 6.70 (1H, t, J 7.7, ArH), 6.75 (1H, d, J 8.1, ArH), 7.24 (1H, td, J 7.7, 1.5, ArH), 7.64 (1H, dd, J 8.0, 1.3, ArH). \delta_C (100 \text{ MHz, CDCl}_3): 21.4 (CH_3), 36.6 (CH_2), 40.4 (CH_2), 112.4 (CH_2), 116.9 (CH), 117.4 (CH), 120.5 (q), 129.1 (CH), 133.8 (CH), 141.3 (q), 145.1 (q). \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1}\text{): } 3477 \text{ (s), } 3376 \text{ (s, br), } 3285 \text{ (s, br), } 2961 \text{ (s), } 2933 \text{ (s), } 2872 \text{ (m), } 1620 \text{ (s), } 1599 \text{ (s), } 1568 \text{ (s), } 1483 \text{ (s), } 1455 \text{ (s), } 1319 \text{ (s, br), } 1154 \text{ (s, br), } 1092 \text{ (s), } 1043 \text{ (s), } 910 \text{ (s), } 840 \text{ (m), } 755 \text{ (s), } 733 \text{ (s), } 697 \text{ (m). ES}^+ \text{ mass spectrum (m/z, %): } 241 ([M+H]^+, 12\%), 240 ([M^+]^+, 80\%), 227 (5\%), 186 (5\%), 156 (25\%), 108 (16\%), 93 (5\%), 80 (13\%), 65 (4\%). \text{HRMS (ESI+): found [M+H]^+ 241.1036, C}_{11}H_{17}N_2O_2S requires 241.1040. \]

2-Amino-N-(2,3-dimethylbut-3-enyl)benzenesulfonamide (480c) was obtained as yellow oil (0.280 g, 58% yield) from 2-(2-aminobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (402c; 0.570 g, 1.897 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 0.95 (3H, d, J 6.9, CH_3), 1.53 (3H, s, CH_3), 2.25 (1H, sextet, J 7.0, CH), 2.73 (1H, ddd, J 13.0, 8.8, 4.3, CH-H), 2.90 (1H, ddd, J 12.5, 7.5, 2.1, CH-H), 4.71 (2H, s, br, =CH_2), 4.82 (1H, s, br, NH), 4.86 (2H, s, br, NH_2), 6.78 (1H, d, J 8.1, ArH), 6.82 (1H, t, J 7.6, ArH), 7.34 (1H, td, J 8.4, 1.4, ArH), 7.71 (1H, dd, J 8.0, 1.4, ArH). \delta_C (100 \text{ MHz, CDCl}_3): 16.8 (CH_3), 18.6 (CH_3), 40.5 (CH), 46.2 (CH_2), 112.5 (CH_2), 117.6 (CH), 117.7 (CH), 121.3 (q), 129.6 (CH), 134.1 (CH), 145.0 (q), 146.0 (q). \nu_{\text{max}} \text{ (thin film cm}^{-1}\text{): } 3476 \text{ (br, s), } 3378 \text{ (br, s), } 2974 \text{ (m), } 2922 \text{ (m), } 1621 \text{ (s), } 1600 \text{ (s), } 1484 \text{ (s), } 1455 \text{ (s), } 1319 \text{ (s), } 1144 \text{ (s), } 1088 \text{ (s), } 1027 \text{ (s), } 911 \text{ (s), } 755 \text{ (s), } 735 \text{ (s). ES}^+ \text{ mass spectrum (m/z, %): } 255 ([M+H]^+, 5\%), 254 ([M^+]^+, 12\%), 253 (69\%), 227 (4\%), 187 (5\%), 139 (6\%), 80 (11\%). \text{HRMS (ESI+): found [M+H]^+ 255.1137, C}_{12}H_{19}N_2O_2S requires 255.1136. \]
7.4.2 Synthesis of aziridino 1,2,6-benzothiadiazocine 1,1-dioxides

To a stirred mixture of the 2-amino-N-(but-3-enyl)benzenesulfonamides (480a-c; 1.0 eq) and sodium hydrogen carbonate (0.159-0.336 g, 3.0 eq) in anhydrous acetonitrile (~10 ml) was added finely powdered iodine (0.479-1.014 g, 3.0 eq) portionwise at ambient temperature. The resulting mixture was further stirred until cyclisation was complete according to TLC analysis. The mixture was quenched with saturated aqueous sodium thiosulfate, which was added until decolorisation occurred, and the resulting mixture was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and the solvent evaporated in vacuo to give a crude product which was purified by flash column chromatography (eluent: PE:EtOAc/ 3:2). The aziridino 1,2,6-benzothiadiazocine-1,1-dioxides were obtained as follows:

**Aziridino-5-methyl-1,2,6-benzothiadiazocine-1,1-dioxide (496b)** was obtained as yellow oil (0.161 g, 49% yield) from 2-amino-N-(3-methylbut-3-enyl)benzenesulfonamide (480b; 0.320 g, 1.332 mmol).

δ₁ (400 MHz, CDCl₃): 1.35 (3H, s, CH₃), 1.51 (1H, t, J 11.2, NHCH-H), 2.02 (1H, ddd, J 8.4, 5.9, 2.5, CH₃CCH-H), 2.11 (1H, s, aziridino CH), 2.31 (1H, s, aziridino CH), 3.34 (1H, m, br, CH₃CCH-H), 3.80 (1H, m, br, NHCH-H), 5.25 (1H, t, J 6.2, NH), 6.85 (1H, d, J 7.9, ArH), 6.98 (1H, t, J 7.3, ArH), 7.34 (1H, td, J 8.4, 1.4, ArH), 7.82 (1H, dd, J 7.9, 1.3, ArH). δC (100 MHz, CDCl₃): 20.2 (CH₃), 35.8 (CH₂), 39.2 (CH₂), 40.2 (CH₂), 44.0 (q), 121.7 (CH), 122.0 (CH), 128.6 (CH), 133.0 (CH), 135.0 (q), 147.8 (q). νₘₐₓ (thin film cm⁻¹): 3101 (s), 3021 (m), 2990 (m), 2896 (m), 2896 (m), 1591 (s), 1566 (s), 1472 (s), 1439 (m), 1418 (m), 1382 (m), 1363 (s), 1285 (m), 1258 (s), 1216 (s), 1158 (s), 1109 (s), 1069 (m), 1048 (m), 995 (m), 935 (m), 878 (s), 866 (s), 758 (s, br), 702 (s), 669 (s). ES⁺ mass spectrum (m/z, %): 241 (6%), 240 (15%), 239 ([M+H]⁺, 100%), 192 (9%), 156 (6%), 123 (5%), 84 (6%), 59 (7%), 58 (72%). HRMS (ES⁺): found [M+H]⁺ 239.0845, C₁₁H₁₅N₂O₂S requires 239.0849.
Aziridino-4,5-dimethyl-1,2,6-benzothiadiazocine-1,1-dioxide (496c) was obtained as yellow oil (0.048 g, 30% yield) from 2-amino-N-(2,3-dimethylbut-3-enyl)benzenesulfonamide (480c; 0.160 g, 0.629 mmol)

$\delta_{H}$ (400 MHz, CDCl$_3$): 0.74 (3H, d, J 7.0, CHCH$_3$), 0.93 (3H, s, CCH$_3$), 2.01 (1H, sextet, J 7.2, CHCH$_3$), 2.24 (1H, s, aziridino CH), 2.40 (1H, s, aziridino CH), 3.26 (2H, m, br, NHCH$_2$), 6.96 (1H, d, J 8.0, ArH), 7.07 (1H, t, J 7.6, ArH), 7.43 (1H, t, J 8.2, ArH), 7.67 (1H, m, NH), 7.76 (1H, d, J 7.7, ArH). $\delta$$_C$ (100 MHz, CDCl$_3$): 14.9 (CH$_3$), 22.0 (CH$_3$), 35.3 (CH$_2$), 35.7 (CH), 47.5 (q), 48.0 (CH$_2$), 120.0 (q), 120.6 (CH), 121.8 (CH), 129.2 (CH), 132.4 (CH), 146.9 (q). $\nu_{max}$ (thin film cm$^{-1}$): 3317 (s), 3068 (m), 3020 (m), 2968 (m), 2935 (m), 1587 (s), 1471 (s), 1421 (s), 1381 (s), 1342 (m), 1313 (s), 1278 (m), 1215 (s), 1154 (s), 1116 (m), 1094 (m), 1076 (s), 1035 (m), 934 (m), 852 (m), 827 (s), 756 (s), 693 (m), 668 (m), 600 (m). ES+ mass spectrum (m/z, %): 255 (6%), 254 (14%), 253 ([M+H]$^+$, 100%), 188 (5%), 185 (34%), 98 (3%), 69 (4%), 59 (45%). HRMS (ES+): found [M+H]$^+$ 253.1006, C$_{12}$H$_{17}$N$_2$O$_2$S requires 253.1005.

7.4.3 Synthesis of 2-azido-N-(but-3-enyl)benzenesulfonamides

A stirring solution of the 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a-c; 1.0 eq) in aqueous hydrochloric acid/ tetrahydrofuran (1:1; ~10-20 ml) was heated under reflux for 3 h. On cooling the mixture was washed with brine (10 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO$_4$, filtered under gravity and the volatiles were removed in vacuo. The crude residual product was purified by flash silica column chromatography (eluent: PE:EtOAc/ 3:2). The 2-azido-N-(but-3-enyl)benzenesulfonamides were obtained as follows:

2-Azido-N-(but-3-enyl)benzenesulfonamide (501a) was obtained as pale yellow oil (0.108 g, 71% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (400a; 0.183 g, 0.613 mmol).
\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.12 (2H, q, J 6.7, CH_2), 2.97 (2H, q, J 6.5, NCH_2), 5.07 (2H, d, J 11.1, =CH_H), 5.18 (1H, t, J 5.9, =CH_H), 5.65 (1H, ddd, J 17.2, 10.3, 3.4, NH_H), 7.24 (1H, t, J 7.7, Ar_H), 7.30 (1H, d, J 8.1, Ar_H), 7.61 (1H, t, J 7.7, Ar_H), 7.96 (1H, d, J 7.9, Ar_H). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 33.4 (CH_2), 42.3 (CH_2), 117.8 (CH_2), 119.3 (CH), 124.7 (CH), 129.6 (q), 120.5 (CH), 133.9 (CH), 134.2 (CH), 137.4 (q). \]

\[ \nu_{max} \text{ (thin film cm}^{-1}\text{): 3368 (s), 2934 (m), 2134 (s), 1620 (s), 1599 (s), 1565 (s), 1483 (s), 1455 (s), 1437 (s), 1318 (s), 1089 (s), 1028 (m), 996 (m), 908 (s), 755 (s), 694 (s). }\]

ES+ mass spectrum (m/z, %): 253 ([M+H]^+, 8%), 252 ([M^+]^+, 40%), 224 (5%), 198 (7%), 183 (11%), 104 (20%), 90 (25%), 80 (3%). HRMS (ESI+): found [M+H]^+ 253.0761, C_{10}H_{13}N_{4}O_{2}S requires 253.0759.

2-Azido-N-(3-methylbut-3-enyl)benzenesulfonylamine (501b) was obtained as pale yellow oil (0.325 g, 81% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (400b; 0.471 g, 1.508 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.52 (3H, s, CH_3), 2.12 (2H, t, J 6.8, NHCH_2CH_2), 2.94 (2H, quartet, J 6.5, NHCH_2H), 4.62 (1H, d, J 0.9, =CH-H), 4.75 (1H, d, J 1.4, =CH-H), 5.21 (1H, t, br, J 5.9, NH_H), 7.19 (1H, td, J 7.9, 1.0, Ar_H), 7.24 (1H, dd, J 8.1, 0.9, Ar_H), 7.55 (1H, td, J 7.7, 1.2, Ar_H), 7.89 (1H, dd, J 7.8, 1.5, Ar_H). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 21.3 (CH_3), 36.7 (CH_2), 40.5 (CH_2), 112.4 (CH_2), 119.1 (CH), 124.4 (CH), 129.3 (q), 130.2 (CH), 133.8 (CH), 137.2 (q), 141.4 (q). \]

\[ \nu_{max} \text{ (thin film cm}^{-1}\text{): 3308 (s, br), 2937 (s, br), 2135 (s), 1650 (m), 1575 (s), 1472 (s), 1445 (s), 1332 (s), 1164 (s), 1126 (m), 1066 (s), 897 (s), 820 (s), 759 (s), 652 (s). Cl+(NH_3) mass spectrum (m/z, %): 284 (23%), 267 ([M+H]^+, 7%), 259 (13%), 258 (100%), 256 (28%), 241 (90%), 239 (63%), 202 (18%), 190 (48%), 173 (41%), 94 (56%), 84 (76%). HRMS (EI+): found 266.0837, C_{11}H_{14}N_{4}O_{2}S requires 266.0837.

2-Azido-N-(2,3-dimethylbut-3-enyl)benzenesulfonylamine (501e) was obtained as yellow oil (0.575 g, 78% yield) from 2-(2-azidobenzenesulfonyl)-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxide (400e; 0.860 g, 2.635 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.00 (3H, d, J 6.9, CH_3), 1.56 (3H, s, CH_3), 2.35 (1H, sextet, J 7.0, CH), 2.73 (1H, ddd, J 12.6, 9.0, 4.3, CH-H), 2.94 (1H, ddd, J 12.4, 7.5, 2.2, CH-H), 4.76 (1H, s, =CH-H), 4.89 (1H, s, =CH-H), 4.99 (1H, m, br, NH_H), 7.24-7.35 (2H, m, Ar_H), 7.63 (1H, td, J 8.8, 1.3, Ar_H), 8.00 (1H, dd, J 7.9, 1.2, Ar_H). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 16.9 (CH_3), 18.6 (CH_3), 40.6 (CH), 46.4 (CH_2), 112.3 (CH_2), 119.2 (CH), 124.8 (CH), 129.5 (q), 130.8 (CH), 134.0 (CH), 137.5 (q), 146.1 (q). \]

\[ \nu_{max} \text{ (thin film cm}^{-1}\text{): 3305 (w, br), 2925 (s, br), 2133 (s), 1612 (m), 1575 (m), 1471 (s), 1445 (m), 1332 (s), 1289 (m), 1264 (s), 1164 (s), 1066 (m), 895 (s), 819 (m), 733 (s). ES+ mass spectrum (m/z, %): 281 ([M+H]^+, 72%), 253 (39%), 224 (9%), 188 (24%), 183 (100%), 174 (100%). }\]
(14%), 156 (6%), 108 (23%), 92 (46%). HRMS (El+): found 281.1026, C_{12}H_{17}N_{4}O_{2}S requires 266.1026.

7.4.4 Synthesis of pyrrolo-1,2,4-benzothiadiazine 1,1-dioxides

A solution of 2-azido-N-(but-3-enyl)benzenesulfonamide (501a-c; 1.0 eq) in dimethylformamide (~5-15 ml) was heated under reflux for 2-3 hrs. On cooling, the solvent was removed in vacuo and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/3:2). The pyrrolo-1,2,4-benzothiadiazine 1,1-dioxides were obtained as follows:

Pyrrolo-1,2,4-benzothiadiazine 1,1-dioxide (516a) was obtained as a yellow oil (0.017 g, 18% yield) from 2-azido-N-(but-3-enyl)benzenesulfonamide (501a; 0.103 g, 0.407 mmol).

\[
\delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.91-2.01 (1H, m, CH-H), 2.09-2.24 (2H, m, CH2), 2.26-2.41 (1H, m, CH-H), 3.16-3.23 (1H, m, CHCH-H), 3.45-3.61 (1H, m, CHCH-H), 4.28 (1H, s, CH), 5.47 (1H, d, J 4.4, NH), 6.62 (1H, d, J 8.3, ArH), 6.81 (1H, t, J 7.5, ArH), 7.28 (1H, t, J 7.8, ArH), 7.65 (1H, d, J 7.9, ArH).
\]

\[
\delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 21.7 (CH2), 33.6 (CH2), 46.9 (CH2), 71.2 (CH), 115.4 (CH), 117.4 (q), 118.1 (CH), 125.3 (CH), 133.4 (CH), 142.3 (q).
\]

\[
\nu_{\text{max}} \text{ (thin film ern - cm}^{-1}\text{): 3371 (br, m), 3269 (br, w), 2922 (s), 1599 (m), 1482 (s), 1453 (s), 1317 (s), 1242 (s), 1153 (s), 1101 (m), 1047 (m), 986 (m), 873 (m), 760 (s). ES+ mass spectrum (m/z, %): 225 ([M+H]^{+}, 96%), 214 (8%), 188 (27%), 174 (16%), 156 (9%), 118 (27%), 92 (17%), 85 (16%), 70 (12%). HRMS (ES+): found [M+H]^{+} 225.0689, C_{10}H_{13}N_{2}O_{2}S requires 225.0692.
\]

Pyrrolo-1,2,4-benzothiadiazine 1,1-dioxide (516b) was obtained as yellow oil (0.076 g, 45% yield) 2-azido-N-(3-methylbut-3-enyl)benzenesulfonamide (501b; 0.190 g, 0.713 mmol).

\[
\delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.78 (3H, s, CH3), 1.85-2.03 (2H, m, CH3CCH2), 2.04-2.10 (1H, m, CH-H), 2.17-2.27 (1H, m, CH-H), 3.37 (1H, ddd, J 15.4, 9.7, 4.0, CH-H), 3.67 (1H, ddd, J 14.7, 10.0, 3.7, CH-H), 4.56 (1H, s, NH), 6.63 (1H, d, J 8.3, ArH), 6.78 (1H, t, J 7.7, ArH), 7.25 (1H, t, J 8.5, ArH), 7.62 (1H, d, J 7.9, ArH).
\]

\[
\delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 19.9 (CH2), 26.9 (CH3), 42.5 (CH2), 50.9 (CH2), 79.0 (q), 115.8 (CH), 117.8 (CH), 125.3 (CH), 133.2 (CH), 142.0 (q), 145.0 (q).
\]

\[
\nu_{\text{max}} \text{ (thin film ern - cm}^{-1}\text{): 3371 (br, m), 3269 (br, w), 2922 (s), 1599 (m), 1482 (s), 1453 (s), 1317 (s), 1242 (s), 1153 (s), 1101 (m), 1047 (m), 986 (m), 873 (m), 760 (s). ES+ mass spectrum (m/z, %): 225 ([M+H]^{+}, 96%), 214 (8%), 188 (27%), 174 (16%), 156 (9%), 118 (27%), 92 (17%), 85 (16%), 70 (12%). HRMS (ES+): found [M+H]^{+} 225.0689, C_{10}H_{13}N_{2}O_{2}S requires 225.0692.
\]
Experimental part IV

Pyrrolo-1,2,4-benzothiadiazine 1,1-dioxide (517c) was obtained as yellow oil (0.076 g, 45% yield) 2-azido-N-(2,3-dimethylbut-3-enyl)benzenesulfonamide (501c; 0.130 g, 0.464 mmol).

δ_H (400 MHz, CDCl₃): 1.73 (3H, s, CH₃), 1.78 (3H, s, CH₃), 1.88 (1H, dd, J 12.9, 10.2, CH₃CH-HCH₃), 2.21 (1H, dd, J 13.0, 7.1, CH₃CH-HCH₃), 2.41-2.48 (1H, m, CH₃CHH₂N), 3.23 (1H, dd, J 10.3, 7.0, NCH-H), 3.58 (1H, t, J 10.0, NCH-H), 4.56 (1H, s, NH), 6.61 (1H, d, J 8.3, ArH), 6.76 (1H, t, J 7.9, ArH), 7.24 (1H, td, J 8.4, 1.3, ArH), 7.68 (1H, dd, J 8.0, 1.3, ArH). δ_C (100 MHz, CDCl₃): 18.6 (CH₃), 27.2 (CH₃), 28.3 (CH), 51.0 (CH₂), 57.9 (CH₂), 79.8 (q), 115.3 (CH), 117.5 (CH), 129.3 (CH), 133.2 (CH), 142.3 (q), 145.0 (q). ν_max (thin film cm⁻¹): 3479 (m), 3366 (s), 3295 (s), 2965 (s), 2932 (s), 2875 (m), 1707 (m), 1677 (m), 1605 (s), 1484 (s), 1453 (s), 1322 (s), 1261 (m), 1224 (m), 1157 (s), 1072 (m), 1037 (m), 995 (m), 751 (s). ES+ mass spectrum (m/z, %): 271 (20%), 253 ([M+H]⁺, 100%), 188 (5%), 185 (10%), 173 (11%), 98 (35%), 59 (23%). HRMS (ES+): found [M+H]⁺ 253.1008, C₁₂H₁₇N₂O₂S requires 253.1005.

7.4.5 Synthesis of 2-triphenylphosphoranyl-N-(3-methylbut-3-enyl)benzenesulfonamide (502b)

A stirring solution of the 2-(2-N-(triphenylphosphoranylidene)sulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (401b; 0.631 g, 1.154 mmol, 1.0 eq) in aqueous hydrochloric acid/tetrahydrofuran (1:1; 15 ml) was heated under reflux for 3 hrs. On cooling the mixture was washed with brine (10 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO₄, filtered under gravity and the volatiles were removed in vacuo. The crude residual product was purified by flash silica column chromatography (eluents: PE:EtOAc/
Chapter 7 Experimental part IV

3.2. The 2-triphenylphosphoranyl-N-(3-methylbut-3-enyl)benzenesulfonyl amide (502b) was obtained as pale yellow solid (0.478 g, 83% yield).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.53 (3H, s, CH\text{3}), 2.04 (2H, t, J 6.9, NHCH}_2\text{CH}_2), 2.93 (2H, m, NHCH}_2\text{CH}_2), 4.40 (2H, s, –CH}_2\text{H), 6.47 (1H, d, J 8.2, ArH), 6.66 (1H, s, br, NH), 6.72 (1H, t, J 7.5, ArH), 7.03 (1H, td, J 8.9, 1.6, ArH), 7.40-7.62 (9H, m, 9x ArH), 7.70-7.80 (6H, m, 6x ArH), 7.89 (1H, dd, J 8.6, 1.4, ArH). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 22.1 (\text{CH}_3), 37.4 (\text{CH}_2), 41.5 (\text{CH}), 111.9 (\text{CH}_2), 116.5 (\text{CH}), 122.0 (\text{CH}), 115.3 (\text{CH}), 128.9 (q), 129.0 (\text{CH, PPh}_3), 129.1 (\text{CH, PPh}_3), 129.6 (q), 129.7 (q), 129.9 (\text{CH}), 132.3 (\text{CH}), 132.3 (\text{CH}), 132.4 (\text{CH, PPh}_3), 132.5 (\text{CH, PPh}_3), 132.6 (q), 142.1 (q), 149.1 (q). \]

\[ \nu_{\text{max}} (\text{thin film cm}^{-1}): 3227 (\text{br, m}), 3059 (\text{m}), 3020 (\text{s}), 2973 (\text{m}), 2936 (\text{m}), 1649 (\text{m}), 1585 (\text{s}), 1552 (\text{m}), 1465 (\text{s}), 1438 (\text{s}), 1341 (\text{s}), 1289 (\text{m}), 1216 (\text{s}), 1155 (\text{s}), 1109 (\text{s}), 1064 (\text{m}), 1043 (\text{m}), 1016 (\text{m}), 999 (\text{m}), 754 (\text{s}). \]

ES+ mass spectrum (m/z, %): 503 (10%), 502 (30%), 501 ([M+H]+, 90%), 279 (8%), 174 (3%), 152 (3%), 85 (5%), 59 (6%). HRMS (ES+): found [M+H]+ 501.1777, C\text{30}H\text{29}N\text{2}O\text{2}PS requires 501.1760.

7.4.6 Synthesis of 2-nitro-N-(but-3-enyl)benzenesulfonamides

\[
\begin{align*}
\text{507a:} & \quad X=\text{SO}_2 \\
\text{507b:} & \quad X=\text{CO} \\
\text{508a:} & \quad X=\text{SO}_2 \\
\text{508b:} & \quad X=\text{CO}
\end{align*}
\]

A stirring solution of the 2-(2-nitroaryl)-1,2-thiazine 1-oxide (507a or 507b; 1.0 eq) in aqueous hydrochloric acid / tetrahydrofuran (1:1; ~10-20 ml) was heated under reflux for 3 h. On cooling the mixture was washed with brine (10 ml) and extracted with ethyl acetate (3x 10 ml). The organic phase was dried over anhydrous MgSO\text{4}, filtered under gravity and the volatiles were removed in vacuo. The crude product was purified by flash silica column chromatography (eluent: PE:E\text{tOAc}/ 3:2). The homoallylic nitro were obtained as follows:

2-Nitro-N-(3-methylbut-3-enyl)benzenesulfonamide (508a) was obtained as pale yellow oil (0.165 g, 43% yield) from 2-(2-nitrobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (507a; 0.451 g, 1.422 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.63 (3H, s, CH\text{3}), 2.25 (2H, t, J 6.7, NHCH}_2\text{CH}_2), 3.24 (2H, quartet, J 6.4, NHCH}_2\text{CH}_2), 4.69 (1H, s, =CH-H), 4.82 (1H, s, =CH-H), 5.34 (1H, t, br, J 5.3, NH), 7.74-7.82 (2H, m, ArH), 7.84-7.93 (1H, m, ArH), 8.12-8.18 (1H, m, ArH). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 21.6 (\text{CH}_3), 37.2 (\text{CH}_2), 41.3 (\text{CH}_2), 113.4 (\text{CH}_2), 125.4 (\text{CH}), 131.0 (\text{CH}), 132.7 (q), 132.8 (\text{CH}), 187 \]
133.7 (CH), 141.0 (q), 148.0 (q). $v_{\text{max}}$ (thin film cm$^{-1}$): 3281 (br, s), 2928 (m), 1659 (s), 1620 (s), 1562 (s), 1528 (s), 1447 (m), 1319 (m), 1247 (m), 1144 (s), 1087 (m), 910 (m), 849 (m), 755 (s), 696 (m). ES+ mass spectrum (m/z, %): 271 ([M+H]$^+$, 3%), 226 (5%), 202 (15%), 186 (75%), 141 (33%), 92 (10%), 76 (50%). CI+ mass spectrum (m/z, %): 288([M+NH$_4]^+$, 100%), 271 ([M+H]$^+$, 15%). HRMS (EI+): found [M+H]$^+$ 271.0719, C$_{11}$H$_{13}$N$_2$O$_4$S requires 271.0722.

2-Nitro-N-(3-methylbut-3-enyl)benzamide (508b) was obtained as yellow oil (0.127 g, 51% yield) from 2-(2-nitrobenzeneamide)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (507b; 0.301 g, 1.070 mmol).

$\delta_H$ (400 MHz, CDCl$_3$): 1.78 (3H, s, $CH_3$), 2.35 (2H, t, $J$ 6.8, $CH_2CH_2NH$), 3.58 (2H, quart, $J$ 6.9, $CH_2NH$), 4.79 (1H, s, MeC=CH$_2$), 4.85 (1H, s, MeC=CH$_2$), 6.00 (1H, s, br, NH), 7.49 (1H, dd, $J$ 7.5, 1.5, ArH), 7.56 (1H, td, $J$ 7.8, 1.5, ArH), 7.65 (1H, td, $J$ 7.5, 1.3, ArH), 8.03 (1H, dd, $J$ 8.1, 1.1, ArH). $\delta_C$ (100 MHz, CDCl$_3$): 21.9 (CH$_3$), 36.9 (CH$_2$), 37.6 (CH$_2$), 112.5 (CH$_2$), 124.5 (CH), 128.7 (CH), 130.3 (CH), 133.0 (q), 133.6 (CH), 142.3 (q), 146.5 (q), 166.3 (q, CONH). $v_{\text{max}}$ (thin film cm$^{-1}$): 3278 (bs), 3089 (m), 2939 (m), 1682 (s), 1660 (s), 1562 (s), 1528 (s), 1447 (m), 1348 (s), 1318 (m), 1247 (m), 1077 (m), 915 (m), 859 (m), 756 (s), 669 (m). ESI+ mass spectrum (m/z, %): 257 ([M+Na]$^+$, 20%), 235 ([M+H]$^+$, 60%).

### 7.4.7 Synthesis of N-(2-nitrobenzoyl)-3-iodo-3-methylpyrrolidine

To a stirred mixture of the 2-nitro-N-(but-3-enyl)benzamide (508a or 508b; 1.0 eq) and sodium hydrogen carbonate (0.226-0.326 g, 3.0 eq) in anhydrous acetonitrile (~10 ml) was added finely powdered iodine (0.682-0.986 g, 3.0 eq) portionwise at ambient temperature. The resulting mixture was further stirred until cyclisation was complete according to TLC analysis. The mixture was then quenched with saturated aqueous sodium thiosulfate, which was added until decolorisation occurred, and the resulting mixture was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO$_4$, filtered and the solvent evaporated in vacuo to give a crude product which was purified by flash column chromatography (eluent: PE:EtOAc/ 3:2). The 3-iodo-3-methyl pyrrolidine were obtained as follows:

188
N-(2-nitrosulfonyl)-3-iodo-3-methylpyrrolidine (509a) was obtained as yellow oil (0.270 g, 53% yield) from 2-nitro-N-(3-methylbut-3-enyl)benzenesulfonamide (508a; 0.350 g, 1.295 mmol).

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{): 1.27 (3H, s, CH}_3\text{), 1.80 (1H, m, ICCH}_3\text{CH-H), 1.97 (1H, m, ICCH}_3\text{CH-H), 3.18 (1H, d, J 10.0, NCH-H), 3.29 (1H, d, J 10.0, NCH-H), 3.59 (1H, m, NCH-HCH}_2\text{), 3.84 (1H, m, NCH-HCH}_2\text{), 7.81 (3H, m, 3x ArH), 8.13 (1H, d, J 7.0, ArH).} \]

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{): 19.6 (CH}_2\text{), 25.1 (CH}_3\text{), 31.8 (CH}_2\text{), 42.4 (CH}_2\text{), 52.7 (q), 125.0 (CH), 131.1 (CH), 132.3 (CH), 133.2 (q), 134.6 (CH), 146.8 (q).} \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1}\text{): 2934 (s), 2914 (m), 1590 (s), 1578 (s), 1532 (s, br), 1440 (s), 1367 (s, br), 1315 (s), 1253 (m), 1175 (m), 1122 (s), 1084 (s), 1025 (m), 990 (m), 853 (s), 756 (m), 659 (m), 626 (m).} \]

N-(2-nitrobenzoyl)-3-iodo-3-methylpyrrolidine (509b) was obtained as yellow oil (0.295 g, 91% yield) from 2-nitro-N-(3-methylbut-3-enyl)benzeneamide (508b; 0.210 g, 0.896 mmol).

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{): 1.46 (3H, s, CH}_3\text{), 1.83 (1H, dt, J 13.8, 5.9, ICCH}_3\text{CH-H), 2.06 (1H, dt, J 13.9, 6.3, ICCH}_3\text{CH-H), 3.27 (1H, d, J 10.5, NCH-H), 3.34 (1H, d, J 10.5, NCH-H), 3.53 (2H, t, J 6.1, NCH}_2\text{), 7.47 (1H, t, J 7.7, ArH), 7.55 (1H, t, J 7.5, ArH), 7.67 (1H, d, J 7.6, ArH), 7.75 (1H, d, J 8.0, ArH).} \]

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{): 13.3 (CH}_2\text{), 24.8 (CH}_3\text{), 29.8 (CH}_2\text{), 40.8 (CH}_2\text{), 75.6 (q), 123.5 (CH), 129.3 (q), 130.1 (CH), 130.4 (CH), 132.2 (CH), 148.5 (q), 153.7 (q).} \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1}\text{): 2980 (s), 2934 (s), 2865 (s), 1733 (m), 1668 (s, br), 1611 (s), 1578 (s), 1532 (s, br), 1445 (s), 1356 (s, br), 1300 (s), 1253 (m), 1122 (s), 1084 (s), 1025 (m), 913 (m), 859 (s), 784 (s), 761 (m), 722 (s), 701 (s), 679 (m), 648 (m).} \]

ES+ mass spectrum (m/z, %): 362 (15%), 361 ([M+H]+, 100%), 235 (10%), 211 (4%), 179 (15%), 150 (17%). HRMS (ES+): found [M+H]+ 361.0040, C\text{12H}_{14}\text{N}_{2}\text{O}_{3}\text{I requires 361.0044.}
Experimental-Part V

7.5.1 Synthesis of N-Fmoc protected pyrrolidine-2-methanol\textsuperscript{173}

\[
\begin{align*}
\text{Fmoc-Cl} & \quad \text{NaHCO}_3 \\
\text{DCM, r.t.} & \quad \text{HO}\text{N}_2
\end{align*}
\]

To a solution of the (S)-prolinol (522; 2.00 g, 19.773 mmol, 1.0 eq) in anhydrous dichloromethane (30 ml) was added sodium hydrogen carbonate (3.500 g, 41.522 mmol, 2.1eq) and 9-fluorenylmethyl chloroformate (5.00 g, 41.522 mmol, 2.1 eq) under an atmosphere of dry nitrogen. The reaction mixture was stirred at ambient temperature for 12 hrs, and distributed between dichloromethane/water (1:1; 30 ml) and extracted with dichloromethane (3x 15 ml), dried over MgSO\textsubscript{4}, and filtered under gravity. Evaporation of the solvent gave the crude product as an orange oil, which was purified by flash chromatography (eluent: PE:EtOAc/ 3:2) to yield N-Fmoc protected pyrrolidine-2-methanol (523; 5.263 g, 82% yield) as a colourless oil.

\[\delta_H (400 \text{ MHz, CDCl}_3): 1.63-2.00 (4H, m, CHCH_2CH_2), 3.00 (1H, s, br, OH), 3.30-3.52 (2H, m, CHCH_2OH), 3.60-3.70 (2H, m, NCH_2), 3.99 (1H, m, CHCH_2OH), 4.22 (1H, t, J 6.8, Fmoc CH), 4.35-4.60 (2H, m, Fmoc CH_2), 7.32 (2H, t, J 7.4, 2x ArH), 7.40 (2H, t, J 7.3, 2x ArH), 7.60 (2H, d, J 7.2, 2x ArH), 7.75 (2H, d, J 7.4, 2x ArH). \]  
\[\delta_C (100 \text{ MHz, CDCl}_3): 23.6 (CH_2), 28.0 (CH_2), 46.8 (CH_2), 46.9 (CH), 60.1 (CH), 65.5 (CH_2), 67.1 (CH_2), 119.6 (2x CH), 124.5 (2x CH), 126.7 (2x CH), 127.4 (2x CH), 140.9 (q), 143.6 (q), 143.7 (q), 154.8 (q), 156.3 (q). \]  
\[v_{\text{max}} \text{ (thin film cm}^{-1})\text{: 3428 (br, s), 2953 (s), 2879 (s), 1682 (s), 1418 (s), 1356 (s), 1246 (s), 1194 (s), 1049 (s), 985 (m), 908 (s), 878 (m), 759 (s), 739 (s), 647 (s). \]
7.5.2 Synthesis of N-Fmoc protected (S)-prolinal

To a solution of N-Fmoc protected (S)-prolinol (523; 0.863 g, 2.669 mmol, 1.0 eq) in anhydrous dichloromethane (5 ml) was added finely powdered Dess-Martin periodinane (1.245 g, 2.935 mmol, 1.1 eq) at ambient temperature under an atmosphere of dry nitrogen for 1 h. Evaporation of the solvent gave a residue, which was purified by flash column chromatography (eluent PE:EtOAc/3:2). The N-Fmoc protected (S)-prolinal (524) was obtained as yellow oil (1.653 g, 92% yield).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.75-2.01 (2H, m, CH_2CHCHO), 2.02 (2H, m, NCH_2CH_2), 3.55 (2H, m, NCH_2), 4.02/4.21 (1H, 2x t, J 6.1, Fmoc CH), 4.25-4.37 (1H, m, CHCHO), 4.39-4.60 (2H, m, Fmoc CH_2), 7.30-7.45 (2H, m, 2x ArH), 7.50-7.70 (2H, m, 2x ArH), 7.73-7.85 (2H, m, 2x ArH), 9.25/9.58 (1H, 2x s, CHO). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 23.5/24.4 (CH_2), 26.5/27.7 (CH_2), 46.6 (CH_2), 47.1 (CH), 64.7/65.1 (CH) 67.2/67.4 (CH_2), 119.9 (2x CH), 124.6 (CH), 124.7 (CH), 124.9 (CH), 125.0 (CH), 127.0 (CH), 127.6 (CH), 141.1 (q), 141.2 (q), 143.6 (q), 143.8 (q), 154/155.2 (q), 199.7/199.8 (q). \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1}\text{): 2980 (s), 2884 \text{ (s), 2812 (m), 2714 (w), 1736 (s), 1702 (s), 1580 (m), 1478 (m), 1451 (s), 1418 (s), 1372 (m), 1355 (s), 1243 (s), 1187 (m), 1124 (s), 1047 (s), 992 (m), 760 (s), 741 (s). \]

EI+ mass spectrum (m/z, %): 322 ([M+H]^+, 26%), 282 (16%), 180 (15%), 179 (100%), 158 (43%), 144 (23%), 142 (13%), 114 (44%), 89 (70%), 59 (10%). HRMS (ESI+): found [M+H]^+ 322.1434 C_{20}H_{20}N_{03} requires 322.1433.

7.5.3 Synthesis of (2S)-N-(9'-fluorenylmethoxycarbonyl)-pyrrolidine-2-ethene

To a stirring suspension of methyltriphenylphosphonium bromide (0.709 g, 1.985 mmol) in anhydrous THF (15 ml) was added n-BuLi (1.6 M solution in hexane, 1.24 ml, 1.985 mmol).
dropwise at -78°C under an atmosphere of dry nitrogen. Stirring of the reaction mixture was continued for a further 30 minutes at -10°C, followed by dropwise addition of a solution N-Fmoc-(S)-prolinol (524; 0.581 g, 1.808 mmol) in anhydrous THF (8 ml) and the whole reaction mixture was allowed to stir at ambient temperature for 4 hr. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml) and extracted with ethyl acetate (2x 20 ml). The organic phase was collected, dried (MgSO₄), filtered and the solvent was removed in vacuo and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (2S)-N-(9'-fluorenylmethoxycarbonyl)-pyrrolidine-2-ethene as a mixture of rotamers (525; 0.182 g, 31 % yield) in the form of a yellow oil.

δH (400 MHz, CDCl₃): 1.75-2.14 (4H, m, CHCH₂CH₂), 3.50 (2H, m, NCH₂), 4.15-4.61 (4H, m, CHCH=CH₂, Fmoc CH & CH₂), 4.90-5.25 (2H, m, =CH₂), 5.77 (1H, m, =CH), 7.28-7.36 (2H, m, 2x ArH), 7.37-7.50 (2H, m, 2x ArH), 7.58-7.70 (2H, m, 2x ArH), 7.73-7.85 (2H, m, 2x ArH). δC (100 MHz, CDCl₃): 22.4/23.5 (CH₂), 31.2/32.0 (CH₂), 46.4/46.7 (CH₂), 47.4 (CH), 59.0/59.5 (CH), 66.9 (CH₂), 114.1/114.3 (CH₂), 119.9 (2x CH), 120 (CH), 124.9 (q), 125.1 (2x CH), 126.9 (2x CH), 127.6 (2x CH), 137.9 (q), 138.3 (q), 141.3 (q), 144.2 (q). νmax (thin film cm⁻¹): 2981 (s), 2882 (m), 1749 (m), 1677 (s), 1425 (s), 1383 (m), 1337 (m), 1265 (m), 1194 (m), 1110 (s), 1052 (m), 908 (m), 773 (s).

7.5.4 Synthesis of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-methanol

To a stirred solution of (S)-prolinol (522; 3.00 g, 29.68 mmol, 1.0 eq) in 4M NaOH (20 ml) was added ethyl chloroformate (3.4 ml, 38.56 mmol, 1.2 eq) over 10 min at 0°C and the mixture was stirred at the same temperature for 30 min, followed by ambient temperature for further 30 min. The reaction mixture was neutralized with 2M HCl and extracted with dichloromethane (3x 10 ml). The extract was dried (MgSO₄), filtered and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (eluent: Pe:EtOAc/ 2:3) to yield the (S)-(−)-1-ethoxycarbonylpyrrolidine-2-methanol (531; 4.80 g, 93% yield) as a thick yellow oil.

νmax (thin film cm⁻¹): 3433 (s, br), 2979 (s), 2880 (s), 1749 (m), 1677 (s), 1425 (s), 1383 (m), 1337 (m), 1265 (m), 1194 (m), 1110 (s), 1052 (m), 908 (m), 773 (s).
7.5.5 Synthesis of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde

Method A

To a stirred solution of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-methanol (531; 3.50 g, 20.20 mmol, 1.0 eq) and triethylamine (20 ml, 141.45 mmol, 7.0 eq) in DMSO (20 ml) and dichloromethane (2 ml) was added portionwise sulfur trioxide pyridine complex (12.90 g, 80.83 mmol, 4.0 eq) at 0°C. The reaction mixture was stirred at 0°C for 1 hr and diluted with diethyl ether (10 ml). The ethereal solution was washed with brine (15 ml) and extracted with dichloromethane (3x 15 ml), dried (MgSO₄), and filtered. The volatiles were removed in vacuo and the residue was purified by flash column chromatography (eluent: PE:EtOAc/ 3:2) to yield the (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde (532; 2.88 g, 83% yield) as a yellow oil.

Method B

To a solution of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-methanol (531; 3.79 g, 21.88 mmol, 1.0 eq) in anhydrous dichloromethane (40 ml) was added pyridinium chlorochromate (8.02 g, 37.20 mmol, 1.7 eq) and the whole was stirred vigorously for 3 hours under an atmosphere of dry nitrogen. The dark reaction mixture was quenched with ether (100 ml) and the supernatant liquid was removed by decantation. The black tar residue was washed thoroughly with ethyl acetate (3x 30 ml) and the combined organic layers were collected, dried (MgSO₄), and filtered under gravity. Evaporation of the solvent gave the crude product as a brown oil, which was purified by flash chromatography (eluent: PE:EtOAc/ 3:2) to yield (S)-(-)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde (532; 2.10 g, 56% yield) as an yellow oil.

Method C

A solution of oxalyl chloride [2M solution in dichloromethane] (5.2 ml, 10.39 mmol, 1.2 eq) in anhydrous dichloromethane (15 ml) was cooled to -78°C. Following the dropwise addition of a solution of anhydrous dimethylsulfoxide (1.5 ml, 20.77 mmol, 2.4 eq) in anhydrous dichloromethane (5 ml), the reaction mixture was stirred for 5 min. A solution of (S)-(-)-1-ethoxycarbonylpyrrolidine-2-methanol (531; 1.50 g, 8.66 mmol, 1.0 eq) in dichloromethane (5 ml) was added to the reaction mixture. After 5 min of stirring diisopropylethylamine (7.5 ml, 43.28
mmol, 5 eq) was added, and the reaction mixture was allowed to warm to ambient temperature for 1 hr. Upon completion the reaction mixture was diluted with diethyl ether/water (1:1; 10 ml) mixture and extracted with dichloromethane (3x 15 ml), dried (MgSO₄), and filtered under gravity. Evaporation of the solvent gave the crude product as a orange oil, which was purified by flash column chromatography (eluent: PE:EtOAc/3:2) to yield (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde (532; 1.13 g, 76% yield) as a yellow oil.

δ_H (400 MHz, CDCl₃): 1.09-1.27 (3H, m, CH₃), 1.68-2.15 (4H, m, 2x CH₂), 3.36-3.57 (2H, m, CH₂), 4.00-4.15 (3H, m, CH₂CH₃ + CH₃), 9.47 (1H, d, J 12.0, CHO). δ_C (100 MHz, CDCl₃): 13.9/14.0 (CH₃), 23.1/23.9 (CH₂), 25.9/27.2 (CH₂), 45.9/46.4 (CH₂), 60.9 (CH₂), 64.1/64.5 (CH), 154.1/154.9 (q), 199.6 (CH). v_max (thin film cm⁻¹): 2980 (s), 2917 (m), 2849 (m), 1736 (s), 1699 (s, br), 1466 (m), 1420 (s), 1382 (s), 1347 (s), 1266 (s), 1186 (m), 1121 (s), 1022 (m), 772 (s). EI+ mass spectrum (m/z, %): 173 (3%), 172 ([M+H]+, 65%), 142 (30%), 127 (7%), 100 (15%), 99 (90%). HRMS (ESI+): found [M+H]+ 172.0943 C₈H₁₄N⁰₃ requires 172.0941.

7.5.6 Synthesis of (S)-(−)-2-ethenyl-1-ethoxycarbonylpyrrolidine

Method A

A suspension of NaH (60% mineral oil dispersion; 0.201 g, 1.1 eq) in dry hexane (3 ml) was stirred under an atmosphere of dry nitrogen for 10 min, after which the hexane was removed by syringe and the sodium hydride was washed in the same manner with three further aliquots of hexane (3 ml). Anhydrous DMSO (3 ml) was added to the flask containing neat NaH, and the mixture was heated with stirring at 65-75°C until the evolution of hydrogen ceased. The mixture was cooled to 0°C, and a solution of methyltriphenylphosphonium bromide (2.50 g, 1.1 eq) in DMSO (8 ml) was added over 10 min, and the mixture was allowed to warm to ambient temperature for 1½ hr. A solution of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde (532; 1.10 g, 6.43 mmol, 1.0 eq) in DMSO (5 ml) was added to the above solution and the mixture was stirred at ambient temperature for 2 hr. Upon completion the reaction mixture was diluted with water (30 ml) and extracted with hexane (3x 10 ml), dried over MgSO₄ and filtered under gravity. Evaporation of the solvent gave the crude product as a pale yellow oil, which was purified by flash
chromatography (eluent: PE:EtOAc/ 3:2) to yield the (S)-(−)-2-ethenyl-1-ethoxycarbonyl-pyrrolidine (533; 0.55 g, 50% yield) as a yellow oil.

**Method B**

To a stirring suspension of methyltriphenylphosphonium bromide (2.70 g) in anhydrous THF (20 ml) was added n-BuLi (1.6 M solution in hexane, 7.26 mmol, 4.54 ml) dropwise at -78°C under an atmosphere of dry nitrogen. Stirring of the reaction mixture was continued for a further 30 minutes at -10°C, followed by dropwise addition of a solution (S)-(−)-1-ethoxycarbonyl-pyrrolidine-2-carbaldehyde (532; 1.13 g, 6.60 mmol, 1.0 eq) in anhydrous THF (5 ml) and the whole reaction mixture was allowed to stir at ambient temperature for 4 hr. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml) and extracted with ethyl acetate (2x 20 ml). The organic phase was collected, dried (MgSO₄), filtered and the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (S)-(−)-2-ethenyl-1-ethoxycarbonyl-pyrrolidine as a mixture of rotamers (533; 0.55 g, 49% yield) in the form of a yellow oil.

δ<sub>H</sub> (400 MHz, CDCl₃): 1.24 (3H, m, br, CH₃), 1.72 (1H, s, br, CH₂CH-HCH₂), 1.84 (2H, m, br, NCHCH₂), 2.00 (1H, m, br, CH₂CH-HCH₂), 3.44 (2H, s, br, NCH₂), 4.13 (2H, q, br, OCH₂), 4.32 & 4.39 (1H, m, br, NCH), 5.09 (2H, m, =CH₂), 5.74 (1H, s, br, =CH). δ<sub>C</sub> (100 MHz, CDCl₃): 14.0/14.1 (CH₃), 22.4/23.3 (CH₂), 31.1/31.8 (CH₂), 46.1/46.3 (CH₂), 57.9/58.7 (CH), 60.6 (CH₂), 113.7/114.0 (CH₂), 138.1/138.4 (CH), 154.6/155.0 (q). v<sub>max</sub> (thin film cm⁻¹): 3448 (w), 2981 (s), 2882 (m), 2281 (m), 1736 (s), 1698 (s, br), 1467 (m), 1421 (s), 1382 (s), 1346 (s), 1266 (m), 1173 (m), 1124 (s), 1068 (m), 1023 (m), 912 (m), 772 (s). ES+ mass spectrum (m/z, %): 171 (5%), 170 ([M+H]+, 25%), 142 (36%), 127 (17%), 99 (13%), 98 (100%). HRMS (ESI+): found [M+H]+ 170.1176, C₉H₁₆NO₂ requires 170.1176.
7.5.7 Synthesis of (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-ethene

To a vigorously stirred suspension of finely ground KOH (2.59 g, 46.12 mmol, 26 eq) in ethylene glycol (8 ml) and hydrazine hydrate (0.28 ml, 8.87 mmol, 5.0 eq) under an atmosphere of dry nitrogen was added (S)-(−)-2-ethenyl-l-ethoxycarbonylpyrrolidine (533; 0.30 g, 1.77 mmol, 1.0 eq), and the mixture was heated under reflux (~195°C) for 4 hr. The reaction mixture was cooled to ambient temperature and diluted with (1:1) diethyl ether/water (8 ml) mixture and extracted with diethyl ether (3x 5 ml), and dried over finely ground NaOH. Triethylamine (0.37 ml, 2.66 mmol, 1.5 eq) was added to the above ethereal solution containing the amine (526) at 0°C under an atmosphere of dry nitrogen and the mixture was stirred for 10 min, followed by a dropwise addition of a solution of the acid chloride (0.48 g, 2.643 mmol, 1.5 eq) in diethyl ether (5 ml) and the whole reaction mixture was allowed to stir at ambient temperature for 18 hr. The reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (2x 10 ml). The organic phases were combined, dried over MgSO₄, and filtered under gravity. The volatiles were removed in vacuo and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-ethene as a mixture of rotamers (527; 0.21 g, 49% yield) in the form of a yellow oil.

δH (400 MHz, CDCl₃): 1.62&1.87 (3H, m, CH₂-CHH), 1.93&2.05 (1H, m, CH₂-CHH), 3.07&3.24 (1H, 2x m, CHH), 3.48&3.69 (1H, 2x m, CHH), 4.00&4.71 (1H, 2x m, br, CH), 4.55&5.22 (1H, 2x d, J 17.0&17.1, =CH-H), 4.77&5.06 (1H, 2x d, J 10.3&10.4, =CH-H), 5.43&5.76 (1H, 2x ddd, J 16.6, 10.2, 4.1 & J 16.1, 10.4, 5.6, =CH), 6.94-7.23 (3H, m, ArH), 7.21-7.34 (1H, m, ArH). δC (100 MHz, CDCl₃): 21.6/23.1 (CH₂), 30.4/31.8 (CH₂), 45.3/47.7 (CH₂), 57.9/60.6 (CH), 113.9/114.4 (CH₂), 118.0 (CH), 124.2/124.7 (CH), 127.4/127.7 (CH), 129.2 (q), 129.6/129.8 (CH), 135.5 (q), 136.5/137.1 (CH), 166.3/166.9 (q). νmax (thin film cm⁻¹): 2974 (s), 2879 (s), 2128 (s), 1718 (m), 1633 (s, br), 1598 (s), 1578 (m), 1480 (s), 1449 (s), 1415 (s), 1293 (s), 1148 (m), 1089 (m), 1041 (m), 990 (m), 920 (s), 753 (s). ES+ mass spectrum (m/z, %): 243 ([M+H]⁺, 32%), 215 (67%), 177 (24%), 147 (15%), 146 (50%), 120 (57%), 118 (13%), 81 (29%), 79 (70%). HRMS (ESI+): found [M+H]⁺ 243.12403, C₁₃H₁₃N₄O requires 243.12403.
7.5.8 Synthesis of 11a-hydroxy-11-methyl-pyrrolo[2,1-c][1,4]benzodiazepine-5-one

A solution of (2S)-N-(2-azidobenzoyl)-pyrrolidine-2-ethene (527; 0.271 g, 1.11 mmol) in DMF (20 ml) was heated at reflux for 3 hr. The reaction mixture was cooled, and evaporation of the solvent gave the crude product as an orange oil, which was purified by flash chromatography (eluent: PE:EtOAc/ 3:2) to yield the pyrrolo[2,1-c][1,4]benzodiazepine (539; 0.091 g, 38% yield) as a pale yellow oil.

$\delta_H$ (400 MHz, CDCl$_3$): 1.52 (3H, s, CH$_3$), 1.91-2.05 (1H, m, CH$_2$), 2.08-2.19 (1H, m, CH$_2$), 2.70 (2H, q, J 8.6, 5.0, CH$_2$), 3.18 (1H, td, J 14.5, 3.0, CH$_2$), 4.68 (1H, dt, J 10.4, 3.7, CH$_2$), 5.24 (1H, s, OH), 6.70 (1H, d, J 8.0, ArH), 6.82 (1H, t, J 7.5, ArH), 7.30 (1H, t, J 7.8, ArH), 7.89 (1H, d, J 7.8, ArH). $\delta_C$ (100 MHz, CDCl$_3$): 22.1 (CH$_3$), 22.2 (CH$_2$), 35.6 (CH$_2$), 37.5 (CH$_2$), 75.1 (q), 114.2 (q), 114.7 (CH), 118.8 (CH), 128.6 (CH), 133.9 (CH), 143.3 (q), 163.2 (q), 203.7 (q). $\nu_{\text{max}}$ (thin film cm$^{-1}$): 3315 (br), 3009 (m), 2972 (m), 2929 (m), 2871 (m), 1729 (s), 1628 (s, br), 1507 (s), 1421 (m), 1389 (m), 1319 (m), 1294 (m), 1217 (m), 1158 (m), 1029 (m), 1011 (m), 892 (s), 754 (s). ES+ mass spectrum (m/z, %): 253 (25%), 231 (85%), 213 (19%), 201 (18%), 120 (100%), 112 (17%), 89 (17%), 84 (12%). HRMS (ESI+): found [M+H]$^+$ 231.1129, C$_{13}$H$_{15}$N$_2$O$_2$ requires 231.1128.
7.5.9 Synthesis of aziridinopyrrolobenzodiazepin-5-one (538)

**Method A**

A solution of (2S)-N-(2-azidobenzoyl)-pyrrolidine-2-ethene (527; 0.131 g, 0.541 mmol) in anhydrous acetonitrile (20 ml) under an atmosphere of dry nitrogen was heated at refluxed for 20 hr. Upon completion (TLC) the reaction mixture was cooled, and evaporation of the solvent gave the crude product as a yellow oil, which was purified by flash chromatography (eluent: PE:EtOAc/3:2) to yield the aziridinopyrrolobenzodiazepin-5-one 538 as an inseparable mixture (~ 3:1 a:b) with 540 (0.078 g, 60% yield) as a pale yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.0 (1H, d, J 3.4, \text{ aziridine CH}_2), 2.04-2.16 (3H, m, \text{ CH}_2+\text{CHH}), 2.18-2.26 (1H, m, \text{ CHH}), 2.53 (1H, d, J 4.5, \text{ aziridine CH}_2), 2.78 (ddd, J 9.5, 4.1, 3.9, \text{ aziridine CH}_3), 3.34 (1H, ddd, J 9.4, 2.9, 1.6, \text{ pyrrolidine CH}), 3.62-3.69 (1H, m, \text{ NCH}_2), 3.81-3.95 (1H, m, \text{ NCH}_2), 7.01 (1H, dt, J 7.9, 0.7, \text{ ArH}), 7.11 (1H, d, J 8.1, \text{ ArH}), 7.44-7.52 (1H, m, \text{ ArH}), 7.74 (1H, d, J 7.9, \text{ ArH}). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 23.1 (\text{CH}_2), 29.4 (\text{CH}_2), 32.7 (\text{CH}_2), 44.8 (\text{CH}), 46.1 (\text{CH}_2), 58.1 (\text{CH}), 122.0 (\text{CH}), 122.9 (\text{CH}), 126.8 (q), 129.7 (\text{CH}), 131.2 (\text{CH}), 145.6 (q), 150.3 (q). \]

\[ \nu_{\text{max}} \text{ (thin film cm}^{-1})]: 3317 (s, br), 3063 (m), 2979 (s), 2877 (s), 1625 (m), 1456 (s), 1405 (s), 1340 (m), 1287 (m), 1248 (m), 1203 (m), 1100 (m), 1039 (m), 922 (m), 766 (s), 730 (s), 704 (s). \]

ES+ mass spectrum (m/z, %): 288 (14%), 251 (15%), 242 (17%), 215 (100%), 201 (9%), 187 (5%), 145 (5%), 122 (33%), 88 (5%). HRMS (ESI+): found [M+H]^+ 215.1178, C_{13}H_{13}N_2O requires 215.1179.

**Method B**

A solution of (2S)-N-(2-azidobenzoyl)-pyrrolidine-2-ethene (527; 0.300 g, 1.242 mmol) in anhydrous chloroform (30 ml) under an atmosphere of dry nitrogen was heated at reflux for 20 hr. Upon completion (TLC) the reaction mixture was cooled, and evaporation of the solvent gave the crude product as a yellow oil, which was purified by flash chromatography (eluent: PE:EtOAc/3:2) to yield the aziridinopyrrolobenzodiazepin-5-one (538) as a 1:1 mixture with (540); 0.171 g, 66% yield) in the form of a yellow oil.
7.5.10 Synthesis of (2S)-N-(2-azidoaroyl)-2-hydroxymethylpyrrolidine

Potassium carbonate (0.331 g, 2.0 eq) dissolved in water (5 ml), was added in one portion to a stirring solution of (S)-prolinol (522; 0.12 ml, 1.0 eq) in dichloromethane (1 ml). After stirring for 5 min, a solution of 2-azidobenzoyl chloride (0.220 g, 1.0 eq) in dichloromethane (5 ml) was added to the reaction mixture and the resultant mixture was stirred at ambient temperature for 4 hr. The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed \textit{in vacuo} and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (2S)-1-(2'-azidobenzoyl)-2-hydroxymethyl pyrrolidine (541; 0.182 g, 61\% yield) as a yellow oil.

δ₁H (400 MHz, CDCl₃): 1.51-1.82 (3H, m, CH₂+CHH), 1.87-1.99 (1H, m, CHH), 2.96-3.14 (2H, m, CH₂), 3.57 (2H, d, J 4.9, OCH₂), 4.07-4.18 (1H, m, CH), 4.77 (1H, s, br, OH), 6.94-7.06 (2H, m, ArH), 7.12 (1H, d, J 7.5, ArH), 7.25 (1H, t, J 7.8, ArH). δC (100 MHz, CDCl₃): 23.7 (CH₂), 27.6 (CH₂), 48.8 (CH₂), 60.0 (CH), 64.6 (CH₂), 117.9 (CH), 124.6 (CH), 127.1 (CH), 128.7 (q), 130.0 (CH), 135.2 (q), 167.9 (q). νmax (thin film cm⁻¹): 3396 (s, br), 2972 (s), 2879 (s), 2129 (s), 1736 (s), 1616 (s, br), 1491 (s), 1452 (s), 1428 (s), 1373 (m), 1294 (s), 1243 (m), 1161 (m), 1149 (m), 1090 (m), 1049 (s), 755 (s). ES+ mass spectrum (m/z, %): 269 ([M+Na]⁺, 100\%), 247 ([M+H]⁺, 65\%), 219 (98\%), 201 (12\%), 177 (11\%), 133 (13\%), 122 (17\%), 120 (45\%), 85 (18\%), 59 (30\%). HRMS (ESI+): found [M+Na]⁺ 269.1008, C₁₂H₁₄N₄O₂Na requires 269.1009.
7.5.11 Synthesis of (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbaldehyde

To a solution of (2S)-N-(2-azidoaroyl)-2-hydroxymethylpyrrolidine (541; 2.283 g, 9.270 mmol, 1.0 eq) in anhydrous dichloromethane (50 ml) was added pyridinium chlorochromate (3.337 g, 15.481 mmol, 1.67 eq) and the whole was stirred vigorously for 3 hours under an atmosphere of dry nitrogen. The dark reaction mixture was quenched with ether (50 ml) and the supernatant liquid was removed by decantation. The black tar residue was washed thoroughly with ethyl acetate (3× 30 ml) and the combined organic layers were collected, dried (MgSO₄), and filtered under gravity. Evaporation of the solvent gave the crude product as a brown oil, which was purified by flash chromatography (eluent: PE:EtOAc/ 3:2) to yield (2S)-N-(2-azidoaroyl)-pyrrolidine-2-carbaldehyde (542; 0.983 g, 43% yield) as an yellow oil.

δ_H (400 MHz, CDCl₃): 1.85-1.98 (2H, m, NCH₂CH₂), 2.00-2.13 (1H, m, CHCH-H), 2.13-2.25 (1H, m, CHCH-H), 3.29-3.45 (2H, m, NCH₂), 4.63 (1H, m, NCHCHO), 7.10-7.28 (2H, m, 2x ArH), 7.30-7.50 (2H, m, 2x ArH), 9.70 (1H, s, CHO). δ_C (100 MHz, CDCl₃): 22.2/24.3 (CH₂), 25.9/27.2 (CH₂), 46.1/48.1 (CH₂), 64.2/65.9 (CH), 118.1 (CH), 124.6/124.7 (CH), 127.5 (CH), 128.0 (q), 130.4 (CH), 135.7 (q), 166.8/167.0 (q), 197.5/198.9 (q). v_max (thin film cm⁻¹): 2958 (s), 2869 (s), 2125 (s), 1725 (s), 1598 (s), 1579 (s), 1487 (s), 1447 (s), 1299 (s), 1255 (s), 1166 (m), 1129 (s), 1077 (m), 952 (m), 894 (m), 754 (s), 693 (s), 649 (s).
7.5.12 Synthesis of N-protected dibromoalkene

\[ \text{R} = \text{CO}_2\text{Et} \]

\[ \text{R} = \text{Boc} \]

**General Procedure:**

A solution of \( t\)-BuOK (2.8 eq) in anhydrous THF (5 ml) was added dropwise to a stirring suspension of dibromomethyltriphenylphosphonium bromide (3.0 eq) in anhydrous THF (~20 ml) at ambient temperature under an atmosphere of dry nitrogen. Stirring of the reaction mixture was continued for a further 5 min, followed by dropwise addition of a solution of the \( N\)-protected aldehyde (532 or 552; 1.0 eq) in anhydrous THF (5 ml) and the whole reaction mixture was allowed to stir at ambient temperature for \( \frac{1}{2} - 1 \) hr. Upon completion the reaction mixture was quenched with water (~20 ml) and extracted with ethyl acetate (2x 10 ml). The organic phase was collected, dried over MgSO\(_4\), and filtered under gravity. Evaporation of the volatiles *in vacuo* provided the crude product, which was purified by flash column chromatography (eluents: PE:EtOAc/2:3) to yield the \( N\)-protected dibromoalkene (543 or 553) as follows:

\( (S)\)-(−)-1-ethoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene) (543) was obtained as a rotameric mixture in the form of a yellow oil (0.531 g, 65% yield) from (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbaldehyde (532; 0.430 g, 2.51 mmol, 1.0 eq).

\[ \delta_\text{H} (400 \text{ MHz, CDCl}_3): 1.05 (3\text{H, m, br, CH}_3), 1.56 (1\text{H, m, br, CH}_2), 1.63-1.70 (2\text{H, m, br, CH}_2), 1.91-2.03 (1\text{H, m, br, CH}_2), 3.18-3.30 (2\text{H, m, br, CH}_2), 3.88 (2\text{H, m, br, CO}_2\text{CH}_2), 4.18-4.30 (1\text{H, m, br, CH}_2), 6.15 (1\text{H, m, =CH}_2). \delta_\text{C} (100 \text{ MHz, CDCl}_3): 13.3/13.9 (\text{CH}_3), 21.9/22.6 (\text{CH}_2), 29.4/30.1 (\text{CH}_2), 43.9/44.7 (\text{CH}_2), 57.5/58.5 (\text{CH}), 59.0/59.4 (\text{CH}_2), 87.4 (q), 137.7/137.9 (\text{CH}), 152.7/153.1 (q). \nu_{\text{max}} (\text{thin film cm}^{-1}) : 2980 (s), 2883 (s), 1735 (s), 1698 (s), 1470 (s), 1435 (s), 1389 (s), 1356 (s), 1250 (m), 1168 (m), 1115 (s), 1080 (m), 910 (m), 772 (s). \text{ES}^+ \text{ mass spectrum (m/z, %)}: 328 ([\text{M+H}]^+, 8\%), 316 (16\%), 289 (7\%), 288 (31\%), 256 (9\%), 186 (9\%), 156 (11\%), 142 (100\%), 128 (13\%), 98 (7\%), 70 (15\%). \text{HRMS (ESI+)}: \text{HRMS (ESI+)}: \text{found} [\text{M+H}]^+ 328.9321, \text{C}_{9}\text{H}_{14}\text{Br}_2\text{NO}_2 \text{requires} 328.9320.

\( (S)-(−)-1-t\)-butoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene) (553) was obtained in rotameric form as a yellow oil (0.321 g, 89% yield) from (S)-(−)-1-t-butoxycarbonylpyrrolidine-2-carbaldehyde (552; 0.201 g, 1.00 mmol, 1.0 eq).
\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.47 (9\text{H, s, (CH}_3)_3), 1.74 (1\text{H, m, CH}_2), 1.80-1.94 (2\text{H, m, CH}_2), 2.11-2.24 (1\text{H, m, CH}_2), 3.20-3.60 (2\text{H, m, CH}_2), 4.30-4.50 (1\text{H, m, CH}), 6.37 (1\text{H, m, =CH}). \]

\[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 22.8 (\text{CH}_2), 29.4 ((\text{CH}_3)_3), 31.2 (\text{CH}_2), 46.2 (\text{CH}_2), 60.4 (\text{CH}), 80.0 (q), 88.5 (q), 140.2 (\text{CH}), 154.5 (q). \]

\[ \nu_{\text{max}} \text{(thin film cm}^{-1}): 2976 (s), 2930 (m), 2877 (m), 1698 (s, br), 1614 (m), 1477 (s), 1456 (s), 1393 (s), 1366 (s), 1248 (s), 1165 (s), 910 (m), 860 (m), 796 (s), 772 (s). \]

ES+ mass spectrum (m/z, %): 355 ([M+], 27%), 299 (15%), 276 (4%), 254 (7%), 220 (4%), 197 (2%), 115 (7%), 97 (10%), 85 (9%), 71 (2%). HRMS (ESI+): found [M+H]\(^+\), 356.9637, \( \text{C}_{11}\text{H}_{17}\text{Br}_2\text{NO}_2 \) requires 356.9635.

7.5.13 Synthesis of N-protected alkyne

![Diagram of reaction](543: R=CO\textsubscript{2}Et, 553: R=Boc)

General Procedure:

A solution of \( t\)-BuOK (2.5 eq) in anhydrous THF (3 ml) was added dropwise to a stirring solution of N-protected dibromoalkene (543 or 553; 1.0 eq) in anhydrous THF (~10 ml) at ambient temperature under an atmosphere of dry nitrogen. Stirring of the reaction mixture was continued for a further 30 min, and the reaction mixture was quenched with water (~20 ml) and extracted with ethyl acetate (2x 10 ml). The organic phase was collected, dried over MgSO\(_4\), and filtered under gravity. Evaporation of the volatiles in vacuo gave the crude product which was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the N-protected alkyne (544 and 554) as follows:

\( (S)\)-(\-)1-ethoxycarbonylpyrrolidine-2-prop-1-yne (544) \) was obtained as a rotameric mixture in the form of a yellow oil (0.270 g, 100% yield) from \( (S)\)-(\-)1-ethoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene) (543; 0.530 g, 1.63 mmol, 1.0 eq).

\[ \delta_{\text{H}} (400 \text{ MHz, CDCl}_3): 1.18 (3\text{H, t, J 7.8, } \text{CH}_2\text{CH}_3), 1.86 (1\text{H, m, br, NCH}_2\text{CH}-\text{H}), 2.00 (1\text{H, m, br, NCH}_2\text{CH}-\text{H}), 2.19 (1\text{H, m, br, CHCH}-\text{H}), 2.54 (1\text{H, m, br, CHCH}-\text{H}), 3.30 (1\text{H, m, br, NCH}_2), 3.45 (1\text{H, m, br, NCH}_2), 4.00-4.20 (2\text{H, q, J 7.9, CH}_2\text{CH}_3), 4.42\&4.49 (1\text{H, 2x m, br, alkyne CH}), 5.53 (1\text{H, dd, J 4.1, 2.0, CH}). \]

\[ \delta_{\text{C}} (100 \text{ MHz, CDCl}_3): 14.6 (\text{CH}_3), 28.0 (\text{CH}_2), 47.2 (\text{CH}_2), 61.2 (\text{CH}_2), 75.5 (\text{CH}_2), 81.5 (\text{CH}), 120.8 (\text{CH}), 124.2 (q), 152.6 (q). \]

\[ \nu_{\text{max}} \text{(thin film cm}^{-1}): \]
3286 (s), 3243 (s), 2981 (s), 2933 (m), 2110 (m), 1698 (s, br), 1606 (s), 1467 (m), 1415 (s), 1384 (s), 1333 (s), 1268 (m), 1172 (m), 1135 (s), 1062 (s), 932 (s), 765 (s).

(S)-(-)-1-t-butoxycarbonylpyrrolidine-2-prop-1-yne (554) was obtained as a yellow oil (0.110 g, 100% yield) from (S)-(-)-1-t-butoxycarbonylpyrrolidine-2-(1,1-dibromoprop-1-ene) (553; 0.201 g, 0.563 mmol, 1.0 eq).

\[ \text{H} (400 \text{ MHz, CDCl}_3): 1.50-1.70 (3\text{H}, \text{m, CHCH}_2\text{CH}-), 1.94-2.07 (1\text{H}, \text{m, CHCH}_2\text{CH-}), 3.00-3.30 (2\text{H}, \text{m, NCH}_2), 4.18&4.30 (2\text{x m, br, alkyne CH}), 5.34 (1\text{H}, \text{dd, J 4.0, 1.8, CH}). \]

\[ \delta_c (100 \text{ MHz, CDCl}_3): 26.9 (\text{CH}_2), 27.4 ((\text{CH}_3)_3), 46.0 (\text{CH}_2), 59.3 (\text{CH}_2), 80.9 (\text{CH}), 119.3 (\text{CH}), 123.8 (q), 169.8 (q). \]

Both compounds were used without further characterization due to their noticeable instability at room temperature.

7.5.14 Synthesis of (2S)-N-(2'-azidobenzoyl)-2-ethynylpyrrolidine

\[ \text{Method A} \]

To a vigorously stirred suspension of finely ground KOH (1.70 g, 31.10 mmol, 26 eq) in ethylene glycol (5 ml) and hydrazine hydrate (0.20 ml, 5.98 mmol, 5.0 eq) under an atmosphere of dry nitrogen was added (S)-(−)-1-ethoxycarbonylpyrrolidine-2-prop-1-yne (544; 0.20 g, 1.20 mmol, 1.0 eq), and the mixture was heated under reflux (~195°C) for 3 hr. The reaction mixture was cooled to ambient temperature and diluted with (1:1) diethyl ether/water mixture (8 ml) and extracted with diethyl ether (3x 5 ml), and the combined organic extracts were dried over finely ground NaOH. Triethylamine (0.25 ml, 1.79 mmol, 1.5 eq) was added to the above ethereal solution containing the amine (545) at 0°C under an atmosphere of dry nitrogen and was stirred for 10 min, followed by a dropwise addition of a solution of the acid chloride (0.50 g, 1.5 eq) in diethyether (5 ml) and the whole reaction mixture was allowed to stir at ambient temperature for 18 hr. Upon completion, the reaction mixture was diluted with water (20 ml) and extracted with
diethyl ether (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed \textit{in vacuo} and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (2S)-1-(2-azidobenzoyl)-2-ethynylpyrrolidine (546; 0.032 g, 11% yield) as a rotameric mixture in the form of yellow oil.

**Method B**

![Diagram of reaction](image)

Trifluoroacetic acid (0.36 ml, 4.632 mmol, 4.5 eq), was added to a solution of (S)-(−)-1-tert-butoxycarbonylpyrrolidine-2-prop-1-yn (547; 0.201 g, 1.029 mmol, 1.0 eq) in anhydrous dichloromethane (5 ml) under an atmosphere of dry nitrogen. The reaction mixture was stirred at ambient temperature for 3 hr, and neutralized with aqueous sodium hydroxide to pH 7 and extracted with dichloromethane (2x 5 ml), dried over MgSO₄, and filtered under gravity. Triethylamine (0.25 ml, 1.79 mmol, 1.5 eq) was added to the above ethereal solution containing the amine (544) at 0°C under an atmosphere of dry nitrogen and was stirred for 10 min, followed by a dropwise addition of a solution of the acid chloride (0.51 g, 1.5 eq) in dichloromethane (5 ml) and the whole reaction mixture was allowed to stir at ambient temperature for 18 hr. Upon completion, the reaction mixture was diluted with water (20 ml) and extracted with diethyl ether (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed \textit{in vacuo} and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/ 2:3) to yield the (2S)-1-(2-azidobenzoyl)-2-ethynylpyrrolidine (546; 0.093 g, 37% yield) as a rotameric mixture in the form of yellow oil.

δH (400 MHz, CDCl₃): 1.63-1.79 (1H, m, CH-H), 1.83-2.05 (1H, m, CH-H), 3.02-3.26 (2H, m, CH₂), 3.36-3.63 (1H, m, NCH-H), 3.66-3.79 (1H, m, NCH-H), 4.37 (1H, dd, J, 7.9, 4.0, CH), 7.07-7.17 (2H, m, 2x ArH), 7.20 (1H, s, alkyne-CH), 7.29-7.38 (1H, m, ArH), 7.40-7.51 (1H, m, ArH). δC (100 MHz, CDCl₃): 22.2/24.2 (CH₂), 28.0/29.6 (CH₂), 45.8/48.8 (CH₂), 56.3/58.4 (CH), 114.6 (q), 118.5/119.6 (CH), 124.9/125.1 (CH), 127.6/127.9 (CH), 129.9/130.1 (CH), 132.1/133.4 (CH), 136.1 (q), 139.9 (q), 167.8 (q). v_max (thin film cm⁻¹): 3394 (m, br), 3058 (m), 2971 (s), 2922 (s), 2877 (m), 2435 (m), 2127 (s, br), 1717 (s), 1634 (s, br), 1598 (m), 1579 (m), 1488 (s), 1448
(s), 1418 (s), 1293 (s, br), 1256 (m), 1164 (m), 1148 (m), 1074 (s, br), 897 (m), 754 (s), 734 (m), 682 (m). EI+ mass spectrum (m/z, %): 242 (6%), 241 ([M+H]+, 4%), 240 ([M]+, 4%), 212 (16%), 186 (60%), 114 (20%), 88 (100%), 77 (25%). HRMS (EI+): found [M+H]+ 241.1084, C13H13N4O requires 241.1086.

7.5.15 Synthesis of 1,2,3-triazolopyrrolo[2,1-c][1,4]benzodiazepine (547)

A solution of (2S)-1-(2'-azidobenzoyl)-2-ethynylpyrrolidine (546; 0.093 g, 0.39 mmol) in anhydrous toluene (8 ml) under an atmosphere of dry nitrogen was heated at reflux for 4 hr. Upon completion (TLC) the reaction mixture was cooled, and evaporation of the solvent gave the crude product as an orange oil, which was purified by flash column chromatography (eluent: PE EtOAc/2:3) to yield the 1,2,3-triazolopyrrolo[2,1-c][1,4]benzodiazepine (547; 0.015 g, 16% yield) as a pale yellow oil.

δH (400 MHz, CDCl3): 2.09-2.18 (2H, m, CH2), 2.50-2.60 (2H, m, CH2), 3.69-3.86 (2H, m, NCH2), 4.76 (lH, dd, J 7.2, 4.9, CH), 7.56 (1H, td, J 7.6, 1.0, ArH), 7.64 (1H, s, triazolo CH), 7.69 (1H, td, J 7.7, 1.5, ArH), 7.99 (1H, dd, J 8.1, 1.0, ArH), 8.11 (1H, dd, J 7.9, 1.4, ArH). δC (100 MHz, CDCl3): 22.7 (CH2), 29.4 (CH2), 47.6 (CH2), 49.6 (CH), 123.0 (CH), 127.2 (q), 128.8 (CH), 129.0 (CH), 132.0 (CH), 132.7 (CH), 133.1 (q), 138.9 (q), 164.0 (q). vmax (thin film cm−1): 3113 (m), 3031 (m), 2877 (m), 1637 (s, br), 1607 (s), 1579 (m), 1488 (s), 1473 (s), 1433 (s), 1412 (s), 1350 (m), 1244 (s), 1217 (s), 1180 (m), 1151 (m), 1129 (m), 1090 (m), 1048 (m), 987 (s), 974 (m), 884 (m), 820 (m), 788 (s), 755 (s, br). EI+ mass spectrum (m/z, %): 240 ([M]+, 7%), 211 (12%), 184 (30%), 143 (50%), 115 (85%), 114 (22%), 89 (22%), 88 (100%), 77 (21%), 76 (60%), 75 (21%), 63 (39%), 62 (20%), 50 (50%). HRMS (EI+): found [M+H]+ 241.1088, C13H13N4O requires 241.1084.
7.5.16 Synthesis of (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbonitrile

Finely ground iodine (1.095 g, 8.645 mmol, 3 eq) was added portionwise to a stirred mixture of (2S)-1-(2′-azidobenzoyl)-2-hydroxymethyl pyrrolidine (531; 0.498 g, 2.875 mmol, 1.0 eq) and ammonia/water solution (10 ml; 7:3 conc. ammonia:water) at ambient temperature. After stirring for 10 min, the resultant mixture was heated at 65-75°C for 20 hr. The reaction mixture was cooled to ambient temperature, and was diluted with aqueous sodium sulphite (10 ml) and extracted with diethyl ether (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed in vacuo and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc/2:3) to yield the (S)-(−)-1-ethoxycarbonylpyrrolidine-2-carbonitrile (557; 0.289 g, 60% yield) as a yellow oil.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
1.16 (3H, t, J 9.2, OCH₂CH₃), 1.21 (1H, m, NCH₂CH₂-H), 2.04 (1H, m, NCH₂CH₂-H), 2.20 (1H, m, CHCH₂-H), 3.34 (1H, m, CHCH₂-H), 3.48 (1H, m, NCH₂-H), 4.03 (2H, q, J 7.1, OCH₂CH₃), 4.12 (1H, m, NCH₂-H), 4.52 (1H, m, NCHCN). \[ \delta_C (100 \text{ MHz, CDCl}_3): \]
13.8/14.2 (CH₃), 23.4/24.3 (CH₂), 30.4/31.4 (CH₂), 45.5/45.8 (CH₂), 46.6/47.0 (CH), 61.5/61.6 (CH₂), 118.6 (q), 170.7 (q). \[ \nu_{\text{max}} \text{(thin film cm}^{-1}): \]
2984 (s), 2896 (s), 2241 (s), 1707 (s), 1528 (s), 1415 (s), 1382 (s), 1346 (s), 1244 (s), 1184 (s), 1123 (s), 1096 (m), 1039 (m), 1014 (m), 914 (s), 877 (s), 773 (s).

7.5.17 Synthesis of (2S)-1-(2′-azidobenzoyl)-pyrrolidine-2-carbonitrile

Method A

Finely ground iodine (0.390 g, 1.52 mmol, 1.1 eq) was added portionwise to a stirred mixture of (2S)-1-(2′-azidobenzoyl)-2-hydroxymethyl pyrrolidine (541; 0.340 g, 1.38 mmol, 1.0 eq) and ammonia/water solution (10 ml; 7:3 conc. ammonia:water) at ambient temperature. After
stirring for 10 min, the resultant mixture was heated at 65-75°C for 20 hr. The reaction mixture was cooled to ambient temperature, and was diluted with aqueous sodium sulphite (10 ml) and extracted with diethyl ether (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed in vacuo and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc/2:3) to yield the (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile (559; 0.271 g, 36% yield) as a yellow oil.

Method B

Potassium carbonate (1.03 g, 4.0 eq) dissolved in water (5 ml), was added in one portion to a stirring solution of (L)-prolinamide (567; 0.201 g, 1.0 eq) in dichloromethane (5 ml). After stirring for 5 min, a solution of 2-azidobenzoyl chloride (0.64 g, 2.0 eq) in dichloromethane (5 ml) was added to the reaction mixture and the resultant mixture was stirred at ambient temperature for 20 hr. Upon completion the reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (2x 10 ml). The organic phase was collected, dried over MgSO₄, and filtered under gravity. The volatiles were removed in vacuo and the crude residue was purified by flash column chromatography (eluent: PE:EtOAc/2:3) to yield the (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile (559; 0.202 g, 48% yield) as a yellow oil, as a mixture of rotamers.

\[
\delta^\text{H} (400 \text{ MHz, CDCl}_3): 2.02 (1\text{H, m, CH-H}), 2.15 (1\text{H, m, CH-H}), 2.32 (1\text{H, m, CH-H}), 3.28 (1\text{H, m, CH-H}), 3.39 (1\text{H, m, NCH-H}), 3.72 (1\text{H, m, NCH-H}), 4.87 (1\text{H, dd, J 8.0, 4.0, CHCN}), 7.19 (2\text{H, m, ArH}), 7.31 (1\text{H, dd, J 8.0, 4.0, ArH}), 7.45 (1\text{H, td, J 8.0, 4.0, ArH}). \\
\delta^\text{C} (100 \text{ MHz, CDCl}_3): 23.0-24.8 (\text{CH}_2), 30.2-32.0 (\text{CH}_2), 46.0 (\text{CH}), 45.6-47.5 (\text{CH}_2), 118.1 (q), 118.5 (\text{CH}), 125.1 (\text{CH}), 127.6 (q), 127.9 (\text{CH}), 131.0 (\text{CH}), 136.2 (q), 166.9 (q). \\

v_{\text{max}} \text{ (thin film cm}^{-1}\text{): 2984 (m), 2958 (m), 2884 (m), 2424 (m), 2242 (m), 2131 (s), 1645 (s), 1599 (s), 1578 (m), 1488 (s), 1449 (s), 1408 (s), 1292 (s), 1163 (m), 1148 (m), 904 (m), 756 (s), 732 (m). \text{ ES+ mass spectrum (m/z, %): 242 ([M+H]^+, 2%), 215 (17%), 214 (24%), 186 (14%), 104 (100%), 76 (30%). HRMS (ESI+): found [M+H]^+ 242.1036, C_{12}H_{12}N_{5}O requires 242.1036.}
7.5.18 Synthesis of 1,2,3,4-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine

A solution of (2S)-1-(2'-azidobenzoyl)-pyrrolidine-2-carbonitrile (559; 0.100 g, 0.41 mmol) in anhydrous toluene (10 ml) under an atmosphere of dry nitrogen was heated at reflux for 6 hr. The reaction mixture was cooled, and evaporation of the solvent gave the crude product as a yellow oil, which was purified by flash chromatography (eluent: PE:EtOAc/ 2:3) to yield the 1,2,3,4-tetrazolopyrrolo[2,1-c][1,4]benzodiazepine (560; 0.099 g, 99% yield) as a pale yellow oil.

δ_H (400 MHz, CDCl₃): 2.19 (2H, m, CH₂), 2.59 (1H, m, CH-H), 3.18 (1H, m, CH-H), 3.72 (1H, m, NCH-H), 3.85 (1H, m, NCH-H), 4.84 (1H, dd, J 8.3, 3.1, CHCN), 7.64 (1H, t, J 8.0, ArH), 7.75 (1H, t, J 8.0, ArH), 7.94 (1H, d, J 8.0, ArH), 8.17 (1H, d, J 8.0, ArH). δ_C (100 MHz, CDCl₃): 23.5 (CH₂), 28.2 (CH₂), 48.2 (CH₂), 49.7 (CH), 122.5 (CH), 127.2 (q), 129.9 (CH), 130.4 (q), 132.3 (CH), 133.2 (CH), 154.6 (q), 163.4 (q). ν_max (thin film cm⁻¹): 2957 (m), 2927 (m), 2884 (m), 1733 (m), 1639 (s, br), 1606 (s), 1579 (m), 1490 (s), 1471 (s), 1411 (s), 1241 (m), 1152 (m), 1125 (m), 1095 (m), 832 (m), 785 (m). ES+ mass spectrum (m/z, %): 268 (23%), 242 ([M+H]^+, 100%), 236 (63%), 214 (14%), 140 (9%), 122 (7%). HRMS (ESI+): found [M+H]^+ 242.1040, C₁₂H₁₂N₅O requires 242.1036.
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The synthesis of pyrrolo[1,2-b][1,2,5]benzothiadiazepines from 1,2-thiazine 1-oxides—sulfonamide analogues of the pyrrolobenzodiazepine antitumour natural products

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Abstract—Pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) and the corresponding pyrrolobenzothiadiazepines (PBTDs) are attractive targets as natural and synthetic antitumour antibiotics and as non-nucleosidic reverse transcriptase inhibitors. A concise synthesis of the PBTD class is presented, which starts from 0-azidobenzenesulfonamide and its conversion into 2-(0-azidobenzenesulfonyl)-1,2-thiazine 1-oxides via Diels–Alder reaction. After a one-pot ring contraction, desulfurisation and aromatisation process, accompanied by concomitant same pot conversion of the azide group into a primary amine via the Staudinger reaction, these 1,2-thiazine-1-oxides yield a 1-(o-aminobenzenesulfonyl)pyrrole. N-Formylation of the amine and Bischler-Napieralski ring closure onto the pyrrole completes the PBTD synthesis.

The pyrrolo[2,1-c][1,4]benzodiazepines (PBDs) are of interest due to the antitumour antibiotic activity of the PBD natural products, of which DC-811 and prothracarcin 2 (Fig. 1) are typical, and synthetic analogues of which are in clinical development. The related pyrrolo[1,2-b][1,2,5]benzothiadiazepines (PBTD) 3 have received much less interest, but are attractive as sulfonamide analogues of the antitumour antibiotic PBDs, and also as non-nucleosidic inhibitors of reverse transcriptase. The 1,2,5-benzothiadiazepines have also attracted attention for the range of activities that they possess as analogues of the CNS-active 1,4-benzodiazepines and also as tumour necrosis factor-alpha converting enzyme (TACE) inhibitors, and as inhibitors of metalloproteinases in general. Almost all reported syntheses of the PBDs and PBTDs use proline as the source of the five-membered ring, with only a few methods relying on a de novo pyrrole construction methodology and there are no methods, which construct the pyrrole from a diene. Although relatively unexploited, the synthesis of simple (unfused) pyrroles from dienes has proven its importance to the synthetic chemist. In this letter we report that 2-arylsulfonyl substituted 1,2-thiazine-1-oxides 4 (see Fig. 1), which are easily constructed from a diene via a Diels–Alder reaction, can be transformed in a one-pot process into the 1-arylsulfonyl-substituted pyroles 5, which can then be easily converted into the PBTD nucleus.

Our interest in this area came about as part of a programme of studies aimed at exploring the uses of 1,2-thiazine-1-oxides in heterocyclic synthesis. We previously reported that 2-(o-azidobenzenesulfonyl)-1,2-thiazine-1-oxides 4 are precursors for the synthesis of unsaturated bicyclic 1,2,5-benzothiadiazepines via conversion into β,ω-iminophosphoranyl ketones and subsequent aza-Wittig reaction. One of the key transformations in this process was the construction of 1-(o-azidobenzenesulfonyl)1,2-thiazine-1-oxides 4 via a Diels–Alder reaction, which relied upon the in situ generation of the unstable N-sulfinyl dienophile 6 (see Fig. 1) by treating the sulfonamide with pyridine and thionyl chloride. The Diels–Alder reaction was high yielding but gave, on occasion, the 1-(o-azidobenzenesulfonyl)pyrrole 7 (Fig. 1) as a minor product (<5%). We became interested in optimising the yield of this pyrrole as it is a potential intermediate for the synthesis of PBTDs. The origin of this pyrrole product would seem to be base

Keywords: Pyrrolobenzodiazepine; Pyrrolobenzothiadiazepine; Pyrrole; 1,2-Thiazine-1-oxide; Azide.
catalysed ring opening of the 1,2-thiazine-1-oxide 4, subsequent closure to a pyrrolidine 8 and loss of HSOH to give the pyrrole 7, as shown in Scheme 1. Indeed, Harrington has also observed the low yielding formation of pyrroles from 1,2-thiazine-1-oxides under similar basic conditions, and went on to optimise the sequence to great effect via the addition of a thiophile, trimethyl phosphite, in a synthetic approach to simple (unfused) 1-(p-toluenesulfonyl)pyrroles.

The use of trimethyl phosphite in this conversion was attractive to us as we anticipated that we could undertake concurrent conversion of the azide group in compound 7 into an amine via the hydrolysis of an intermediate iminophosphorane \([\text{ArN}=\text{P(OMe)}_3]\), formed after Staudinger reaction of the azide with the phosphite. Our retrosynthetic strategy for the PBD nucleus 3 is shown in Scheme 2 and relies upon the installation of the imine bond as the final step, giving the formylated precursor 9 or 10, and hence leading to the 1-(o-aminobenzencesulfonyl)pyrrole 11 as the key target for formylation. Functional group interconversion (azide to amine) leads back to compound 7, and the key transformation of 1,2-thiazine-1-oxide into pyrrole gives the readily available (see below) 2-(o-azidobenzencesulfonyl)-1,2-thiazine-1-oxides 4 as starting materials.

The 2-(o-azidobenzencesulfonyl)-1,2-thiazine-1-oxides 4 were constructed using a hetero Diels–Alder reaction between the appropriate diene and the N-sulfinyl heterocumulene, derived from o-azidobenzencesulfonylamine, as shown in Scheme 3. o-Azidobenzencesulfonylamine was obtained from o-aminobenzencesulfonylamine in over 90% yield via diazotisation and treatment with sodium azide. o-Aminobenzencesulfonylamine could not be used directly as the starting material for the sulfinylation reaction as this resulted in the formation of the dithiadiazine. The N-sulfanyl 6 was best formed from a 1:1:2 ratio of sulfonamide 12, thionyl chloride and pyridine,
and had to be formed in situ, as attempted isolation resulted in its hydrolysis back to the sulfonamide.
Thus, the 2-(o-azidobenzenesulfonyl)-1,2-thiazine-1-oxides obtained from o-azidobenzenesulfonamide in yields of 78%, 82% and 93%, respectively, and were next treated with a 2:1 molar equivalent mixture of trimethyl phosphate:triethylamine in methanol. The desired 1-(o-aminobenzenesulfonyl)pyrroles were isolated in yields of 50%, 73% and 50%, respectively, after basic aqueous (2 M NaOH) work-up, good yields considering the multi-step nature of the process. The phosphoramidates could be converted into the amine in 85–90% yields using gaseous hydrogen chloride in THF.

The conversion of the 1-(o-aminobenzenesulfonyl)pyrroles into the PBTD nucleus required the introduction of a single carbon. Vilsmeier formylation of the pyrrole ring in compound 11 gave the desired product (shown in Scheme 2) but, in the event, this would not cyclise, probably due to the deactivation of the aldehyde by delocalisation into the pyrrole ring. However, N-formylation using a preformed mixture of acetic anhydride and formic acid gave the N-formylated product. Vilsmeier formylation of the iminophosphorane resulted in its hydrolysis back to the sulfonamide.

Scheme 3. Reagents and conditions: (i) NaNO₂, HCl(aq) then NaN₃. (ii) SOCl₂, pyridine, THF, 0°C, 3 h. (iii) R¹H⁺CR₂⁻CR₃⁻CH₂. (iv) P(OMe)₃, Et₃N, MeOH, 25°C, then 2 M NaOH(aq). (v) HCl(g), THF, room temp. (vi) HCO₂H, MeCO₂O, THF. (vii) POCl₃, (CH₂Cl)₂.

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References and notes

19. Experimental procedures and typical spectroscopic details:

16. Zwierak, A.; Piotrowicz, B.

15. 2-(o-azidobenzenesulfonyl)pyrroles 11: For example, compound 11e (0.135 g, 50%) was obtained as pale yellow oil from 1,2-thiazine 1-oxide 4c (0.350 g, 1.07 mmol). δH (400 MHz, CDCl3): 1.91 (6H, s, 2 × Me), 4.5-4.7 (2H, br s, NH2), 6.63 (1H, d, J 8.2, ArH), 6.71 (1H, t, J 7.6, ArH), 6.84 (2H, s, 2 × pyrrole-H), 7.25 (1H, t, J 7.4, ArH), 7.61 (1H, d, J 8.1, ArH). δC (100 MHz, CDCl3): 101.0 (Me), 117.4 (CH), 117.6 (CH), 121.7 (CH), 124.2 (q), 128.2 (CH), 154.5 (CH), 154.6 (q). vmax (thin film, cm⁻¹): 3457 (s, NH), 3377 (s, NH), 2966 (m), 2919 (s), 1599 (s), 1584 (s), 1455 (m), 1348 (m), 1296 (m), 1068 (s), 829 (s), 744 (m), 699 (m), 610 (m), 588 (m). EI+ mass spectrum (m/z, %): 250 (100%), 185 (25%), 156 (20%), 108 (35%), 94 (100%), 65 (80%), 39 (50%). HRMS (EI+): Found [M+H+] 251.0845, C12H14N2O2S requires 251.0849.

Preparation of 1-(2-formamidobenzenesulfonyl)pyrroles 10: Formic acid (2.25 equiv) was added into acetic anhydride (2 equiv) at 0°C and the solution was stirred at room temperature for 2h. This solution was added to a solution of the 1-(2-aminobenzenesulfonyl)pyrrole 11 (0.10-0.20 g, 1 equiv) in anhydrous tetrahydrofuran (5 mL) and the reaction mixture was stirred at room temperature for 20h. The crude product was purified by silica column chromatography (petroleum ether–ethyl acetate 40:60). As an example, compound 10c (0.120 g, 83%) was obtained as a pale yellow oil from 1-(2-aminobenzenesulfonyl)pyrrole 11c (0.130 g, 0.52 mmol). δH (400 MHz, CDCl3): 1.97 (6H, s, 2 × Me), 6.85 (2H, s, 2 × pyrrole-H), 7.23 (1H, t, J 7.7, ArH), 7.61 (1H, t, J 7.7, ArH), 7.77 (1H, d, J 8.0, ArH), 8.52 (1H, d, J 7.9, ArH), 8.56 (1H, s, CH2O), 9.45 (1H, br s, NH), δC (100 MHz, CDCl3): 101.0 (Me), 117.5 (CH), 123.0 (CH), 124.2 (CH), 125.7 (q), 125.8 (q), 126.1 (q), 128.8 (CH), 153.1 (CH), 158.8 (CHO). vmax (thin film, cm⁻¹): 3290 (m, NH), 3020 (w), 2921 (w), 1706 (s), 1674 (s), 1579 (m), 1514 (m), 1403 (m), 1358 (m), 1290 (m), 1216 (m), 1160 (s), 1071 (m), 669 (m), 611 (m). EI+ mass spectrum (m/z, %): 278 (79%), 277 (60%), 250 (10%), 228 (60%), 184 (85%), 156 (20%); 120 (50%), 95 (100%). HRMS (EI+ + Na+): Found [M+NaH+] 296.1063, C13H14N2O2SNa requires 296.1063.

Preparation of pyrrolobenzothiadiazepines 3: A solution of 1-(2-formamidobenzenesulfonyl)pyrrole 10 (0.10-0.1g, 1 equiv) and phosphorus oxychloride (21.6 equiv) in 1,2-dichloroethane (2 mL) was heated at reflux temperature for 3h. Evaporation of the solvent gave a residue, which was purified by silica column chromatography (petroleum ether–ethyl acetate, 40:60). For example, compound 3c (0.040g, 43%) was obtained from 1-(2-formamidobenzenesulfonyl)pyrrole 10c (0.100g, 0.36mmol) as a bright orange oil. δH (400 MHz, CDCl3): 2.06 (3H, s, Me), 2.26 (3H, s, Me), 3.26 (3H, s, Me), 7.33 (1H, s, pyrrole-H), 7.42 (1H, dt, J 8.0, 10.0, ArH), 7.60-7.73 (2H, m, 2 × ArH), 8.04 (1H, dd, J 7.9, 1.2, ArH), 8.62 (1H, s, N=CH). δC (100 MHz, CDCl3): 9.6 (Me), 9.9 (Me), 120.8 (CH), 123.6 (q), 125.3 (CH), 126.2 (CH), 129.9 (CH), 130.1 (q), 132.5 (q), 144.3 (CH), 144.1 (q), 148.6 (CH). vmax (cm⁻¹): 2924 (w), 1603 (s), 1582 (s), 1458 (m), 1365 (s), 1294 (m), 1181 (s), 1137 (m), 1107 (m), 910 (s), 832 (m), 767 (m), 733 (m). HRMS (EI+): Found [M+H+] 261.0691, C13H14N2O2S requires 261.0692.
RESEARCH ARTICLE

The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

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This paper presents a new approach to the synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides, sulfonamide analogues of the ‘privileged’ 1,4-benzodiazepine pharmacophore. The key steps during this synthesis are the hetero Diels-Alder reaction of an N-sulfinylamine dienophile with a diene to give a 1,2-thiazine 1-oxide which is then converted into a N-(o-azidobenzenesulfonyl)-1,2-amino alcohol via a [2,3]-sigmatropic rearrangement involving an intermediate allylic sulfoxide and sulfenate ester. Staudinger reaction of the o-azido group and hydrolysis of the intermediate iminophosphorane gave the corresponding N-(o-aminobenzenesulfonyl)-1,2-amino alcohols. Fmoc protection at nitrogen, oxidation of the alcohol, and Fmoc deprotection furnished directly the 1,2,5-benzothiadiazepine 1,1-dioxides in 57-69% yield. An alternative method which uses triazene chemistry is also presented, but was consistently lower yielding. A second route to 1,2,5-benzothiadiazepine 1,1-dioxides using 2-nitrobenzenesulfonamide as the dienophile precursor proceeded without incident to give N-(o-nitrobenzenesulfonyl)-1,2-amino ketones which underwent reductive cyclisation to furnish the target heterocycle.

Keywords: Azide; 1,2-Thiazine 1-oxide; Benzodiazepine; Benzothiadiazepine; Allylic sulfoxide; N-sulfinylamine

1. Introduction

The synthesis and biological applications of the 1,4-benzodiazepine pharmacophore 1 continue to attract considerable attention in the literature [1–8]. The related 1,2,5-benzothiadiazepine 1,1-dioxides 2, however, have been subject to much less scrutiny [9–12]. Early interest in 1,2,5-benzothiadiazepine 1,1-dioxides was inspired by their potential use as CNS active compounds [13–14]. More recently it has been shown that, whilst 1,2,5-benzothiadiazepines continue to attract attention as CNS active antidepressives [15–17], they have also exhibited activity as antiarrhythmic agents [18], as inhibitors of metalloproteinase and farnesy protein transferases [19–21], and as potent tumour necrosis factor-α (TNF-α) converting
enzyme (TACE) inhibitors [22]. Tricyclic 1,2,5-benzothiadiazepines have attracted particular attention as non-nucleosidic reverse transcriptase inhibitors (NNRTIs) [23–28], a class of compounds that includes the pyrrolo fused system 3 [23–25] and other tricycles such as the heterocycle system 4, where the latter is the sulfonamide analogue of the well known class of NNRTIs that includes the clinically used nevirapine [26–28]. Benzothiazepine analogues 5 of the anti-HIV drug TIBO with specific anti-HIV type 1 activity have also been reported [29] (figure 1). Finally, it is of note that the pyrrolo fused 1,2,5-benzothiadiazepines 3 have also attracted attention [30–32] as sulfonamide analogues of the minor groove DNA-interactive antitumour antibiotic natural and synthetic pyrrolobenzodiazepines [33].

The synthetic routes to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus include many approaches to the pyrrolobenzothiadiazepines 3 which proceed via 3,4- or 4,5-bond formation of the 1,2,5-benzothiadiazepine ring. These include reductive cyclisation of (2-nitrobenzenesulfonyl)-1H-pyrrole derivatives [23, 34], the cyclisation of 1-(2-formamidobenzenesulfonyl)pyrrole with phosphorus oxychloride [30, 34], the reaction of 2-(1H-pyrrol-1-yl)benzenesulfonamide with triphosgene [35, 36], the cyclisation of 1-(2-amino-5-chlorobenzenesulfonyl)pyrrole-2-carboxyhydrazide with loss of hydrazine [37], the cyclisation of 1-(2-fluorobenzenesulfonyl)-1H-pyrrole-2-carboxamides [23], and the reaction of 1-(2-aminobenzenesulfonyl)pyrrole with ethyl glyoxylate [14]. Approaches to simple bicyclic 1,2,5-benzothiadiazepine 1,1-dioxides 2 include synthesis by ring expansion of 1,2,4-benzothiadiazines [38], 1,2-bond formation by intramolecular sulfonamide formation [39, 40], and 2,3-bond formation by intramolecular elimination of ethanol from N-β, β-diethoxyethyl-N-alkylanilines [41]. 4,5-Bond formation is a common approach to this system, and has been achieved by cyclisation of 2-(2-aminobenzenesulfonyl)propanoic acid [25]; by reductive cyclisation of 2-nitro-o-phenacylbenezensulfonamide [42]; by the use of 2-N-[(2-aminobenzenesulfonyl)methylamino]acrylate in an intramolecular Michael reaction [43]; via the use of an intramolecular aza-Wittig reaction [44]; via the ozonolysis and subsequent ring closure of N-(2-nitrobenzenesulfonyl) N-allylic systems [22]; and from the cyclisation of N-(2-aminobenzenesulfonyl) N-ethylbromo systems [22]. 5,6-Bond formation by intramolecular SNAr reaction has also been reported [23].

In the current paper, we report a new approach to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus that begins with a 1,3-diene. Our methodology is the only route that allows this important heterocyclic system to be accessed from dienes, and also provides access to hitherto unreported 1,2,5-benzothiadiazepines.

As part of an ongoing programme of work directed towards the use of 1,2-thiazine 1-oxides as building blocks in heterocyclic synthesis, we have already reported routes to 1,4-benzodiazepines [7, 44] and isoxazolo fused benzothiazines [45]. Herein we report the conversion of 1,2-thiazine 1-oxides into a series of 1,2,5-benzothiazainepine 1,1-dioxides. Our original plan is shown in scheme 1. Hence, the 1,2-thiazine 1-oxides 8 (X = synthetic equivalent of NH$_2$) that are central to our methodology would be accessible from a hetero-Diels-Alder reaction involving the N-sulfinylamine dienophiles 7 which are in turn easily

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**Figure 1.** Examples of some important benzothiadiazepines.
available from the action of thionyl chloride upon the benzenesulfonamides 6. Subsequent ring opening of the 1,2-thiazine 1-oxides 8 would give an allylic sulfoxide 9 which is ideally set up for a [2,3]-sigmatropic, Evans-Mislow, rearrangement [46-53]. Desulfurisation of the resultant sulfenate ester 10 and oxidation of the alcohol 11 should then form the ketone 12, which is the precursor for an envisaged straightforward cyclisation into the 1,2,5-benzothiadiazepine nucleus 2. We present the results of this endeavour herein and report the successful synthesis of the alcohols 11 (X = NH2; R3, R4, R5 = Me/H) from 2-aminobenzenesulfonamide (6, X = NH2) via selective functionalization of the sulfonamide nitrogen in 58 to 63% overall yield. The successful conversion of the alcohols 11 (X = NH2; R3, R4, R5 = Me/H) into the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus is also discussed. This paper also presents a concise second route to the 1,2,5-benzothiadiazepine 1,1-dioxide nucleus which relies upon the conversion of 2-nitrobenzenesulfonamide (6, X = NO2) into 1,2,5-benzothiadiazepine 1,1-dioxides via alcohols 11 (X = NO2; R3, R4, R5 = Me/H) using a similar strategy.

2. Results and discussion

The N-sulfinyl group that we required as the dienophile is best accessed via sulfinylation [48-53] of the corresponding sulfonamide. We observed that the greater reactivity of the 2-amino nitrogen of 2-aminobenzenesulfonamide (6, X = NH2; scheme 2) towards thionyl chloride precluded reaction at the sulfonamide nitrogen in 2-aminobenzenesulfonamide. We elected, therefore, to diazotise the 2-amino nitrogen and convert it into an azide, with a view to the subsequent conversion of the azide back into an amine at a later stage in the synthesis. Thus, diazotisation of 2-aminobenzenesulfonamide 6 under standard conditions (5M HCl, NaN02, 0°C) followed by reaction with sodium azide gave a reproducible 90% yield of 2-azidobenzenesulfonamide 13, as shown in scheme 2. Reaction of compound 13 with thionyl
chloride gave the N-sulfinyl dienophile 14 which was noted to be unstable upon exposure to the moisture in air, and was hence generated and used in situ. Hetero Diels-Alder reaction [48-53] of the N-sulfinyl dienophile 14 gave the 2-(o-azidobenzenesulfonyl)-1,2-thiazine 1-oxides 15a-c in ~80% yield from compound 13 (see table 1) after chromatography. Compound 15c was isolated as a single diastereoisomer with “cis” R\(^3/R\(^5\) stereochemistry in line with that expected from the (E, E)-diene that was used. The stereochemistry at sulfur was not determined due to the fact that this chiral centre was soon to be lost (see below). The treatment of 2-(o-azidobenzenesulfonyl)-1,2-thiazine 1-oxides 15 with an excess of PhMgBr followed by aqueous work-up, and then [2,3]-sigmatropic rearrangement/piperidine mediated desulfurisation [54-56] of the intermediate allylic sulfoxides 16 (scheme 2) gave the (1,3-diaryl triazeny) allylic alcohols 17 in 59-67% yield starting from the 1,2-thiazine 1-oxides 15 (see table 1). The triazene moiety arises as the result of the ring opening of the thiazine 1-oxide with PhMgBr accompanied by the expected [57] reaction of PhMgBr at the azide group to form the triazene. The treatment of the triazenes 17 with boiling aqueous methanol gave the corresponding amines 18 in 60 to 70% yield, a hydrolysis of triazenes which has parallels in the literature [58-61].

The relative stereochemistry of compounds 17c and 18c (R\(^3\) = Me) was not determined as, at the next stage, the alcohol chiral centre was to be oxidised. It is of interest to note, however, that others have reported that such reactions proceed with a high degree of stereoselectivity
Table 1. % Yields for isolated, purified products.

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R_3 )</th>
<th>( R_4 )</th>
<th>( R_5 )</th>
<th>15 (from 13)</th>
<th>17 (from 15)</th>
<th>21 (from 15)</th>
<th>18 (from 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>82</td>
<td>67</td>
<td>99</td>
<td>86</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>78</td>
<td>64</td>
<td>&gt;99</td>
<td>89</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>80</td>
<td>59</td>
<td>&gt;99</td>
<td>82</td>
</tr>
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when performed with other substrates [48,49,51–53], a point reflected by the fact that we found compounds 17c and 18c to be single diastereoisomers. In the one situation where it is appropriate, i.e. also for compounds 17c and 18c (\( R_4 = H, R_5 = Me \)), the alkene geometry was found to be (E). This can be explained by invoking a 5-membered ring envelope transition state for the \([2, 3]-\)sigmatropic rearrangement, in which the methyl group that occupies position 6 (see figure 2) in the allylic sulfoxide 16c is in a pseudo-equatorial position leading to (E)-alkene geometry in the intermediate sulfenate ester 19, geometry which is carried through to compounds 17c and 18c.

Using the procedure shown in scheme 2, the highest overall yield that was obtained for compound 18 was that for 18a (\( R_3 = R_4 = R_5 = H \)), which was obtained in only 34% yield from 2-aminobenzenesulfonamide 6. An improved procedure for the conversion of the 2-(o-azidobenzenesulfonyl)-1,2-thiazine 1-oxides 15 into the desired amines 18 was therefore sought.

Our improved procedure is set out in scheme 3. The reaction of the azide group in compounds 15 with triphenylphosphine resulted in a quantitative Staudinger reaction [62] to give the iminophosphoranes 20. The \textit{in situ} hydrolysis [63–66] of the iminophosphoranes 20 with wet THF at reflux gave the 2-(o-aminobenzenesulfonyl)-1,2-thiazine 1-oxides 21a–c in near quantitative yields from the azides 15 (see table 1) after column chromatographic removal of triphenylphosphine oxide. It is noteworthy that these hydrolytic conditions were selective for the iminophosphorane group, and that no competing hydrolysis (see later – scheme 6) of the 1,2-thiazine 1-oxide rings was observed. In the next step, ring opening of the thiazine 1-oxides 21 with PhMgBr gave the phenyl allylic sulfoxides 22. Conversion of the crude phenyl allylic sulfoxides 22 into the desired \( N-(o\)-aminobenzenesulfonyl\))-1,2-vicinal amino alcohols 18 was best achieved by treatment with hot methanolic trimethyl phosphite, a process which occurs via a \([2, 3]-\)sigmatropic rearrangement to give the intermediate sulfenate esters.

Figure 2. Origin of (E)-alkene geometry.
SCHEME 3 Synthesis of key intermediate 18 using iminophosphoranes. Reaction conditions: (i) PPh$_3$ (1 equiv.), THF, 25 °C, 3–4 hours (inert atmosphere), then H$_2$O (8 equiv.), THF, reflux, 15–20 hours (open air). (ii) PhMgBr (2 equiv.), THF, −40 °C, 2 hours; NH$_4$Cl(aq.). (iii) P(OMe)$_3$, MeOH, 60 °C, 10–15 hours.

23, which then undergo desulfurisation with the trimethyl phosphite [46–53]. Products 18a–c were obtained in 82–89% yield from the 2-(o-aminobenzenesulfonyl)-1,2-thiazine 1-oxides 21 (see table 1). The next step in the sequence was to be an alcohol oxidation, and hence the relative stereochemistry of the two chiral centres in compound 18c ($R^4 = H$, $R^3 = Me$) was not determined, but it was again noted (see above) to be a single diastereoisomer, as expected [48,49,51–53]. Compound 18c was also noted to have (E)-alkene geometry, as discussed above. By this procedure, the highest yield that was obtained for this multi-reaction sequence was again that of compound 18a ($R^3 = R^4 = R^5 = H$), which was now obtained in 63% overall yield starting from 2-aminobenzenesulfonamide 6. Compounds 18b and 18c were obtained in similarly acceptable overall yields of 62% and 58%, respectively, from 2-aminobenzenesulfonamide 6.

With a higher yielding and reproducible synthesis of compounds 18a–c now in hand, we next set about to convert them into the desired 1,2,5-benzothiadiazepine 1,1-dioxides, a process that we anticipated would be trivial. In the event, all attempts to affect the oxidation of the N-(o-aminobenzenesulfonyl)-1,2-amino alcohols 18a–c into the corresponding ketones proved unsuccessful under a variety of conditions (for example, Dess–Martin, Swern, TPAP, Corey’s reagent, MnO$_2$, etc), possibly due to a competing reaction at the primary amine. Fortunately, Fmoc protection of the primary amine group (72–81%) allowed the successful oxidation (Dess–Martin, 76–85%) to give the Fmoc protected derivatives 24a–c, as shown in scheme 4. Standard Fmoc deprotection methods (using secondary amines such as piperidine, diethylamine and dicyclohexylamine) resulted in a multi-spot TLC profile in all cases from which the only identifiable products implied that the amine had undergone Michael addition to the α, β-unsaturated ketone moiety. Such a reaction has been noted by other workers whilst attempting to remove Fmoc with piperidine in the presence of a Michael acceptor [43].
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

Therefore found that a tertiary amine base, triethylamine (TEA), could be used to bring about the removal of Fmoc. These conditions also turned out to be rigorous enough to bring about cyclisation. Thus, treatment of the Fmoc-protected ketone derivatives 24a–c with excess TEA in anhydrous dichloromethane at reflux resulted in the complete disappearance by TLC of the starting material after 15 hours and in the isolation, in each case, of a major new product. The new products were not the deprotected compounds 25 (scheme 4), nor the expected cyclisation products 26, but were in fact the 3-hydroxy-1,2,5-benzothiadiazepines 27a–c which were isolated in yields of 57–69%.

With regards to a possible mechanism, it is plausible that the 3-hydroxy-1,2,5-benzothiadiazepines 27 may arise as a result of a series of tautomerisms in starting material 24 to give enol tautomer 28, followed by the formation of tautomer 29 as shown in scheme 5. Deprotection of tautomer 29 then produces the corresponding amine 30. Clearly, the exact sequence of events leading to intermediate 30 could be ordered differently so that deprotection occurs first and is followed by the tautomerism sequence. In any event, cyclisation of intermediate 30 would give the carbinolamine 31 which could then give the isolated product 27, possibly via an intramolecular process such as that involving the intermediate epoxide 32, as outlined in scheme 5. Alternatively, loss of water across the C4–N5 bond of compound 31, and the subsequent intermolecular re-addition of water across the N2–C3 double bond of the sulfonimine, would give the isolated product 27.

In the final part of this work, as shown in scheme 6, we investigated the use of 2-nitrobenzenesulfonamide as a precursor for a shorter synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides. In this respect, we were surprised to find that, whilst we were able to convert 2-nitrobenzenesulfonamide into the dienophile 33 and isolate the Diels–Alder adduct 34c derived from hexadiene, we were unable to isolate the butadiene or isoprene adducts 34a and 34b. This was due to their ready conversion into the corresponding homoallylic sulfonamides 36 (R4 = H or Me) in the presence of atmospheric moisture. The formation of homoallylic sulfonamides 36 is due to attack of water at the 1,2-thiazine sulfur atom in compounds 34a and b, followed by ring opening of the 1,2-thiazine to give an allylic sulfonic acid 35 with subsequent retro-ene loss of SO2, an overall process that has precedent in the literature [48–53]. We believe that the presence of a methyl group at the 6-position of the 1,2-thiazine ring in the hexadiene adduct 34c (R3 = Me) offers sufficient steric hindrance to prevent the initial

\[ \text{SCHEME 4 Synthesis of 3-hydroxy-1,2,5-benzothiadiazepines.} \]
attack of water at sulfur, hence allowing this adduct to be isolated, whereas adducts 34a and 
b (R^5 = H) are able to accommodate ready access of water to the sulfur and can thus go on 
to produce the homoallylic sulfonamides 36. Hexadiene adduct 34c was isolated in 60% 
yield and was converted into the alcohol 37c in 89% yield and thence into the corresponding 
ketone 38c in 84% yield, again with the expected (see above) (E)-alkene geometry, as 
shown in scheme 6. The treatment of this ketone with zinc in acetic acid gave access to the 
4-alkenyl-1,2,5-benzothiadiazepine 1,1-dioxide 39c in 45% yield. Interestingly, we were able 
to show that the air sensitive isoprene and butadiene adducts 34a and 34b could be converted 
in situ into the alcohols 37a and 37b using the PhMgBr/P(OMe)_3 sequence in overall yields 
of 38% and 45%, respectively, for the four step process from 2-nitrobenzenesulfonamide. 
The same 'in situ' process when applied to the hexadiene system gave another method for 
accessing the alcohol 37c which was obtained in 44% overall yield for the four steps from 
2-nitrobenzenesulfonamide. Finally, oxidation of alcohols 37a and b was achieved in yields 
of 78% and 89% to give the ketones 38a and b. Ring closure using zinc in acetic acid gave 
the 4-alkenyl-1,2,5-benzothiadiazepine 1,1-dioxides 39a and 39b in 50% and 49% yields, 
respectively.

3. Summary

In conclusion, two efficient entries (3 examples of each) into the 1,2,5-benzothiadiazepine 
1,1-dioxide system have been reported which rely upon the synthesis of N-(o-
aminobenzenesulfonyl)-1,2-vicinal amino alcohols or N-(o-nitrobenzenesulfonyl)-1,2-vicinal 
amino alcohols from 1,2-thiazine 1-oxides, which are derived in turn from 
2-aminobenzenesulfonamide and 2-nitrobenzenesulfonamide, respectively. A hetero-Diels-
Alder reaction between a diene and a N-sulfinyl dienophile was used to install the 1,2-thiazine
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

Scheme 6 1,2,5-Benzothiadiazepines from 2-nitrobenzenesulfonamide. Reaction conditions: (i) SOCl₂, pyridine, THF or SOCl₂ (1.5 equiv.), benzene, reflux, 72 hours. (ii) diene. (iii) PhMgBr, THF, −40°C then H₂O. (iv) P(OMe)₃, MeOH, heat. (v) Dess-Martin periodinane. (vi) Zn/AcOH, reflux.

1-oxide grouping which, after conversion into an allylic sulfoxide, underwent a [2,3]-sigmatropic rearrangement and desulfurisation to produce the 1,2-amino alcohol functionality. For the 2-aminobenzenesulfonamide series, the conversion of the o-amino group into an azide allowed the selective functionalization of the sulfonamide nitrogen. The azide could be converted back into the amine very efficiently via the hydrolysis of an intermediate iminophosphorane, or, less efficiently, via the hydrolysis of an intermediate triazene. The N-(o-aminobenzenesulfonyl)-1,2-vicinal amino alcohols so obtained proved to be useful precursors for the synthesis of 3-hydroxy substituted 1,2,5-benzothiadiazepine 1,1-dioxides. For the 2-nitrobenzenesulfonamide series, the Diels-Alder-[2,3]-sigmatropic rearrangement – desulfurisation sequence gave N-(o-nitrobenzenesulfonyl)-1,2-vicinal amino alcohols which served as useful precursors for the synthesis of 4-alkenyl substituted 1,2,5-benzothiadiazepine 1,1-dioxides.

4. Experimental section

4.1 General considerations

All starting materials and reagents were used as commercially available. Pyridine, triethylamine, piperidine, diisopropylamine, and N,N-diisopropanylamine, were dried over 4 Å molecular sieves prior to use. Solvents for chromatography were of analytical grade.
Petroleum ether used for chromatography was of the 40–60 °C boiling point range. Anhydrous grade solvents were used as supplied, without additional drying, except where stated. Unless otherwise stated, all reactions were conducted using oven-dried glassware under a positive pressure of dry, oxygen-free nitrogen. All reactions were monitored by thin-layer chromatography using aluminium plates coated with silica gel with F254 fluorescent indicator. Various mixtures of petroleum ether (40–60 °C) and ethyl acetate were used as the eluent and visualisation of the plates was achieved using ultraviolet light and/or vanillin stain. Flash column chromatography was performed using flash grade silica gel (70–230 mesh; 60 Å) using the eluent described in the experimental protocol.

\[^1\]H and \[^{13}\]C NMR spectra were recorded on a Bruker DPX-400 or Bruker AC-250 spectrometer operating at 400 MHz (or 100 MHz) and 250 MHz (or 63 MHz) frequency, respectively. Coupling constants (\(J\)) are reported in Hertz (Hz) and resonances are designated as follows: singlet (\(s\)); doublet (\(d\)); triplet (\(t\)); quartet (\(q\)); quintet (quint). Broad signals in \(^1\)H NMR are denoted as 'br' and signals corresponding to quaternary carbon atoms in \(^{13}\)C NMR are indicated as 'q'. Low resolution mass spectra (LRMS) were recorded on a Micromass Quattro II Triple Quadrupole or a VG Micromass 7070 H mass spectrometer operating at a positive ion mode under electron impact (EI), chemical ionisation (CI), or electrospray ionisation (ESI) methods. Molecular ions are reported as their mass, with the percentage abundance quoted in brackets. High resolution mass spectra (HRMS) were recorded on a Finnegan MAT 900 XTL instrument operated by the EPSRC National Mass Spectrometry service at the University of Wales Swansea, UK, and are reported for compounds of >99% purity (NMR) which were single spot pure by TLC. Infrared spectra (IR) were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument as thin films between NaCl plates (oils) or as KBr disks (solids). Absorptions are listed as wavenumber (cm\(^{-1}\)), with their absorption intensity indicated parenthetically as broad (\(b\)), strong (\(s\)), medium (\(m\)) or weak (\(w\)).

4.2 Synthesis of 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (15)

4.2.1 General procedure, Method A. To a suspension of o-azidobenzenesulfonamide (13; 5–8 mmol, 1.0 eq) in anhydrous benzene (30–50 ml) [CAUTION: SUSPECTED CARCINOGEN – see Method B for an alternative] was added, under an atmosphere of dry nitrogen, thionyl chloride (1.5 eq), and the whole was heated at reflux in an oil bath for 3 days (~72 hours), or until the sulfonamide had completely dissolved. The reaction mixture was allowed to cool to room temperature and the solvent and excess thionyl chloride were removed in vacuo to yield the \(N\)-sulfinyl-o-azidobenzenesulfonamide (14) as a brown oil. To the crude \(N\)-sulfinyl-o-azidobenzenesulfonamide (14) in anhydrous tetrahydrofuran (20–30 ml) was added, under nitrogen, the diene (1.6 eq), and the reaction mixture was stirred at room temperature for 6–16 hours, whilst being monitored by TLC. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/1:1) to yield the 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (15), as follows:

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15a) was obtained as a yellow solid (1.235 g, 82% yield) from o-azidobenzenesulfonamide (13; 1.000 g, 5.05 mmol) and 1,3-butadiene (large excess, ~10 eq), mp: 122–124 °C.

\[\delta_H (400 \text{ MHz, CDCl}_3): 3.45 \text{ (1 H, ddd, } J 16.5, 6.2, 2.3, \text{ } CH_2S=O), 3.61 \text{ (1 H, ddd, } J 16.5, 5.1, 2.5, \text{ } CH_2S=O), 3.83 \text{ (1 H, ddd, } J 17.4, 5.2, 2.3, \text{ } CH_2N), 4.11-4.17 \text{ (1 H, m, } CH_2N), 5.73-5.79 \text{ (1 H, m, } HC=CH\text{), 5.96-6.01 \text{ (1 H, m, } HC=CH\text{), 7.28 \text{ (1 H, td, } J 7.8, 0.9, \text{ ArH), 7.34 \text{ (1 H, dd, } J 8.0, 0.8, \text{ ArH), 7.66 \text{ (1 H, td, } J 7.8, 1.5, \text{ ArH), 8.01 \text{ (1 H, dd, } J 8.0, 1.5, \text{ ArH).} \]

\[\delta_C (100 \text{ MHz, CDCl}_3): 39.0 \text{ (CH}_2\text{), 50.6 \text{ (CH}_2\text{), 114.6 \text{ (CH), 120.3 \text{ (CH), 124.3 \text{ (CH),}}\right]
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

124.6 (CH), 127.7 (q), 131.6 (CH), 139.1 (q), $\nu_{\text{max}}$ (cm$^{-1}$): 3010 (w), 2919 (w), 2133 (s), 1575 (m), 1470 (s), 1352 (s), 1282 (s), 1170 (s), 1103 (s), 1060 (s), 1003 (m), 868 (m), 771 (s), 653 (m). EI+ mass spectrum (m/z, %): 298 ([M]+, 4%), 282 ([M-O]+, 1%), 270 ([M-N2]+, 2%), 250 ([M-SO]+, 3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). Cl+ mass spectrum (m/z, %): 316 ([M+NH4]+, 100%), 299 ([M+H]+, 1%), 283 ([M-N2]+, 2%), 250 ([M-SO]+, 3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). HRMS (ESI+): found [M+NH4]+ 316.0534, C10H10N4O2S2 requires 316.0538. C, H, N(%): found C 40.4, H 3.4, N 18.6; C10H10N4O2S2 requires C 40.3, H 3.4, N 18.8.

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (15b) was obtained as a yellow solid (1.845 g, 78% yield) from o-azidobenzenesulfonamide (13; 1.500 g, 7.57mmol) and isoprene (1.21 ml, 12.11 mmol), mp: 146-148 °C.

$\delta_H$ (400 MHz, CDCl3): 1.80 (3 H, s, CH3), 3.23 (1 H, dd, J 16.2, 1.8, CH2S=O), 3.57-3.62 (1 H, dm, J 16.2, CH2S=O), 3.75-3.82 (1 H, dm, J 17.0, CHN), 5.66 (1 H, d, J 1.9, MeC=CH), 7.24 (1 H, t, J 7.7, ArH), 7.32 (1 H, d, J 8.1, ArH), 7.64 (1 H, td, J 7.8, 1.4, ArH), 7.99 (1 H, dd, J 8.0, 1.4, ArH). $\delta_C$ (100 MHz, CDCl3): 24.2 (CH3), 39.3 (CH2), 54.3 (CH2), 117.6 (CH), 120.2 (CH), 124.5 (CH), 127.7 (q), 131.5 (CH), 135.1 (CH), 139.0 (q). $\nu_{\text{max}}$ (cm$^{-1}$): 3011 (w), 2916 (w), 2134 (s), 1575 (m), 1473 (s), 1444 (m), 1350 (s), 1293 (m), 1172 (s), 1103 (s), 1064 (m), 1010 (w), 832 (m), 757 (s), 655 (m). EI+ mass spectrum (m/z, %): 298 (2%), 282 (1%), 270 (3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). Cl+ mass spectrum (m/z, %): 316 ([M+NH4]+, 100%), 299 ([M+H]+, 1%), 283 ([M-N2]+, 2%), 250 ([M-SO]+, 3%), 172 (5%), 156 (10%), 116 (25%), 104 (20%), 90 (40%), 76 (35%), 64 (50%), 54 (30%), 39 (100%). HRMS (ESI+): found [M+H]+ 313.0425, C11H12N4O3S2 requires 313.0429. C, H, N(%): found C 42.4, H 3.7, N 17.8; C11H12N4O3S2 requires C 42.3, H 3.9, N 17.9.

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (15c) was obtained as a yellow solid (1.580 g, 80% yield) from o-azidobenzenesulfonamide (13; 1.200 g, 6.054 mmol) and (E, E)-2,4-hexadiene (1.10 ml, 9.69 mmol), mp: 137-139 °C.

$\delta_H$ (250 MHz, CDCl3): 1.27 (3 H, d, J 7.0, CH3CHS=O), 1.46 (3 H, d, J 7.4, CH2CHN), 3.29-3.41 (1 H, m, MeCHS=O), 4.55-4.68 (1 H, m, MeCHN), 5.45 (1 H, dd, J 11.0, 2.5, 1.5, HC=CH), 5.91 (1 H, dt, J 11.0, 3.2, HC=CH), 7.25-7.35 (2H, m, 2xArH), 7.62-7.69 (1 H, m, ArH), 8.06 (1 H, dd, J 8.0, 0.9, ArH). $\delta_C$ (63 MHz, CDCl3): 15.9 (CH3), 22.2 (CH3), 51.2 (CH), 53.3 (CH), 119.8 (CH), 120.1 (CH), 124.8 (CH), 129.7 (CH), 130.4 (q, 131.1 (CH), 135.0 (CH), 138.7 (q). $\nu_{\text{max}}$ (cm$^{-1}$): 3010 (w), 2929 (w), 2131 (s), 1575 (m), 1472 (s), 1441 (m), 1353 (m), 1262 (s), 1166 (s), 1121 (s), 1060 (m), 1003 (m), 877 (m), 752 (s), 657 (m). EI+ mass spectrum (m/z, %): 327 ([M+H]+, 2%), 310 ([M-O]+, 2%), 288 ([M-N2]+, 4%), 278 ([M-SO]+, 3%), 208 (10%), 198 (5%), 183 (5%), 171 (10%), 154 (8%), 144 (10%), 105 (15%), 96 (20%), 90 (30%), 82 (100%), 76 (25%), 67 (60%). Cl+ mass spectrum (m/z, %): 330 ([M+NH4]+, 97%), 313 ([M+H]+, 15%), 284 ([M-N2]+, 90%). HRMS (ESI+): found [M+H]+ 313.0425, C11H14N4O3S2 requires 313.0429. C, H, N(%): found C 42.4, H 3.7, N 17.8.

The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

4.2.2 Method B (avoiding the use of benzene). To a solution of o-azidobenzenesulfonamide (13, ~5-10 mmol, 1.0 eq) and anhydrous pyridine (2.0 eq) in anhydrous tetrahydrofuran (30-60 ml), under an atmosphere of dry nitrogen, was added, dropwise with stirring over a period of 3 hours, a solution of thionyl chloride (1.0 eq) in anhydrous tetrahydrofuran (5-8 ml). Stirring of the reaction mixture was continued for a further 30 minutes, followed by dropwise addition of the appropriate 1,3-diene (the appropriate 1,3-diene (1.6 eq), and the whole was allowed to stir at room temperature for 6-16 hours whilst being monitored by TLC. In the case of the
1,3-butadiene adduct (15a), the diene was condensed at low temperature (−20 °C) and subsequently added to the mixture, maintaining the low temperature of the reaction for 4–6 hours. After completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash column silica chromatography (eluents PE:EtOAc/1:1). The 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (15) were obtained as follows:

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15a) was obtained as a yellow solid (0.872 g, 58% yield) from o-azidobenzenesulfonamide (13; 1.000 g, 5.05 mmol) and 1,3-butadiene (large excess, ~10 eq).

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (15b) was obtained as a yellow solid (1.512 g, 60% yield) from o-azidobenzenesulfonamide (13; 1.600 g, 8.07 mmol) and isoprene (1.29 ml, 12.92 mmol).

2-(o-Azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (15c) was obtained as a yellow solid (1.720 g, 70% yield) from o-azidobenzenesulfonamide (13; 1.500 g, 7.57 mmol) and 2,4-hexadiene (1.38 ml, 12.11 mmol). [For full characterization data of these compounds, see Method A, above].

4.3 Synthesis of (o-aminobenzenesulfonamidyl)alkenols (18)

4.3.1 Method 1. Synthesis via the triazene route (see scheme 2). Synthesis of [3'-(o-benzenesulfonamidyl)-1'-phenyltriazene] alkenols (17). A solution of phenylmagnesium bromide (3 M in ether, 3.0 eq) was added to a stirred solution of the 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15; ~1.0–3.5 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10–20 ml) at −78 °C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<−40 °C) for 3–4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at −20 °C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 × 20 ml) and the combined organic layers were washed with water (2 × 20 ml) and brine (10 ml). The organic phase was collected, dried (MgSO4), filtered and the solvent evaporated off to yield the phenyl allylic sulfoxide (16), which was not purified further. To a solution of the crude allylic sulfoxide (16) in anhydrous methanol (10–20 ml) was added anhydrous piperidine (5.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 hours, whilst being monitored by TLC. Upon completion of the reaction, the solvent was removed in vacuo and the crude product was purified by flash column chromatography (eluents PE:EtOAc/5:2) to yield the [3'-(o-benzenesulfonamidyl)-1'-phenyltriazene] alkenols (17) as follows:

4-[3'-(o-Benzenesulfonamidyl)-1'-phenyltriazene]-but-1-en-3-ol (17a) was obtained as a yellow oil, which solidified to give a waxy solid (0.777 g, 67% yield), from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15a; 1.000 g, 3.35 mmol), mp 172–174 °C.

δH (400 MHz, CDCl3): 2.92 (1 H, dd, J 12.8, 8.2, CH2NH), 3.19 (1 H, dd, J 12.8, 3.3, CH2NH), 4.37 (1 H, s, br, CHOH), 5.17 (1 H, d, J 10.6, HC=CH2), 5.33 (1 H, d, J 17.2, HC=CH2), 5.81 (1 H, ddd, J 16.6, 10.8, 5.6, H2C=CH), 7.11–7.13 (3 H, m, 3 × ArH), 7.25 (2 H, t, J 7.7, 2 × ArH), 7.31 (1 H, t, J 7.6, ArH), 7.54 (1 H, t, J 7.8, ArH), 7.71 (1 H, d, J 8.1, ArH), 8.02 (1 H, d, J 7.8, ArH). δC (100 MHz, CDCl3): 48.7 (CH2), 71.1 (CH), 117.0 (CH2), 117.5 (CH), 124.9 (CH), 125.3 (CH), 129.2 (CH), 129.3 (CH), 129.7 (q), 133.9 (CH), 135.4 (q), 136.9 (CH), 144.0 (q). vmax (neat oil, cm⁻¹): 3476 (bm), 3291 (m), 3231 (m), 2987 (m), 2928 (m), 2306 (m), 1602 (s), 1527 (m), 1466 (s), 1441 (s), 1421 (s), 1327 (s), 1155 (s), 1126 (m), 1087 (m), 909 (s), 728 (s). ESI+ mass spectrum (m/z, %): 346 ([M]+, 1%), 149 (15%), 105 (20%), 91 (20%), 84 (75%), 77 (60%), 69 (35%), 65 (25%), 57 (40%).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

Spectrum (m/z, %): 715 ([2M+Na]+, 25%), 693 ([2M+H]+, 2%), 369 ([M+Na]+, 100%), 347 ([M+H]+, 10%). HRMS (ESI+): found [M+H]+ 347.1174, C16H18N4O3S requires 347.1178. C, H, N: found C 55.4, H 5.4, N 16.4; C16H18N4O3S requires C 55.5, H 5.2, N 16.2.

4-[3'-o-Benzene sulfonamidyl]-1'-phenyltriazene-2-methyl-but-1-en-3-ol (17b) was obtained as a yellow oil which solidified on standing to give a waxy solid (0.3690 g, 64% yield) from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (15b; 0.5000 g, 1.60 mmol), mp 122-128 °C.

δH (400 MHz, CDCl3): 1.67 (3H, s, CH3), 2.80 (1H, s, br, OH), 2.93 (1H, dd, J 12.7, 8.3, CH2NH), 3.24 (1H, dd, J 12.7, 3.3, CH2NH), 4.26 (1H, dd, J 5.2, 1.6, CHOH), 4.90 (1H, s, MeC=CB2), 5.03 (1H, s, MeC=CH), 6.05 (1H, s, br, NH), 7.19-7.21 (3H, m, 3 × ArH), 7.28-7.32 (3H, m, 3 × ArH), 7.55 (1H, s, br, NH), 7.74 (1H, d, J 8.2, ArH), 8.01 (1H, dd, J 7.9, 1.3, ArH), 11.0 (1H, s, br, NH). δC (100 MHz, CDCl3): 18.5 (CH3), 47.5 (CH2), 73.5 (CH), 112.5 (CH2), 117.1 (q), 117.4 (CH), 123.0 (q), 123.2 (q), 125.1 (CH), 125.3 (CH), 129.2 (CH), 133.9 (CH), 144.0 (q). vmax (cm⁻¹): 3468 (bm), 3290 (m), 3229 (m), 2987 (m), 2927 (m), 2306 (m), 1602 (s), 1526 (m), 1466 (s), 1441 (s), 1420 (s), 1317 (s), 1154 (s), 1123 (m), 910 (m), 730 (s). EI+ mass spectrum (m/z, %): 360 ([M]+, 1%), 156 (10%), 105 (25%), 92 (40%), 84 (20%), 77 (100%), 69 (25%), 65 (45%), 57 (25%). ESI+ mass spectrum (m/z, %): 743 ([2M+Na]+, 30%), 721 ([2M+H]+, 5%), 383 ([M+Na]+, 100%), 361 ([M+H]+, 15%). HRMS (ESI+): found [M+H]+ 361.1333, C17H20N4O3S requires 361.1334. C, H, N (%): found C 56.9, H 5.8, N 15.2; C17H20N4O3S requires C 56.7, H 5.6, N 15.5.

(E)-5-[3'-o-Benzene sulfonamidyl]-1'-phenyltriazene-hex-1-en-4-ol (17c) was obtained as a yellow waxy solid (0.4740 g, 59% yield) from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (15c; 0.7000 g, 2.15 mmol), mp: 149-153 °C.

δH (400 MHz, CDCl3): 1.07 (3H, d, J 6.7, CH3CHNH), 1.62 (3H, dd, J 6.5, 1.4, CB3CH=CH), 3.00 (1H, s, br, OH), 3.34 (1H, dq, J 15.3, 6.4, MeCHNH), 3.94 (1H, t, J 6.5, CHOH), 5.39 (1H, ddd, J 15.3, 7.3, 1.5, MeH=CH=CH), 5.71 (1H, d, J 14.9, 6.6, CH=CHMe), 5.90 (1H, s, br, NH), 7.13 (1H, t, J 7.1, ArH), 7.16-7.21 (2H, m, 2 × ArH), 7.25-7.30 (3H, m, 3 × ArH), 7.53 (1H, td, J 7.8, 1.4, ArH), 7.75 (1H, d, J 8.1, ArH), 8.01 (1H, dd, J 7.9, 1.1, ArH), 11.2 (1H, s, br, NH). δC (100 MHz, CDCl3): 17.4 (CH3), 17.7 (CH3), 54.9 (CH), 75.7 (CH), 117.2 (CH), 117.3 (CH), 122.7 (q), 125.1 (CH), 125.3 (CH), 129.1 (CH), 130.1 (CH), 132.3 (q), 133.7 (CH), 141.3 (q). vmax (cm⁻¹): 3470 (bm), 3289 (m), 3230 (m), 2987 (m), 2928 (m), 2305 (m), 1601 (s), 1527 (m), 1465 (s), 1441 (s), 1422 (s), 1327 (s), 1155 (s), 1123 (m), 910 (m), 896 (m), 739 (s). EI+ mass spectrum (m/z, %): 374 ([M]+, 15%), 303 (25%), 149 (15%), 105 (40%), 92 (30%), 84 (65%), 77 (100%), 69 (65%), 65 (35%), 56 (70%). ESI+ mass spectrum (m/z, %): 743 ([2M+Na]+, 25%), 749 ([2M+H]+, 3%), 397 ([M+Na]+, 100%), 375 ([M+H]+, 10%). HRMS (ESI+): found [M+H]+ 375.1486, C17H22N4O3S requires 375.1491. C, H, N (%): found C 57.4, H 5.8, N 15.2; C17H22N4O3S requires C 56.7, H 5.6, N 15.5.

Synthesis of (o-aminobenzenesulfonamidyl)alkenols (18) from triazenes (17). A solution of the [3'-(o-benzenesulfonamidyl)-I' -phenyltriazene] alkenol (17) (-0.5-1.5 mmol) in standard laboratory reagent grade methanol was heated at reflux in the open air for a total of 5 hours. The reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuo and the crude product was purified by column chromatography (eluent: PE:EtOAc/5:2) to yield 4-(o-aminobenzenesulfonyl)-but-1-en-3-ol (18) in 60-70% yield. As a typical example, 4-(o-aminobenzenesulfonyl)-but-1-en-3-ol (17a) was obtained as a yellow oil (0.2450 g, 70% yield) from 4-[3'-(o-benzenesulfonamidyl)-1'-phenyltriazene]-but-1-en-3-ol (17a; 0.5000 g, 1.44 mmol). [Data for compounds (18a-c) were identical to that provided via the more efficient Method 2, details of which are listed immediately below].
4.3.2 Method 2. Synthesis via the hydrolysis of iminophosphorane (20) (see scheme 3). Synthesis of 2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (21). To a solution of the 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15; ~3–6 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10–20 ml) was added, dropwise with stirring over a period of 1 hour, a solution of triphenylphosphine (1.0 eq) in anhydrous tetrahydrofuran (5–8 ml) under an atmosphere of dry nitrogen. The mixture was stirred for 3–4 hours, after which analysis by TLC showed a single new spot, assumed to be the 2-[o-N-(triphenylphosphoranylidene)benzenesulfonyl]-3,6-dihydro-1,2-thiazine 1-oxides (20).

Water (~8 eq) was added to the mixture and the whole was heated at reflux in the open air for a total of 15 hours, at which stage TLC showed disappearance of the assumed intermediate (20) and the presence of a single new spot together with base-line material which was later identified as triphenylphosphine oxide. The reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuo and the crude product was purified by gravity column chromatography on silica (eluent: PE:EtOAc 2:1) to yield the 2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxides (21) as light yellow oils, which darkened on standing and which were used immediately in the next step. Data for samples of compounds (21a–c) were as follows:

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (21a) was obtained as a yellow oil (0.900 g, 99%) from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15a; 1.000 g, 3.35 mmol).

δH (250 MHz, CDCl3): 3.39 (1 H, ddd, J 16.5, 6.3, 2.4, CH2S=O), 3.61 (1 H, ddd, J 17.1, 5.3, 2.3, CH2N), 3.99–4.10 (1 H, dm, J 17.1, CH2N), 5.12 (2H, s, br, NH2), 5.71 (1 H, m, HCC=CH), 6.72–6.81 (2H, m, 2 x ArH), 7.33 (1 H, td, J 7.7, 1.6, ArH), 7.67 (1 H, dd, J 8.1, 1.5, ArH). δc (63 MHz, CDCl3): 39.0 (CH2), 50.6 (CH2), 114.5 (CH), 117.6 (CH), 117.7 (q), 118.1 (CH), 124.4 (CH), 130.1 (CH), 135.4 (CH), 146.2 (q). 31P spectroscopy showed the sample to be free of phosphorus. Vmax (cm−1): 3432 (m), 3339 (m), 2960 (m), 2918 (m), 1617 (s), 1560 (s), 1545 (m), 1484 (s), 1342 (s), 1166 (s), 1075 (s), 1002 (m), 927 (m), 773 (s), 630 (s). EI+ mass spectrum (m/z, %): 273 ([M+H]+, 3%), 272 ([M]+, 15%), 224 ([M-SO]+, 15%), 218 (30%), 172 (5%), 156 (40%), 140 (10%), 116 (10%), 108 (30%), 92 (100%), 65 (80%), 54 (10%). CI+ mass spectrum (m/z, %): 290 ([M+NH4]+, 100%), 273 ([M+H]+, 60%). HRMS (ESI+): found [M+H]+ 273.0367, C10H12N2O3S2 requires 273.0367.

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (21b) was obtained as a yellow oil (1.454 g, >99%) from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15b; 1.600 g, 5.12 mmol, 1.0 eq).

δH (400 MHz, CDCl3): 1.83 (3 H, s, CH3), 3.22 (1 H, dd, J 16.2, 1.2, CH2S=O), 3.61 (1 H, dt, J 16.2, 1.2, CH2S=O), 3.80 (1 H, dq, J 16.6, 5.8, 2.1, CH2N), 4.00 (1 H, dt, J 16.6, 2.1, CH2N), 5.14 (2H, s, br, NH2), 5.67 (1 H, m, MeC=CH), 6.75 (1 H, dd, J 8.1, 0.6, ArH), 6.80 (1 H, dt, J 7.6, 0.8, ArH), 7.35 (1 H, td, J 7.7, 1.4, ArH), 7.70 (1 H, dd, J 8.1, 1.4, ArH). δc (100 MHz, CDCl3): 24.3 (CH3), 39.3 (CH2), 54.3 (CH2), 117.6 (CH), 117.8 (CH), 117.9 (q), 118.0 (CH), 122.6 (q), 130.2 (CH), 135.4 (CH), 146.1 (q). Vmax (cm−1): 3462 (m), 3338 (m), 2961 (m), 2928 (s), 1625 (m), 1598 (m), 1483 (s), 1438 (s), 1343 (s), 1158 (s), 1093 (s), 1027 (w), 927 (m), 758 (s), 668 (s). EI+ mass spectrum (m/z, %): 286 ([M]+, 4%), 238 ([M-SO]+, 8%), 218 (15%), 172 (10%), 156 (30%), 140 (10%), 108 (35%), 92 (100%), 65 (25%). HRMS (ESI+): found [M+Na]+ 273.0531, C10H12N2O3S2Na requires 273.0536.

2-(o-Aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (21c) was obtained as a yellow oil (1.454 g, >99%) from 2-(o-azidobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (15c; 1.800 g, 5.52 mmol).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

\[ \delta_H (250 \text{ MHz, CDCl}_3): 1.41 (3 \text{ H, d, } J = 7.0, \text{ CH}_2\text{CH}=\text{O}), 1.44 (3 \text{ H, d, } J = 7.5, \text{ CH}_2\text{CHN}), 3.42 (1 \text{ H, dq, } J = 7.6, 1.9, \text{ MeCH}=\text{O}), 4.33 (1 \text{ H, dq, } J = 6.8, 3.4, \text{ MeCHN}), 4.91-4.95 (2 \text{ H, br, NH}_2), 5.38 (1 \text{ H, ddd, } J = 11.0, 2.1, 2.1, \text{ HC}=\text{CH}), 5.84 (1 \text{ H, ddd, } J = 11.0, 3.3, 3.3, \text{ HC}=\text{CH}), 6.75 (1 \text{ H, d, } J = 8.3, \text{ ArH}), 6.78-6.83 (1 \text{ H, m, ArH}), 7.34 (1 \text{ H, td, } J = 7.7, 1.5, \text{ ArH}), 7.75 (1 \text{ H, td, } J = 7.5, 1.5, \text{ ArH}). \]

\[ \delta_C (63 \text{ MHz, CDCl}_3): 15.8 (\text{ CH}_3), 22.9 (\text{ CH}_3), 50.8 (\text{ CH}), 52.9 (\text{ CH}), 117.8 (\text{ CH}), 118.0 (\text{ CH}), 119.8 (\text{ CH}), 120.8 (\text{ q}), 129.5 (\text{ CH}), 135.1 (\text{ CH}), 145.3 (\text{ q}). \]

\[ \nu_{\max} (\text{ cm}^{-1}): 3476 (\text{ w}), 3373 (\text{ w}), 2968 (\text{ m}), 2928 (\text{ m}), 1621 (\text{ m}), 1566 (\text{ w}), 1483 (\text{ s}), 1433 (\text{ s}), 1157 (\text{ s}), 1100 (\text{ s}), 942 (\text{ m}), 880 (\text{ s}), 755 (\text{ s}), 669 (\text{ s}). \]

\[ \text{EI+ mass spectrum (m/z, %): } 300 ([M]+, 2%), 252 ([M-SO]+, 4%), 218 (15%), 172 (4%), 156 (6%), 140 (5%), 108 (20%), 92 (100%), 82 (80%), 77 (20%), 65 (85%). \]

\[ \text{CI+ mass spectrum (m/z, %): } 318 ([M+N14]+, 70%), 301 ([M+H]+, 40%). \]

\[ \text{HRMS (ESI+): found [M+H]+ 301.0675, C12H16N2O3S2 requires 301.0680.} \]

Synthesis of (o-aminobenzenesulfonylamidyl)alkenols (18) from compounds (21). A solution of phenylmagnesium bromide (3 M in ether, 2.0 eq) was added to a stirring solution of the 2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (21; 12-5 mmol, 1.0 eq) in anhydrous tetrahydrofuran (10-20 ml) at -78°C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (<-40 °C) for 3-4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at -20°C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 x 20 ml) and washed with water (2 x 20 ml) and brine (10 ml). The organic phase was collected, dried (MgSO4), filtered and the solvent evaporated off to yield the phenyl allylic sulfoxide (22), which was not purified further. To a solution of the crude allylic sulfoxide (22) in anhydrous methanol (10-20 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10-15 hours. Upon completion of the reaction (TLC), the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the (o-aminobenzenesulfonylamidyl)alkenols (18) as yellow oils which darkened on standing at room temperature, but which were stored without detriment at -15°C and used after 24 hours in the next step. Data for samples of compounds (18a-e) were as follows:

4-(o-Aminobenzenesulfonylamidyl)-but-1-en-3-ol (18a) was obtained as a yellow oil (0.6120 g, 86% yield) from 2-(o-aminobenzenesulfonyl)-3,6-dihydro-1,2-thiazine 1-oxide (21a; 0.8000 g, 2.94 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 2.85 (1 \text{ H, ddd, } J = 13.1, 8.0, 3.2, \text{ CH}_2\text{NH}), 3.08 (1 \text{ H, dq, } J = 13.1, 7.6, \text{ CH}_2\text{NH}), 4.15-4.17 (1 \text{ H, m, CHO}), 4.75 (2 \text{ H, s, br, NH}_2), 5.17 (1 \text{ H, dt, } J = 10.5, 1.0, \text{ HC}=\text{CH}), 5.28 (1 \text{ H, dt, } J = 17.2, 1.2, \text{ HC}=\text{CH}), 5.44 (1 \text{ H, t, br, J = 5.9, SO}_2\text{NH}), 5.73 (1 \text{ H, ddd, } J = 17.1, 10.6, 5.7, \text{ HC}=\text{CH}), 6.78-6.84 (2 \text{ H, m, 2 x ArH}), 7.34 (1 \text{ H, dt, } J = 7.7, 1.5, \text{ ArH}), 7.71 (1 \text{ H, dd, } J = 8.0, 1.4, \text{ ArH}). \]

\[ \delta_C (100 \text{ MHz, CDCl}_3): 48.2 (\text{ CH}_2), 71.1 (\text{ CH}), 117.0 (\text{ CH}), 117.8 (\text{ CH}), 121.5 (\text{ q}), 129.6 (\text{ CH}), 134.3 (\text{ CH}), 145.0 (\text{ q}). \]

\[ \nu_{\max} (\text{ cm}^{-1}): 3476 (\text{ w}), 3377 (\text{ w}), 2987 (\text{ m}), 2897 (\text{ m}), 1619 (\text{ m}), 1600 (\text{ m}), 1573 (\text{ w}), 1483 (\text{ s}), 1456 (\text{ s}), 1332 (\text{ s}), 1156 (\text{ s}), 1073 (\text{ m}), 896 (\text{ m}), 747 (\text{ s}). \]

\[ \text{EI+ mass spectrum (m/z, %): } 242 ([M]+, 15%), 224 ([M-H_2O]+, 15%), 185 (35%), 168 (15%), 156 (50%), 108 (35%), 92 (100%), 65 (98%), 57 (90%). \]

\[ \text{CI+ mass spectrum (m/z, %): } 260 ([M+NH_4]+, 95%), 243 ([M+H]+, 100%). \]

\[ \text{HRMS (ESI+): found [M+H]+ 243.0804, C}_{10}\text{H}_{14}\text{N}_2\text{O}_3\text{S} \text{ requires 243.0803.} \]

4-(o-Aminobenzenesulfonylamidyl)-but-1-en-3-ol (18b) was obtained as a yellow oil (0.6120 g, 86% yield) from 2-(o-aminobenzenesulfonyl)-3,6-dihydro-5-methyl-1,2-thiazine 1-oxide (21b; 1.400 g, 4.89 mmol).

\[ \delta_H (400 \text{ MHz, CDCl}_3): 1.66 (3 \text{ H, s, CH}_3), 2.88 (1 \text{ H, ddd, } J = 12.9, 8.0, 3.5, \text{ CH}_2\text{NH}), 3.15 (1 \text{ H, ddd, } J = 13.1, 8.0, 3.6, \text{ CH}_2\text{NH}), 4.06 (1 \text{ H, dd, } J = 7.8, 3.6, \text{ CHOH}), 4.88 (2 \text{ H, s, br, NH}_2), 4.93 (1 \text{ H, bs, MeC}=\text{CH}), 5.00 (1 \text{ H, d, } J = 0.9, \text{ MeC}=\text{CH}), 5.11 (1 \text{ H, s, br, SO}_2\text{NH}), 6.80 (1 \text{ H, dd, J = 17.1, 10.6, CH}=\text{CH}). \]
(1 H, d, J 8.2, ArH), 6.85 (1 H, td, J 7.7, 1.0, ArH), 6.85 (1 H, dd, J 7.7, 1.0, ArH). 7.36 (1 H, td, J 7.7, 1.7, ArH), 7.74 (1 H, dd, J 8.0, 1.5, ArH). δc (100 MHz, CDCl3): 18.3 (CH3), 47.0 (CH2), 73.4 (CH), 112.4 (CH2), 117.8 (CH), 118.1 (CH), 121.7 (q), 129.7 (CH), 134.3 (CH), 144.1 (q), 145.0 (q). νmax (cm⁻¹): 3477 (bm), 3378 (bm), 2986 (m), 2926 (m), 1619 (m), 1600 (m), 1573 (w), 1483 (s), 1456 (s), 1331 (m), 1155 (s), 1090 (m), 910 (m), 756 (s). EI+ mass spectrum (m/z, %): 256 ([M]+, 3%), 238 ([M-H2O]+, 4%), 185 (30%), 168 (15%), 156 (50%), 108 (35%), 92 (100%), 71 (35%), 65 (90%). CI+ mass spectrum (m/z, %): 274 ([M+NH₄]+, 100%), 257 ([M+H]+, 90%). HRMS (ESI+): found [M+H]+ 257.0956, C₁₁H₁₆N₂O₃S requires 257.0960.

(E)-5-(o-Aminobenzenesulfonylamidyl)-hex-2-en-4-ol (18c) was obtained as a yellow oil (0.8900 g, 82% yield) from 2-(o-aminobenzenesulfonyl)-3,6-dihydro-3,6-dimethyl-1,2-thiazine 1-oxide (21e; 1.200 g, 4.00 mmol).

δH (400 MHz, CDCl3): 1.02 (3H, d, J 6.7, CH₂CHNH), 1.62 (3H, dd, J 6.5, 1.3, CH₂CH₂=CH), 3.13-3.18 (1 H, m, CHMe), 3.80 (1 H, d, J 6.6, CHOH), 3.99 (2H, s, br, N₂H₂), 5.22 (1 H, d, br, J 8.1, SO₂N₂H₂), 5.31 (1 H, ddd, J 15.3, 7.5, 1.6, MeNC≡CH), 5.67 (1 H, dq, J 15.3, 6.6, CH≡CH), 6.78 (1 H, d, J 8.0, ArH), 6.80 (1 H, t, J 7.5, ArH), 7.32 (1 H, td, J 7.7, 1.5, ArH), 7.72 (1 H, dd, J 8.0, 1.4, ArH). δc (100 MHz, CDCl3): 17.7 (CH₃), 17.8 (CH₃), 54.2 (CH), 75.7 (CH), 117.7 (CH), 117.8 (CH), 122.3 (q), 129.5 (CH), 129.7 (CH), 130.0 (CH), 134.0 (CH), 144.9 (q). νmax (cm⁻¹): 3474 (bm), 3374 (bm), 2975 (m), 2931 (m), 1621 (m), 1600 (m), 1568 (w), 1483 (s), 1455 (m), 1318 (s), 1155 (s), 1080 (m), 968 (m), 755 (s). EI mass spectrum (m/z, %): 270 ([M]+, 1%), 252 ([M-H2O]+, 6%), 199 (25%), 182 (20%), 172 (25%), 156 (30%), 108 (35%), 92 (98%), 71 (10%), 65 (100%). CI mass spectrum (m/z, %): 288 ([M+N₂H₄]+, 20%), 271 ([M+H]+, 25%). HRMS (ESI+): found [M+H]+ 271.1116, C₁₁H₁₄N₂O₃S requires 271.1116.

4.4 Synthesis of [o-(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl alkenols (24)

4.4.1 Stage 1. Synthesis of the [o-(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl alkenols. To a solution of the o-(aminobenzenesulfonamidyl)alkenol (18; 0.8-1.6 mmol, 1.0 eq) in anhydrous dichloromethane (10 ml) was added solid sodium hydrogen carbonate (2.1 eq) and 9-fluorenylmethyl chloroformate (2.1 eq) and the reaction mixture was left stirring at room temperature under nitrogen for a total of 6-8 hours, whilst being monitored by TLC. Upon completion of the reaction, the solvent was removed in vacuo and the crude product was purified by column chromatography (eluent: PE:EtOAc/3:1) to yield the desired [o-(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl alkenols, as follows: 4-[o-(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonylamidyl-but-1-en-3-ol was obtained as a colourless solid (0.3085 g, 81% yield) from 4-(o-aminobenzenesulfonyl)-but-1-en-3-ol (18a; 0.200 g, 0.82 mmol), mp 204-205 °C. δH (400 MHz, CDCl3): 2.90 (1 H, d, J 12.8, 8.0, 4.7, CH₂NH), 3.15 (1 H, ddd, J 11.7, 8.0, 3.7, CH₂NH), 3.57 (1 H, s, br, OH), 4.05-4.12 (1 H, m, CHOH), 4.33 (1 H, t, J 7.1, CH₂CH₂OCONH), 4.52 (2H, d, J 7.2, CH₂CH₂OCONH), 5.02 (1 H, q, J 5.7, SO₂NH), 5.18 (1 H, d, J 10.5, HC≡CH₂), 5.25 (1 H, d, J 17.3, HC≡CH), 5.71 (1 H, ddd, J 17.1, 10.8, 5.7, H₂C≡CH₂), 7.22 (1 H, t, J 7.7, ArH), 7.36 (2H, t, J 7.5, 2 × ArH), 7.45 (2H, t, J 7.5, 2 × ArH), 7.59 (1 H, t, J 7.8, ArH), 7.65 (2H, d, J 7.4, 2 × ArH), 7.81 (2H, d, J 7.5, 2 × ArH), 7.90 (1 H, ddd, J 8.0, 1.0, ArH), 8.15 (1 H, d, br, J 7.8, ArH), 8.69 (1 H, s, N₂H₂), δc (100 MHz, CDCl3): 46.9 (CH), 47.9 (CH₂), 67.7 (CH₂), 70.9 (CH), 111.3 (CH₂), 117.5 (q), 118.0 (q), 120.1 (CH), 122.3 (CH), 123.5 (CH), 125.1 (CH), 127.2 (CH), 127.9 (CH), 129.4 (CH), 134.3 (CH), 136.8 (CH), 141.4 (q), 143.6 (q), 153.3 (q, CO₂NH).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

υ_{max} (cm^{-1}): 3512 (bw), 3355 (bm), 2925 (m), 2853 (m), 1735 (s), 1588 (s), 1530 (s), 1469 (m), 1458 (s), 1329 (m), 1250 (m), 1154 (s), 1132 (m), 1082 (m), 1047 (m), 933 (w), 757 (s), 668 (m). ESI+ mass spectrum (m/z, %): 487 ([2M+Na]+, 5%), 465 ([M]+, 15%), 450 (M, 20%). HRMS (CI+): found [M+Na]+ 482.1747, [M]+ 480.1742. C_{26}H_{26}N_{20}SS requires C 65.2, H 5.5, N 5.9.

4-[[9'-Fluorenylmethoxycarbonyl]amino]benzenesulfonamidyl]-2-methyl-but-1-en-3-ol was obtained as a colourless solid (0.5675 g, 76% yield) from 4-[[o-aminobenzenesulfonamidyl] -2-methyl-but-1-en-3-ol (18b, 0.4000 g, 1.56 mmol), mp 186-187 °C.

δ_{H} (400 MHz, CDCl3): 1.60 (3 H, s, CH3), 1.94 (1 H, d, J 3.7, CH), 2.93 (1 H, ddd, J 12.7, 8.4, 4.1, CH2NH), 3.18 (1 H, ddd, J 12.3, 8.2, 4.1, CH2NH), 3.95 (1 H, ddd, J 12.5, 11.9, 3.9, CHO), 4.32 (1 H, t, J 7.1, CHCH2OCONH), 4.52 (2 H, d, J 7.2, CHCH2OCONH), 4.88 (1 H, s, HC=CH2), 4.93 (1 H, s, HC=CH2), 5.07 (1 H, dd, J 8.1, 3.9, SO2NH), 7.21 (1 H, t, J 7.8, ArH), 7.36 (2 H, t, J 7.4, 2 x ArH), 7.44 (2 H, t, J 7.4, 2 x ArH), 7.58 (1 H, t, J 7.2, ArH), 7.65 (2 H, d, J 7.4, 2 x ArH), 7.81 (2 H, d, J 7.5, 2 x ArH), 7.91 (1 H, dd, J 8.0, 1.4, ArH), 8.15 (1 H, d, br, J 8.0, ArH), 8.72 (1 H, s, br, CO2NH). δ_{C} (100 MHz, CDCl3): 18.2 (CH3), 46.7 (CH2), 46.9 (CH), 67.7 (CH2), 73.2 (CH), 112.6 (CH2), 120.1 (CH), 122.2 (CH), 122.8 (q), 123.4 (CH), 125.1 (CH), 127.2 (CH), 127.9 (CH), 129.3 (CH), 134.3 (CH), 136.1 (q), 141.3 (q), 143.6 (q), 153.3 (q, CO2NH).

υ_{max} (cm^{-1}): 3515 (bw), 3354 (bm), 2925 (m), 2850 (m), 1736 (s), 1589 (s), 1530 (s), 1470 (m), 1444 (s), 1329 (s), 1247 (m), 1155 (s), 1133 (m), 1081 (m), 1049 (m), 967 (m), 758 (s), 668 (m). ESI+ mass spectrum (m/z, %): 515 ([M+Na]+, 100%). C, H, N (%): found C 65.5, H 5.4, N 5.9; C_{27}H_{26}N_{20}SS requires C 65.2, H 5.5, N 5.9.

(E)-5-[[9'-Fluorenylmethoxycarbonyl]amino]benzenesulfonamidyl]-hex-2-en-4-ol was obtained as a colourless solid (0.3900 g, 72% yield) from (E)-5-[[o-aminobenzenesulfonamidyl]-hex-2-en-4-ol (18c, 0.3000 g, 1.11 mmol, 1.0 eq), mp 186-187 °C.

δ_{H} (400 MHz, CDCl3): 1.09 (3 H, d, J 6.7, CH3CHNH), 1.59 (3 H, dd, J 6.5, 1.5, CH2CH=CH2=CH), 1.88 (1 H, s, br, OH), 3.21 (1 H, q, J 6.0, MeCHNH), 3.80 (1 H, t, J 6.2, CHO), 4.32 (1 H, t, J 6.7, CHCH2OCONH), 4.51 (2 H, d, J 7.2, CHCH2OCONH), 5.12 (1 H, d, br, J 7.6, SO2NH), 5.24 (1 H, ddd, J 15.3, 7.5, 1.6, MeHC=CH2), 5.64 (1 H, dq, J 15.3, 6.6, HC=CHMe), 7.18 (1 H, t, J 7.1, ArH), 7.36 (2 H, t, J 7.5, 2 x ArH), 7.44 (2 H, t, J 7.4, 2 x ArH), 7.55 (1 H, t, J 7.0, ArH), 7.64 (2 H, t, J 6.8, 2 x ArH), 7.80 (2 H, d, J 7.5, 2 x ArH), 7.91 (1 H, dd, J 8.0, 1.5, ArH), 8.16 (1 H, d, br, J 7.5, ArH), 8.79 (1 H, s, br, CO2NH). δ_{C} (100 MHz, CDCl3): 17.7 (CH3), 18.1 (CH3), 46.9 (CH), 54.2 (CH), 67.6 (CH2), 75.3 (CH), 120.1 (CH), 121.8 (CH), 123.2 (CH), 125.0 (CH), 127.2 (CH), 127.8 (CH), 129.3 (CH), 129.5 (CH), 130.4 (CH), 136.0 (q), 141.3 (q), 143.6 (q), 153.2 (q, CO2NH).

υ_{max} (cm^{-1}): 3512 (bw), 3354 (bm), 2923 (m), 2850 (m), 1736 (s), 1589 (s), 1530 (s), 1470 (m), 1444 (s), 1329 (s), 1247 (m), 1155 (s), 1133 (m), 1081 (m), 1049 (m), 967 (m), 758 (s), 668 (m). ESI+ mass spectrum (m/z, %): 515 ([M+Na]+, 100%). C, H, N (%): found C 65.7, H 5.7, N 5.8; C_{27}H_{26}N_{20}SS requires C 65.8, H 5.7, N 5.7.

4.4.2 Stage 2. Formation of [o-[[9'-fluorenylmethoxycarbonyl]amino]benzenesulfonamidyl] alkenones (24) by oxidation of the [o-[[9'-fluorenylmethoxycarbonyl]amino]benzenesulfonamidyl] alkenols. To a solution of Dess-Martin periodinane (1.1 eq) in anhydrous dichloromethane (10 ml) was added a solution of the o-[[N-(9'-fluorenylmethoxycarbonyl)aminobenzenesulfonamidyl] alkenol from Stage 1 in anhydrous dichloromethane (5 ml) at room temperature and the reaction mixture was stirred for 1 hour, whilst being monitored by TLC. Upon completion of the reaction the solvent was evaporated off and the crude product was purified by flash column chromatography (eluent: PE:EtOAc/3:1)
to yield the \( \{9'-\text{fluorenylmethoxycarbonyl} \text{amino} \} \text{benzenesulfonamidyl} \) alkenones (24), as follows:

4-\( \{9'-\text{Fluorenylmethoxycarbonyl} \text{amino} \} \text{benzenesulfonamidyl} \)-but-1-en-3-one (24a) was obtained as a slightly unstable (noticeable degradation after two days at room temperature) pale yellow oil (0.0477 g, 78% yield) from 4-\( \{9'-\text{fluorenylmethoxycarbonyl} \text{amino} \} \text{benzenesulfonamidyl} \)-but-1-en-3-ol (0.0600 g, 0.13 mmol).

\( \delta_H \) (400 MHz, CDCl3): 1.84 (3 H, s, CH3), 4.18 (2H, d, J 4.6, CH2NH), 4.36 (1H, t, J 7.3, CH2CH2OCONH), 4.51 (2H, d, J 7.4, CH2CH2OCONH), 5.70 (1H, t, J 4.4, SO2NH), 5.84 (2H, dd, J 5.0, 1.5, MeC=CH2), 7.19 (1H, td, J 8.0, 0.8, ArH), 7.37 (2H, td, J 7.6, 0.9, 2 x ArH), 7.45 (2H, t, J 7.3, 2 x ArH), 7.58 (1H, td, J 8.4, 1.2, ArH), 7.68 (2H, d, J 7.4, 2 x ArH), 7.81 (2H, d, J 7.5, 2 x ArH), 8.00 (1H, dd, J 7.8, 1.6, ArH), 8.24 (1H, d, br, J 8.2, ArH), 8.86 (1H, s, br, CO2NH), \( \delta_C \) (100 MHz, CDCl3): 17.2 (CH3), 46.9 (CH), 47.5 (CH2), 67.8 (CH2), 120.0 (CH), 121.8 (CH), 124.3 (CH), 125.1 (CH), 125.9 (q), 127.2 (CH), 129.2 (CH), 130.8 (CH2), 132.7 (CH), 134.5 (CH), 136.4 (q), 141.3 (q), 143.6 (q), 153.1 (q, CO2NH), 192.1 (q, C=O). \( \nu_{\text{max}} \) (cm\(^{-1}\)):

3355 (bm), 2924 (s), 2851 (s), 1733 (s), 1733 (s), 1589 (s), 1529 (s), 1470 (m), 1459 (s), 1330 (s), 1291 (m), 1240 (m), 1155 (s), 1133 (m), 1079 (m), 1048 (m), 756 (s), 667 (m).

ESI+ mass spectrum (m/z, %): 480 ([M+NH4]+, 50%).

(\( E \))-5-\( \{9'-\text{fluorenylmethoxycarbonyl} \text{amino} \} \text{benzenesulfonamidyl} \)-hex-2-en-4-one (24b) was obtained as a pale yellow oil which solidified on standing (0.1700 g, 85% yield) from 4-\( \{9'-\text{fluorenylmethoxycarbonyl} \text{amino} \} \text{benzenesulfonamidyl} \)-2-methyl-but-1-en-3-one (24).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides (473)

ESI+ mass spectrum (m/z, %): 1003 ([2M+Na]+, 15%), 513 ([M+Na]+, 100%), 491 ([M+H]+, 15%). C, H, N (%): found C 66.4, H 5.4, N 5.8; C27H26N2O5S requires C 66.1, H 5.4, N 5.7.

4.5 Synthesis of 2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxides (27)

A solution of the [o-[(9'-fluorenylmethoxycarbonyl)amino]benzenesulfonamidyl] alkenone (24; 0.4-0.5 mmol) in a mixture of triethylamine and anhydrous dichloromethane (1:1 V/V, 10 ml) was heated at reflux under an atmosphere of dry nitrogen whilst being monitored by TLC. Upon completion (approx. 15 hours) of the reaction, the solvent was evaporated off and the crude residue was purified by flash silica column chromatography (eluent: PE:EtOAc/1:1) to yield the 1,2,5-benzothiadiazepine 1,1-dioxides (27) as follows:

4-Ethyl-2,3-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxide (27a) was obtained as a light yellow oil which solidified on standing (0.0716g, 69% yield) from 4-{o-[(9'-fluorenylmethoxycarbonyl) amino]benzenesulfonamidyl} -but-1-en-3-one (24a; 0.2000 g, 0.43 mmol), mp: 89-92 °C.

δH (400 MHz, CDCl3): 1.06 (3H, t, J = 7.0, CH3), 1.37 (3H, t, J = 7.4, CH3), 1.87 (1H, dq, J = 3.8, CH2), 2.08 (1H, m, MeCH2), 3.6-3.8 (1H, bs, OH), 4.49 (1H, d, J = 3.8, CHOH), 7.12 (1H, d, J = 8.2, ArH), 7.45 (1H, t, J = 7.7, ArH), 7.57 (1H, t, J = 7.7, ArH), 7.96 (1H, d, J = 8.0, ArH).

δC (100 MHz, CDCl3): 9.1 (CH2), 28.5 (CH2), 72.3 (CHOH), 117.0 (CH), 121.6 (q), 124.7 (CH), 127.2 (CH), 133.6 (q), 160.0 (q).

υmax (cm⁻¹): 3475 (bm), 3277 (bm), 2963 (m), 2927 (m), 1604 (m), 1560 (w), 1525 (m), 1481 (m), 1440 (w), 1297 (s), 1261 (s), 1158 (s), 1079 (s), 1020 (s), 801 (s), 759 (s). ESI+ mass spectrum (m/z, %): 743 ([3M+Na]+, 5%), 503 ([2M+Na]+, 30%), 481 ([2M+H]+, 6%), 263 ([M+Na]+, 70%), 241 ([M+H]+, 100%). HRMS (ESI+): found [M+H]+ 241.0642, C10H12N2O3S requires 241.0647. C, H, N (%): found C 49.9, H 5.1, N 11.9; C10H12N2O3S requires C 50.0, H 5.0, N 11.7.

2,3-Dihydro-3-hydroxy-4-(i-propyl)-1,2,5-benzothiadiazepine 1,1-dioxide (27b) was similarly obtained as a yellow solid (0.0830g, 62% yield), mp: 117-119 °C from 4-{o-[(9'-fluorenylmethoxycarbonyl) amino]benzenesulfonamidyl} -but-1-en-3-one (24b; 0.2500 g, 0.53 mmol).

δH (400 MHz, CDCl3): 0.87 (3H, d, J = 6.9, CH3), 1.07 (3H, d, J = 6.9, CH3), 2.34 (1H, eq), 7.43 (1H, t, J = 7.4, Me2CH), 3.4-3.5 (1H, bs, OH), 4.33 (1H, d, J = 3.3, CHOH), 7.13 (1H, d, J = 8.2, ArH), 7.43 (1H, t, J = 7.6, ArH), 7.54 (1H, t, J = 7.8, ArH), 7.92 (1H, d, J = 7.9, ArH), 9.40 (1H, s, br, SO2NH).

δC (100 MHz, CDCl3): 15.3 (CH3), 19.0 (CH3), 32.8 (CH), 75.1 (CH), 117.2 (CH), 121.6 (q), 124.5 (CH), 127.1 (CH), 133.0 (CH), 133.6 (q), 160.8 (q).

υmax (cm⁻¹): 3477 (bm), 3261 (bm), 2965 (m), 2930 (m), 1502 (m), 1432 (m), 1442 (w), 1297 (s), 1260 (s), 1161 (s), 1028 (s), 1038 (s), 800 (s), 756 (m). ESI+ mass spectrum (m/z, %): 254 ([M]+, 2%), 237 ([M-OH]+, 4%), 212 ([M-CHMe2]+H]+, 25%), 196 (20%), 147 (70%), 119 (50%), 108 (15%), 91 (45%), 77 (15%), 64 (25%).

4,5-dihydro-3-hydroxy-1,2,5-benzothiadiazepine 1,1-dioxide (27c) was obtained as a yellow solid (0.0830g, 62% yield), mp: 117-119 °C from 4-{o-[(9'-fluorenylmethoxycarbonyl) amino]benzenesulfonamidyl} -hex-2-en-4-one (24c, 0.2500 g, 0.53 mmol).

δH (400 MHz, CDCl3): 1.32 (3H, t, J = 10.2, CH3), 1.63 (2H, m, CH2 CH2 CH2 Me), 1.80 (1H, m, CH2 CH2 CH2 Me), 2.02 (3H, s, CH3), 2.08 (1H, dt, J = 10.4, 7.8, CH2 CH2 CH2 Me), 3.2-3.4 (1H, s, CH2).
bs, \( \text{OH} \)), 4.83 (1 H, bs, CHOH), 6.87 (1 H, dt, \( J = 14.8, 6.9 \), ArH), 7.11 (1 H, s, br, SO\(_2\)NH), 7.35 (1 H, dt, \( J = 7.9, 1.4 \), ArH), 7.55 (1 H, dd, \( J = 5.6, 2.2 \), ArH), 7.73 (1 H, dd, 5.6, 2.2, ArH), 7.79 (1 H, dd, \( J = 8.0, 1.2 \), ArH). \( \delta_c \) (100 MHz, CDCl\(_3\)): 14.0 (CH\(_3\)), 23.7 (CH\(_3\)), 28.1 (CH\(_2\)), 31.7 (CH\(_2\)), 79.0 (q, C(\text{OH})Me), 128.4 (CH), 128.8 (q), 128.8 (CH), 130.9 (CH), 134.2 (CH), 144.6 (q), 167.8 (q).

V\(_{\text{max}}\) (cm\(^{-1}\), chloroform): 3377 (bs), 3100 (bs), 2965 (m), 1624 (m), 1482 (w), 1314 (w), 1154 (m), 1107 (m), 1088 (w). E1+ mass spectrum (m/z, %): 268 ([M]+, 2%), 253 ([M-CH\(_3\)]+), 250 ([M-H\(_2\)O]+, 14%), 217 (25%), 169 (100%), 154 (70%), 108 (15%), 91 (45%), 77 (15%), 64 (25%). ESI+ mass spectrum (m/z, %): 269 ([M+H]+, 100%), 291 ([M+Na]+, 20%), 537 ([2M+H]+, 10%). HRMS (ESH): found [M+H]+ 269.0960, CI\(_2\)H\(_6\)N\(_2\)O\(_3\)S requires [M+H+] 269.0960. C, H, N (%): found C 54.0, H 5.8, N 10.4; CI\(_2\)H\(_6\)N\(_2\)O\(_3\)S requires C 53.7, H 6.0, N 10.4.

4.6 Synthesis of (o-nitrobenzenesulphonamidyl)alkenols (37)

4.6.1 Method 1. Synthesis of compounds (37a/b/c) from o-nitrobenzenesulphonamide ("in situ" method). To a solution of o-nitrobenzenesulphonamide (\( \sim 5 \)–10 mmol, 1.0 eq) and anhydrous pyridine (2.0 eq) in anhydrous tetrahydrofuran (15 ml), under an atmosphere of dry nitrogen, was added, dropwise with stirring over a period of 3 hours, a solution of thionyl chloride (1.0 eq) in anhydrous tetrahydrofuran (5 ml), to yield the crude N-sulfinyl compound (33). Stirring of the crude reaction mixture was continued for a further 30 minutes, followed by dropwise addition of the appropriate 1,3-diene (isoprene and hexadiene used 1.6eq at room temperature; butadiene used 10eq at -20°C), and the whole was left stirring at room temperature for 12–16 hours (isoprene and hexadiene) or at -20 °C for 6–8 hours (butadiene), whilst being monitored by TLC. Upon completion of the reaction, stirring was ceased and, under an atmosphere of dry nitrogen, the supernatant solution was transferred into a second dry flask via a syringe leaving the unwanted pyridinium hydrochloride precipitate behind, which was washed with anhydrous tetrahydrofuran (5 x 10ml) and the washings transferred to the second flask. To the crude adduct solution was added, with stirring, a solution of phenylmagnesium bromide (3M in ether, 2.0 eq) at -78°C under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (-40°C) for 3-4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at -20°C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (4 x 50 ml) and the combined extracts washed with water (2 x 10 ml) and brine (10 ml). The organic phase was collected, dried (MgSO\(_4\)), filtered and the solvent evaporated off to yield the crude phenyl allylic sulfoxide which was not purified further. To a solution of the crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated under reflux for a total of 10–15 hours. Upon completion of the reaction (TLC), the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the (o-nitrobenzenesulphonamidyl)alkenols (37) as follows:

4-(o-Nitrobenzenesulphonamidyl)-but-1-en-3-ol (37a) was obtained as a light yellow solid (1.0230 g, 38% yield) over the four steps from o-nitrobenzenesulphonamide (2.000 g, 9.90 mmol); mp 189-191°C. 

\( \delta_d \) (400 MHz, CDCl\(_3\)): 3.08 (1 H, ddd, \( J = 12.2, 7.3, 4.7 \), CH\(_2\)NH), 4.33 (1 H, m, CHO\(_2\)), 5.11 (1 H, d, \( J = 10.5 \), HC=CH\(_2\)), 5.19 (1 H, d, \( J = 14.8 \), HC=CH\(_2\)), 5.74 (1 H, ddd, \( J = 15.1, 10.7, 6.6 \), HC=CH\(_2\)), 5.97 (1 H, s, br, NH), 7.72–7.77 (2H, m, 2 x ArH), 7.87 (1 H, dt, \( J = 7.8, 1.2 \), ArH), 8.08 (1 H, dd, \( J = 8.2, 0.9 \), ArH). \( \delta_c \) (100 MHz, CDCl\(_3\)): 45.3 (CH\(_2\)), 69.7 (CHO\(_2\)), 112.6 (CH\(_2\)), 118.1 (CH), 127.8 (CH), 129.0 (CH), 131.1 (CH), 134.8 (CH), 140.6 (q), 147.9 (q). \( \text{V}_{\text{max}} \) (cm\(^{-1}\)): 3576 (bm), 3301 (bm), 3083 (bm), 2930 (bm).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

3111 (m), 2928 (w), 1588 (m), 1166 (s), 1086 (m), 1008 (m). ESI+ mass spectrum (m/z, %): 295 ([M+Na]+, 14%), 273 ([M+H]+, 34%). C, H, N (%): found C 44.4, H 4.6, N 10.2; ClOHI2N20SS requires C 44.1, H 4.4, N 10.3.

2-Methyl-4-(o-nitrobenzenesulfonamidyl)-but-1-en-3-ol (37b) was obtained as a yellow waxy solid (0.6330 g, 45% yield) over the four steps from o-nitrobenzenesulfonamide (1.000 g, 4.95 mmol).

\[ \delta_H (400 \text{MHz, } \text{CDCl}_3): 1.69 (3 \text{ H, s, } \text{CH}_3), 2.40 (1 \text{ H, s, br, OH}), 3.08 (1 \text{ H, s, br, OH}), 4.17-4.19 (1 \text{ H, m, CHOH}), 4.91 (1 \text{ H, s, MeC=CH}_2), 5.01 (1 \text{ H, s, MeC=CH}_2), 5.78 (1 \text{ H, s, br, NH}), 7.22-7.77 (2 \text{H, m, } 2 \times \text{ ArH}), 7.83-7.93 (1 \text{ H, m, ArH}), 8.11-8.15 (1 \text{ H, m, ArH}). \]

\[ \nu_{\text{max}} (\text{cm}^{-1}): 3550 (\text{bm}), 3333 (\text{bm}), 3096 (\text{m}), 2953 (\text{m}), 1594 (\text{w}), 1539 (\text{s}), 1441 (\text{m}), 1343 (\text{s}), 1239 (\text{m}), 1166 (\text{s}), 1126 (\text{m}), 1090 (\text{m}), 1024 (\text{m}), 912 (\text{m}), 854 (\text{m}), 783 (\text{m}), 741 (\text{m}). \]

ESI+ mass spectrum (m/z, %): 309 ([M+Na]+, 45%), 287 ([M+H]+, 4%). C, H, N (%): found C 46.4, H 4.8, N 9.8; CIIHI4N20SS requires C 46.1, H 4.9, N 9.8.

(E)-5-(o-Nitrobenzenesulfonamidyl)-hex-2-en-4-ol (37c) was obtained as a yellow solid (0.6490 g, 44% yield), mp: 163-166 °C, over the four steps from o-nitrobenzenesulfonamide (1.000 g, 4.95 mmol).

\[ \delta_H (400 \text{MHz, } \text{CDCl}_3): 1.14 (3 \text{ H, d, } J 6.8, \text{CH}_3\text{CH=CH}), 1.56 (3 \text{ H, d, } J 7.0, \text{CH}_3\text{CHN}), 3.30-3.38 (1 \text{ H, m, MeCHS=O}), 4.57 (1 \text{ H, ddq, } J 11.1, 3.4, 1.8, \text{MeCHN}), 5.45 (1 \text{ H, ddd, } J 11.0, 2.5, 2.0, \text{HC=CH}), 5.96 (1 \text{ H, dd, } J 11.0, 3.4, 2.9, \text{HC=CH}), 7.71-7.91 (3 \text{ H, m, } 3 \times \text{ ArH}). \]

\[ \nu_{\text{max}} (\text{cm}^{-1}): 3550 (\text{bm}), 3365 (\text{bm}), 3097 (\text{m}), 2954 (\text{m}), 1671 (\text{w}), 1594 (\text{w}), 1541 (\text{s}), 1442 (\text{m}), 1410 (\text{m}), 1362 (\text{s}), 1215 (\text{m}), 1169 (\text{s}), 1125 (\text{m}), 1061 (\text{m}), 1025 (\text{m}), 968 (\text{m}), 854 (\text{m}), 784 (\text{m}), 743 (\text{m}). \]

4.6.2 Method 2. (E)-5-(o-Nitrobenzenesulfonamidyl)-hex-2-en-4-ol (37e) from the thiazine 1-oxide (34c). Stage 1: Synthesis of 3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide (34c). To a solution of o-nitrobenzenesulfonamide (1.000 g, 4.95 mmol, 1.0 eq) in anhydrous benzene (15 ml) [CAUTION: SUSPECTED CARCINOGEN – see above for an alternative synthesis of compound 37e] was added, under an atmosphere of dry nitrogen, thionyl chloride (0.54 ml, 7.42 mmol), and the whole was heated at reflux in an oil bath for 3 days (72 hours). The reaction mixture was allowed to cool to room temperature and the solvent and excess thionyl chloride were removed in vacuo to yield N-sulfenyl-o-nitrobenzenesulfonamide (33) as a brown oil. To the crude N-sulfenyl-o-nitrobenzenesulfonamide (33) in anhydrous tetrahydrofuran (15 ml) (CAUTION: SUSPECTED CARCINOGEN – see above for an alternative synthesis of compound 37e) a solution of 3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide (34c) was added, under an atmosphere of dry nitrogen, thionyl chloride (0.54 ml, 7.42 mmol), and the whole was heated at reflux in an oil bath for 3 days (72 hours). The reaction mixture was allowed to cool to room temperature and the solvent and excess thionyl chloride were removed in vacuo to yield N-sulfenyl-o-nitrobenzenesulfonamide (33) as a brown oil. To the crude N-sulfenyl-o-nitrobenzenesulfonamide (33) in anhydrous tetrahydrofuran (15 ml) was added 2,4-hexadiene (0.90 ml, 7.91 mmol) and the reaction mixture was stirred at room temperature whilst being monitored by TLC. After completion of the reaction (16 hours) the solvent was removed in vacuo and the crude product was purified by flash silica chromatography (eluent: PE:EtOAc/2:1) to yield 3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine 1-oxide (34c; 0.9830 g, 60% yield) as a pale yellow solid, mp: 110-112 °C.

\[ \delta_H (400 \text{MHz, } \text{CDCl}_3): 1.39 (3 \text{ H, d, } J 7.4, \text{CH}_3\text{CHS=O}), 1.56 (3 \text{ H, d, } J 7.0, \text{CH}_3\text{CHN}), 3.30-3.38 (1 \text{ H, m, MeCHS=O}), 4.57 (1 \text{ H, ddq, } J 11.1, 3.4, 1.8, \text{MeCHN}), 5.45 (1 \text{ H, ddd, } J 11.0, 2.5, 2.0, \text{HC=CH}), 5.96 (1 \text{ H, dd, } J 11.0, 3.4, 2.9, \text{HC=CH}), 7.71-7.91 (3 \text{ H, m, } 3 \times \text{ ArH}), 8.19 (1 \text{ H, dd, } J 8.3, 1.1, \text{ArH}). \]

\[ \delta_C (100 \text{MHz, } \text{CDCl}_3): 15.7 (\text{CH}_3), 23.5 (\text{CH}_3), \]
Stage 2. Synthesis of (E)-5-(0-nitrobenzenesulfonamidyl)-hex-2-en-4-ol (37c). A solution of phenylmagnesium bromide (3 M in ether, 2.0 eq) was added with stirring to a solution of 3,6-dihydro-3,6-dimethyl-2-(o-nitrobenzenesulfonyl)-1,2-thiazine l-oxide (34c; 1.000 g, 3.03 mmol) in anhydrous tetrahydrofuran (10 ml) at -78 °C, under an atmosphere of dry nitrogen. The reaction mixture was kept at low temperature (< -40°C) for 3-4 hours, whilst being monitored by TLC. Upon completion of the reaction, the mixture was quenched at -20°C with saturated ammonium chloride solution (15 ml) and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 x 10 ml) and washed with water (2 x 10 ml) and brine (10 ml). The organic phase was collected, dried (MgSO4), filtered and the solvent evaporated off to yield the intermediate phenyl allicylic sulfoxide which was not purified further. To a solution of the crude allylic sulfoxide in anhydrous methanol (10 ml) was added trimethyl phosphite (2.0 eq), under an atmosphere of dry nitrogen, and the whole was heated at reflux temperature for a total of 12-15 hours. Upon completion of the reaction (TLC), the solvent was removed in vacuo and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield (E)-5-(0-nitrobenzenesulfonyl)-hex-2-en-4-ol (37c) as a yellow oil (0.8100 g, 89% yield), which solidified on standing and was identical in all aspects to that obtained in Method 1, above.

4.7 Synthesis of (o-nitrobenzenesulfonamidyl)alkenones (38) by oxidation of alkenols (37)

To a solution of Dess-Martin periodinane (1.1 eq) in dry dichloromethane (10 ml) was added a solution of the allylic alcohol (37; 1-2 mmol, 1.0 eq) in dry dichloromethane (5 ml) at room temperature and the reaction mixture was stirred for 1 hour, whilst being monitored by TLC. Once the reaction was complete, the solvent was evaporated off and the crude product was purified by flash silica column chromatography (eluent: PE:EtOAc/5:2) to yield the following products:

4-(o-Nitrobenzenesulfonamidyl)-but-1-en-3-one (38a) was obtained as an unstable (decomposes in less than one day at room temperature), partially characterised yellow oil (0.1980 g, 78% yield) from 4-(o-nitrobenzenesulfonyl)-but-1-en-3-ol (37a; 0.3500 g, 1.29 mmol).

δH (400 MHz, CDCl3): 3.85 (2H, d, J 12.6, CH2NH), 5.71 (1H, dd, J 9.1, 2.3, CH=CH2), 5.98 (1H, dd, J 14.8, 2.5, CH=CH2), 6.34 (1H, dd, J 14.6, 9.3, CH=CH2), 6.40 (1H, s, br, NH), 7.78-7.82 (2H, m, 2 x ArH), 7.81 (1H, dt, J 7.8, 1.2, ArH), 8.10 (1H, dd, J 8.1, 0.9, ArH). δC (100 MHz, CDCl3): 61.2 (CH2), 117.4 (CH2), 125.4 (CH), 130.9 (CH), 131.0 (CH), 132.8 (CH), 133.6 (CH), 136.8 (q), 146.3 (q), 185.1 (q, C = O). υmax (cm⁻¹): 3462 (bm), 3330 (bm), 2945 (w), 1709 (s), 1598 (m), 1553 (s), 1170 (s), 1111 (m), 1008 (m). ESI+ mass spectrum (m/z, %): 293 ([M+Na]+, 100%), 271 ([M+H]+, 20%).

2-Methyl-4-(o-nitrobenzenesulfonamidyl)-but-1-en-3-one (38b) was obtained as a partially characterised unstable (decomposed fully over two days at room temperature) yellow oil (0.2200 g, 89% yield) from 2-methyl-4-(o-nitrobenzenesulfonyl)-but-1-en-3-ol (37b; 0.2500 g, 1.40 mmol).
The synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides from 1,2-thiazine 1-oxides

δH (400 MHz, CDCl3): 1.85 (3H, s, CH3), 4.44 (2H, d, J 4.7, CH2NH), 5.90 (1H, s, MeC=CH2), 5.98 (1H, s, MeC=CH2), 6.36 (1H, br, NH), 7.71–7.82 (2H, m, 2 × ArH), 7.92 (1H, dd, J 8.2, 2.1, ArH), 8.03 (1H, d, J 7.7, ArH). δC (100 MHz, CDCl3): 17.2 (CH3), 48.7 (CH2), 125.6 (CH), 126.3 (CH2), 128.0 (CH), 130.4 (q), 131.9 (q), 133.4 (CH), 133.6 (CH), 142.0 (q), 193.8 (q, C=O).

νmax (cm⁻¹): 3097 (w), 2926 (m), 1732 (s), 1592 (w), 1543 (s), 1458 (s), 1375 (s), 1250 (m), 1171 (s), 1123 (m), 1024 (s), 930 (m), 757 (s), 669 (m).

ESI+ mass spectrum (m/z, %): 307 ([M+Na]+, 80%), 285 ([M+H]+, 45%).

(E)-5-(o-Nitrobenzenesulphonamidyl)-hex-2-en-4-one (38c) was obtained as a more stable yellow oil (0.4170 g, 84% yield) from (E)-5-(o-nitrobenzenesulphonamidyl)-hex-2-en-4-ol (37c; 0.5000 g, 1.67 mmol).

δH (250 MHz, CDCl3): 1.42 (3H, d, J 7.2, CH3CH=CH), 1.91 (3H, dd, J 6.9, 1.6, CH3CHNH), 4.42 (1H, dq, J 7.2, 7.2, CHMe), 6.16 (1H, dd, J 15.6, 1.5, MeHC=CH), 6.48 (1H, d, br, J 7.2, NH), 6.78 (1H, dd, J 15.6, 0.7, MeHC=CH), 6.81 (1H, m, ArH), 6.95 (1H, d, J 7.2, ArH). δC (63 MHz, CDCl3): 18.5 (CH3), 19.5 (CH3), 56.5 (CH), 125.5 (CH), 127.0 (CH), 129.9 (q), 132.7 (q), 133.5 (CH), 134.3 (CH), 146.3 (CH), 195.8 (q, C=O).

νmax (cm⁻¹): 3096 (w), 2925 (m), 1712 (s), 1594 (w), 1542 (s), 1442 (s), 1362 (s), 1250 (m), 1172 (s), 1124 (m), 1024 (s), 928 (m), 744 (s), 655 (m). ESI+ mass spectrum (m/z, %): 299 ([M+H]+, 1%), 229 (50%), 186 (95%), 156 (5%), 109 (20%), 92 (15%), 77 (20%), 69 (100%), 64 (15%). CH mass spectrum (m/z, %): 316 ([M+NRt]+, 100%), 299 ([M+H]+, 3%). HRMS (CI+): found [M+NRt]+ 316.0965, CI2H14N20SS requires 316.0967.

4.8 Synthesis of 1,2,5-benzothiadiazepine 1,1-dioxides (39)

To a solution of the freshly prepared allylic ketone (38, ~0.2–0.4 mmol, 1.0 eq) in glacial acetic acid (10 ml) was added gradually, with stirring, zinc powder (~0.2–0.5 g) over a period of 1 hour at room temperature. After addition was complete, the mixture was heated under reflux for an additional 2–4 hours, whilst being monitored by TLC. The crude mixture was filtered, concentrated in vacuo, and purified by flash column chromatography (eluent: PE:EtOAc/l:1) to yield the 1,2,5-benzothiadiazepine 1,1-dioxides (39), as follows:

2,3,4,5-Tetrahydro-4-ethenyl-1,2,5-benzothiadiazepine 1,1-dioxide (39a) was obtained as a yellow solid (0.0413 g, 50% yield) from 4-(o-nitrobenzenesulphonamidyl)-but-1-en-3-one (38a, 0.1000 g, 0.37 mmol), mp: 133–137 °C.

δH (400 MHz, CDCl3): 3.05 (1H, ddd, J 15.1, 7.5, 4.6, CH2NH), 3.28 (1H, m, CHCH=CH2), 3.37 (1H, ddd, J 13.1, 7.6, 3.6 CH2NH), 4.17 (1H, dd, J 7.4, 3.4, CH2NH), 4.83 (1H, d, J 10.3, HC=CH2), 4.95 (1H, dd, J 16.2, 0.7 HC=CH2), 5.70 (1H, bd, J 9.8, NHCH), 5.8 (1H, ddd, J 15.9, 10.3, 7.9, HC=CH2), 7.73–7.80 (2H, m, 2 × ArH), 7.83 (1H, t, J 7.8, ArH), 8.10 (1H, d, J 8.2, ArH). δC (100 MHz, CDCl3): 47.4 (CH2), 73.4 (CH), 112.6 (CH2), 125.3 (CH), 130.7 (CH), 133.3 (CH), 133.9 (CH), 140.0 (q), 147.8 (q). νmax (cm⁻¹): 3450 (bm), 3363 (bm), 3225 (bm), 2986 (m), 2906 (m), 1604 (m), 1591 (w), 1479 (s), 1145 (s), 1066 (m). ESI+ mass spectrum (m/z, %): 225 ([M+H]+, 100%), 247 ([M+Na]+, 25%). C, H, N (%): found C 53.4, H 5.2, N 12.7; Cl2H14N20SS requires C 53.6, H 5.4, N 12.5.

2,3,4,5-Tetrahydro-4-(2'-propenyl)-1,2,5-benzothiadiazepine 1,1-dioxide (39b) was obtained as a yellow solid (0.0410 g, 49% yield) from 2-methyl-4-(o-nitrobenzenesulphonamidyl)-but-1-en-3-one (38b, 0.1000 g, 0.37 mmol), mp: 133–137 °C.
C. Loukou et al.

(1 H, t, J 7.5, ArH), 7.70 (1 H, d, J 7.9, ArH). δC (100 MHz, CDCl3): 18.3 (CH3), 47.0 (CH2), 73.4 (CH), 112.3 (CH2), 117.8 (CH), 117.9 (CH), 121.4 (q), 129.6 (CH), 134.3 (CH), 144.0 (q), 145.0 (q). νmax (cm⁻¹): 3478 (bm), 3379 (bm), 3250 (bm), 2970 (m), 2921 (m), 1621 (m), 1600 (m), 1570 (w), 1484 (s), 1455 (m), 696 (m). ESI+ mass spectrum (m/z, %): 239 ([M+H]+, 30%). C, H, N (%): found C 55.4, H 6.0, N 11.7; C12H14N2O2S requires C 55.4, H 5.9, N 11.8.

2,3,4,5-Tetrahydro-3-methyl-4-(1'-propenyl)-1,2,5-benzothiadiazepine 1,1-dioxide (39c; ~1:1 mixture of diastereoisomers) was obtained as a yellow oil (0.03810 g, 45% yield) from (E)-5-(o-nitrobenzenesulfonamidyl)-hex-2-en-4-one (38c, 0.1000 g, 0.34 mmol).

δH (400 MHz, CDCl3): 1.10 (3H, d, J 6.6, MeC=CHCHNH), 1.14; 1.18 (3H, 2 x d, J 6.6, MeC=CHCH), 3.54; 3.58 (1H, 2 x m, MeCH), 4.6-4.7 (1 H, s, br, NH), 4.92 (1 H, d, J 7.4, NH), 5.01; 5.07 (1 H, 2 x s, CH2NH), 5.31 (1 H, d, J 15.1, 6.8, MeHC=CH), 5.36-5.47 (1 H, m, MeHC=CH), 6.76 (1 H, d, J 8.5, ArH), 6.79 (1 H, t, J 8.0, ArH), 7.31 (1 H, t, J 7.7, ArH), 7.70 (1 H, d, J 7.9, ArH). δC (100 MHz, CDCl3): 20.8; 20.9 (CH3), 21.8; 21.9 (CH3), 50.6 (CH), 50.8 (CH), 117.7 (CH), 117.8 (CH), 122.6; 122.7 (q), 129.4; 129.5 (CH), 132.3; 132.4 (CH), 132.5; 132.6 (CH), 134.0; 134.1 (CH), 134.5; 134.6 (q), 141.6; 144.9 (q). νmax (cm⁻¹): 3476 (bm), 3378 (bm), 3249 (bm), 2979 (m), 2932 (m), 1622 (m), 1601 (m), 1570 (m), 1484 (s), 1455 (s), 1332 (s), 1155 (s), 1061 (m), 755 (s), 698 (m). EI+ mass spectrum (m/z, %): 253 ([M+H]+, 1%), 252 ([M]+, 4%), 172 (15%), 156 (25%), 112 (75%), 112 (75%), 108 (30%), 92 (100%), 80 (45%), 65 (98%). ESI+ mass spectrum (m/z, %): 253 ([M+H]+, 40%). HRMS (ESI+): found [M+H]+ 253.1012, CI2H16N2O2S requires 253.1010.

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