2-Sulfinyl Oxetanes: Synthesis, Stability and Reactivity

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Dedicated to Professor Steven V. Ley CBE FRS on the occasion of his 70th birthday. Happy Birthday Steve!

Abstract The synthesis of 2-sulfinyl oxetanes is described by a C–C bond-forming cyclisation strategy. Oxetanes bearing electron-poor aryl sulfoxides are shown to be viable targets using this strategy. We report investigations into the sulfoxide magnesium exchange on 2-sulfinyl oxetanes, which resulted in products formed via ligand exchange and ligand coupling pathways. The sulfinyl oxetanes can be readily oxidised to the sulfonyl oxetanes.

Key words oxetanes, heterocycles, cyclisation, sulfoxides, sulfones

Oxetanes are strained four-membered rings and so are of interest as synthetic intermediates in complex molecule synthesis.1 At the same time, they are receiving considerable attention as stable motifs for medicinal chemistry that can improve the physicochemical properties of biologically active molecules.2 This recent interest in the use of oxetanes in drug discovery has stemmed from beautiful studies by Carreira and co-workers, which demonstrated 3,3-disubstituted oxetanes to be attractive replacements for gem-dimethyl and carbonyl groups.3,4 In addition, oxetanes access new design space for medicinal chemists and present well-defined three-dimensional structures due to the rigid ring system.5 With this in mind we are interested in synthesising novel oxetane-containing fragments for fragment based drug discovery (FBDD), in particular less studied 2-substituted examples, and in developing methods to derivatise these strained heterocyclic motifs.

Cyclisation approaches towards oxetane derivatives have traditionally involved intramolecular Williamson ether synthesis; either from acyclic precursors or involving epoxide ring opening and closure (Scheme 1A).6 However, these approaches largely preclude the incorporation of functional groups at the oxetane 2-position. Alternatively, the Paternò–Büchi [2+2] photocycloaddition can prepare highly substituted derivatives.7 We recently reported a new anionic cyclisation approach to the synthesis of 2-substituted oxetanes, which involved formation of the C2–C3 bond.8,9 This strategy permitted the synthesis of a novel series of 2-sulfonyl oxetanes, designed as fragments for FBDD (Scheme 1B).8 These displayed appropriate physical properties for fragment screening, as well as good stability in pH and liver microsomes studies.8b We have also reported a rapid synthesis of 2,2-disubstituted derivatives by an O–H insertion and cyclisation approach, to generate a range of 2,2-disubstituted, 2,2,4-trisubstituted and 2,2,3,4-tetrasubstituted oxetane motifs.8c Building on these studies, we were interested in examining 2-sulfanyl oxetanes, a new functional group combination (Scheme 1C).

Scheme 1 Strategies towards oxetane synthesis

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Certain heterocyclic small-ring sulfoxides have been well studied as interesting groups in their own right, and also as synthetic intermediates. Satoh and others have extensively examined the synthesis of aziridine and epoxide sulfoxides. Furthermore, from these stable precursors sulfoxide exchange has been a powerful method for generating organometallic reagents, forming lithiated or magnesium sulfoxide exchange has been a powerful method for generating organometallic reagents, forming lithiated or magnesium centres. 

Initially the stability of reducing the nucleophilicity of the S–O group and therefore stabilising the cyclisation precursor. 

Pleasingly, when using LiHMDS, sulfinyl oxetane was isolated, indicating the feasibility of this structural type. The preferred conditions [LiHMDS (1.2 equiv) in THF at 0 °C for 1 h 15 min] resulted in up to an 80% yield of two diastereoisomers, which could be separated by chromatography (dr = 1.6:1, Scheme 2). Unfortunately, this reaction proved capricious, giving variable results due to degradation of the starting material under the reaction conditions, similar to that occurring spontaneously with the tolyl example 1a. 

To circumvent this problem, the even more electron-poor 2-pyridyl sulfoxide 1c was examined. On oxidation of 5c, sulfoxide 1c proved to be stable at room temperature and when stored at −20 °C was stable for at least one year with no degradation observed. For this substrate alternative cyclisation conditions were required to achieve high yield (Table 2). 

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield of 4</th>
<th>Yield of 5</th>
<th>Yield of 1</th>
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</thead>
<tbody>
<tr>
<td>a: 4-MeC₆H₄</td>
<td>83%</td>
<td>97%</td>
<td>(unstable)</td>
</tr>
<tr>
<td>b: 4-ClC₆H₄</td>
<td>74%</td>
<td>98%</td>
<td>94%</td>
</tr>
<tr>
<td>c: 2-pyridyl</td>
<td>63%</td>
<td>95%</td>
<td>72%</td>
</tr>
<tr>
<td>d: 2-ClC₆H₄</td>
<td>71%</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>e: 3-ClC₆H₄</td>
<td>71%</td>
<td>92%</td>
<td>68%</td>
</tr>
<tr>
<td>f: 4-F,C₆H₄</td>
<td>61%</td>
<td>99%</td>
<td>66%</td>
</tr>
<tr>
<td>g: 4-NCC₆H₄</td>
<td>44%</td>
<td>82%</td>
<td>90%</td>
</tr>
<tr>
<td>h: 4-NO₂C₆H₄</td>
<td>39%</td>
<td>90%</td>
<td>(unstable)</td>
</tr>
</tbody>
</table>

*Reaction conditions: freshly prepared LDA (1.5 equiv) was added to sulfoxide 1c (0.14 mmol) in THF at specified temperature. 

Yield (combined diastereoisomers) was determined by ²H NMR with respect to an internal standard (1,3,5-trimethoxybenzene).

The dr value was determined by ²H NMR of the crude reaction mixture.

Isolated yield (dr = 1.3:1).
A variety of bases were employed in the reaction, with amine bases being the most efficient. LDA was chosen for further development, providing 39% yield of 2c at 0 °C, with no remaining starting material (Table 2, entry 1). Lower temperatures were investigated to stabilise the intermediate structures. As the temperature was reduced, more starting material was recovered but the conversion was low. However, performing the deprotonation at –78 °C then warming to –20 °C led to improved yields of oxetane 2c (Table 2, entries 4 and 5). Controlling the reaction time gave an excellent yield (Table 2, entry 5, and Scheme 2). A dr value of approximately 1:1 was observed under most conditions examined, including with different bases.

For 2f and 2g a complex mixture of products was obtained, with the isopropyl sulfoxide oxetane 6 as the major product as determined by 1H NMR of the crude reaction mixture (62% conversion from CF₃-containing substrate 2f; 43% from CN-containing substrate 2g). Attempts to quench any possible oxetane anion with electrophiles (3-pentanone; benzaldehyde) were unsuccessful. Essentially identical results were obtained with either diastereoisomer of the sulfoxides. These results suggest that the aryl groups in these cases more successfully stabilise the organometallic product, i.e. that the oxetanyl anion is not well stabilised.

Sulfoxide–lithium exchange was also investigated using n-BuLi; the alkyl oxetanyl sulfoxide was again the major product observed, but only in low quantities due to significant decomposition. These alkylsulfinyl oxetanes were intolerant of silica gel, and attempted purification led to decomposition.

Interestingly, performing the reaction with pyridyl sulfoxide 2c afforded neither of the aryl or oxetanyl sulfoxide products. Instead, a coupling of the initial sulfoxide substituent occurred affording pyridyl oxetane 7 exclusively (Scheme 4). Varying the solvent (Et₂O, THF, hexane), organometallic reagent (i-PrMgCl, i-PrMgCl-LiCl), or sulfoxide diastereoisomer resulted in the same reaction outcome. Using i-PrMgCl gave quantitative conversion to the pyridyl oxetane, which was isolated in 60% yield following chromatography, due to poor stability on silica.

Scheme 3 Sulfoxide–magnesium exchange of sulfinyl oxetane 2e with i-PrMgCl resulting in isopropyl oxetanyl sulfoxide 6
This type of sulfoxide ligand coupling has been previously reported on 2-pyridyl sulfoxides. Oae proposed a mechanism to account for both possible outcomes, whereby attack of the Grignard reagent formed an unstable sulfuryl intermediate that may undergo either ligand exchange or ligand coupling. 22d

Finally, we oxidised sulfinyl oxetanes 2d and 2g to generate the corresponding sulfonyl oxetanes (Scheme 5). This was readily achieved with mCPBA to afford ortho-substituted 8d in high yield as well as novel nitrile-containing sulfonyl oxetane fragment 8g.

In summary, we have developed the synthesis of a series of 2-sulfinyl oxetanes. These novel functional groups could be prepared bearing electron-poor aryl groups. Interesting reactivity was observed on sulfoxide-metal exchange, which indicated that the aryl organometallic was more stabilised than the oxetan Grignard reagent. This cleanly generated isopropylsulfinyl oxetane, whereas the 2-pyridyl derivative led to coupling to form 2-(2-pyridyl)oxetane. However, the anion of unsubstituted oxetane remains elusive. The sulfinyl oxetanes were readily oxidised to sulfonyl oxetanes.

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Supporting Information

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References and Notes


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