Stereoselective synthesis of 2,5-disubstituted-1,4-oxathiane S-oxides

Simon T. Bedford, Richard S. Grainger, Jonathan W. Steed and Patrizia Tisselli

Department of Chemistry, King’s College London, Strand, London, UK WC2R 2LS.
E-mail: richard.grainger@kcl.ac.uk; Fax: 44 (0) 20 7848 2810; Tel: 44 (0) 20 7848 1167

Department of Chemistry, University Science Laboratories, South Road, Durham, UK DH1 3LE. E-mail: jon.steed@durham.ac.uk; Fax: 44 (0) 191 384 4737; Tel: 44 (0) 191 334 2085

Received 8th October 2004, Accepted 15th November 2004
First published as an Advance Article on the web 21st December 2004

β-Allyloxy and β-propargyloxy tert-butyl sulfoxides undergo tandem sulfoxide elimination–intramolecular sulfinic acid addition reactions to produce 1,4-oxathiane S-oxides.

The thermolysis of sulfoxides containing a β-hydrogen atom is a venerable approach to alkene synthesis.1 The reverse reaction, the addition of a sulfinic acid to an alkene, is also known, and is subject to the same constraints in the transition state i.e. the need for the five participating atoms to achieve coplanarity in a concerted syn addition.2 Intramolecularly this can lead to high levels of regio- and diastereochemical control, elegantly demonstrated by Jones and coworkers in the 1970’s in a tandem sulfoxide elimination–sulfinic acid addition approach to cyclic sulfoxides (Scheme 1).3 Thermolysis of tert-butyl sulfoxide 1 generates a sulfinic acid intermediate 2 which adds to the terminal alkene via planar transition state A to give cis-sulfoxide 3 as the sole product. Cyclic transition states leading to the trans-sulfoxide 4 or the sulfoxide 5 that might arise from addition of the sulfur atom to the terminus of the alkene are sterically impossible.

![Scheme 1](image)

Scheme 1  Jones’ tandem sulfoxide elimination–sulfinic acid addition.

We recently reported an extension of this methodology to a novel diastereotopic group selective sulfinic acid addition reaction (Scheme 2).4 The ratio of diastereomeric perhydrobenzothiophene S-oxides 6 and 7 was found to depend on the nature of the group attached to oxygen in the connecting chain, with selectivities ranging from 1 : 1 in the case of R = H, to 4.9 : 1 in the case of R = TBDMS. In the course of this work we investigated the case of the alcohol protected as an allylic ether (5, R = allyl). Thermolysis in this case did not give rise to a mixture 6 and 7, but rather to a mixture of two 1,4-oxathiane S-oxides 11 and 12. Clearly in this case the intermediate sulfinic acid 10 chemoselectively adds to the terminal alkene rather than the diene to form a 6-membered oxathiane ring in preference to a fused 5-membered ring.5

The stereochemistry of the two products was tentatively assigned as shown on the basis of the following rationale. By analogy to the Jones system (Scheme 1), only oxathianes with a cis-stereoechemical relationship between the sulfinyl oxygen and adjacent methyl group are possible as a consequence of the stereochemical requirements of the transition state for addition of a sulfinic acid to an alkene. Hence the two diastereomers should differ only in the relative configuration at position 2 of the 1,4-oxathiane ring. The relative stereochemistry of the major compound was ultimately attained by X-ray analysis of the sulfoximine 13, obtained by treatment of the major isomer 12 with O-mesitylenesulfonylhydroxylamine (MSH).6 The conversion of sulfoxides to sulfoximines with this reagent is known to occur with retention of configuration.

The cyclisation in Scheme 2 constitutes a novel and potentially general approach to 1,4-oxathiane S-oxide ring synthesis if it is, as it would appear to be, independent of the diene ring system.7 In order to investigate the scope this chemistry, we have prepared a number of related cyclisation precursors bearing phenyl and tert-butyl groups in place of the diene in combination with a range of alkene and alkyne coupling partners. These compounds were readily prepared by the simple four step procedure shown in Scheme 3. Addition of two equivalents of the anion of tert-butyl methyl sulfoxide 14 to ethyl benzoate or ethyl pivaloate gave the β-ketosulfoxide 15a and 15b respectively; which were reduced stereoselectively with DIBAL-H at low temperature to give the β-hydroxysulfoxides 16a and 16b.8 Alkylation of these
alcohols with an allylic or propargylic bromide gave the ethers 18–23 in good yield.9

Results of the thermolysis of sulfoxides 18–23 are presented in Table 1. In every case, purification of the oxathiane S-oxides was achieved by direct application of the crude reaction mixture to column chromatography. The xylene eluted first, followed by the mixture of oxathiane S-oxides, which in many cases were separable.5

Thermolysis of allyl ether 18a gave rise to two separable 2,5-disubstituted 1,4-oxathiane S-oxides 24a and 25a (entry 1, Table 1). Crystals suitable for X-ray analysis were obtained for both 24a and 25a and allowed for the unambiguous assignment of the stereochemistry of these oxathiane S-oxides (Fig. 1).‡

Both sulfoxides crystallize in chair conformations with the bulky phenyl group occupying an equatorial position, placing the sulfinyl oxygen equatorial in the case of 24a and axial in the case of 25a. The major compound 25a has all substituents on the ring in a favourable position. The preference for a sulfinyl oxygen to occupy an axial position on a six-membered ring has been ascribed to an attractive van der Waals interaction with hydrogen atoms in a syn 1,3-diaxial relationship,10 and indeed in the X-ray of 25a the sulfinyl oxygen is seen to be bent towards the inside of the ring by these stabilizing interactions.

The conformations adopted by 24a and 25a in the solid state are also maintained in solution. A single set of signals is observed in the 1H and 13C NMR for both 24a and 25a, suggesting they exist as predominantly one conformation in solution.11 In both cases the proton at position 2 of the ring shows a large coupling constant consistent with an axial orientation, placing the aryl group in an equatorial position. The chemical shift of this hydrogen is significantly different in the two diastereomeric oxathiane S-oxides as a consequence of the anisotropic effect of the sulfinyl group (4.53 ppm in 24a vs. 5.17 ppm in 25a). In 25a H-2 is deshielded since it is in a syn 1,3 diaxial relationship with the sulfoxide.12

The above analysis allowed for a convenient method to assign the major and minor compounds in the cyclisations presented

---

**Table 1  Synthesis of oxathianes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclisation precursor</th>
<th>Oxathianes</th>
<th>R</th>
<th>Time/h</th>
<th>Crude ratio</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>24, 25</td>
<td>a Ph</td>
<td>3</td>
<td>1 : 1.8</td>
<td>30% 24a, 40% 25a</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>26, 27</td>
<td>b r-Bu</td>
<td>8</td>
<td>1 : 2.4</td>
<td>68% (24b + 25b)</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>28, 29</td>
<td>a Ph</td>
<td>8</td>
<td>1 : 1.3</td>
<td>64% (26a + 27a)</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>30, 31</td>
<td>b r-Bu</td>
<td>7</td>
<td>1 : 1.6</td>
<td>61% (26b + 27b)</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>32, 33</td>
<td>a Ph</td>
<td>6</td>
<td>ND</td>
<td>0% 28a, 20% 29a</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>34, 35</td>
<td>b r-Bu</td>
<td>8</td>
<td>ND</td>
<td>0% 28b, 36% 29b</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>a Ph</td>
<td>2.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>b r-Bu</td>
<td>3°</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>a Ph</td>
<td>7</td>
<td>1 : 1</td>
<td>11% 32a, 13% 33a</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>b r-Bu</td>
<td>8</td>
<td>1 : 1.5</td>
<td>27% 32b, 47% 33b</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>a Ph</td>
<td>2</td>
<td>2.2 : 1</td>
<td>0% 34a, 25% 35a</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>b r-Bu</td>
<td>5</td>
<td>1 : 1.4</td>
<td>38% 34b, 42% 35b</td>
</tr>
</tbody>
</table>

* Xylene, 0.14 M, reflux.  † Ratio determined by integration in 1H NMR.  ‡ 34% Recovered starting material.
Table in the text. The oxathianes appeared in one chair conformation in solution consistent with the bulky phenyl or tert-butyl group in the equatorial position. Similarly, sulfoxides 11 and 12 each exist in one chair conformation in solution, with the diene ring equatorial in both cases.

The efficiency of the cyclisation is dependent on the substitution pattern on the alkene. Simple, unsubstituted terminal alkynes give good yields of 1,4-oxathiane S-oxides irrespective of the R group (entries 1 and 2). A methyl substituent on the internal carbon of the alkene is tolerated (entries 3 and 4), whereas substitution on the terminal carbon results in much lower yields (entries 5 and 6). A range of unidentifiable by-products were formed upon thermalysis of 20 which did not allow for the determination of the ratio of 28 and 29 in the crude NMR. Hence although only one oxathiane S-oxide was isolated from the reaction after column chromatography it appears to be the equatorial sulfoxide, although the only isomer that could be isolated from the reaction after column chromatography corresponds to the (minor) axial sulfoxide.

In summary, we describe a simple 4-step synthesis of a number of novel oxathiane oxides based on the intramolecular addition of sulfinic acids to alkenes or alkynes tethered through an alkenyl or alkyne group (reactions with 1 → 2S). Diastereomer 25a of allyl ether 18a (0.597 g, 2.24 mmol) in refluxing xylene (16 mL) was kept under argon for 3 h, following the reaction by TLC until the starting material disappeared. The crude reaction mixture was purified by column chromatography (95:5 diethyl ether–methanol). Diastereomer 25a eluted first as a white solid (0.188 g, 40% yield). The product (90% pure by 1H NMR) was characterized as a diastereomer of the sulfenic acid analogue of 1,4-oxathiane 4-oxide 24a (2S,4R,5R)-3-methyl-3-(2-methylpropyl) oxathiane 4-oxide 24a S-oxide irrespective of the relative configuration of the sulfenic acid moiety. Hence the major product (as judged by 1H NMR of the crude reaction mixture) appears to be the equatorial sulfoxide, although the only isomer that could be isolated from the reaction after column chromatography corresponds to the (minor) axial sulfoxide.

Acknowledgements
We thank EPSRC for partial funding of this work (studentship to PT, GR/R20465/01). RSG thanks AstraZeneca and Pfizer for further unrestricted financial support.

Notes and references
1. Crystal data for 13: C12H11NO2S, M = 241.34, colourless prism, 0.40 × 0.35 × 0.20 mm, monochromatic CuKα radiation, 3 = 1.293 g cm−3, Fcalcd = 2080, Nonius Kappa CCD, MoKα radiation, λ = 0.71073 Å, θ = 20(2) K, 2θmax = 54.8°, 3752 reflections collected, 2136 unique (Rexp = 0.0345). Final GoF = 1.003, R1 = 0.0434, wR2 = 0.0804, R indices based on 1417 reflections with I > 2σ(I) (redefinition on F2), 152 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.247 mm−1. Crystal data for 24a: C12H12O2S, M = 210.28, colourless plate, 0.60 × 0.30 × 0.10 mm, monochromatic CuKα radiation, space group P21/n (no. 14), cell parameters: a = 6.6000(5), c = 11.5454(8) Å, β = 91.308(5)°, V = 517.97(7) Å3, Z = 2, Dcalcd = 1.348 g cm−3, Fcalcd = 224, Nonius Kappa CCD, MoKα radiation, λ = 0.71073 Å, θ = 120(2) K, 2θmax = 50.0°, 1518 reflections collected, 1518 unique (Rexp = 0.0000). Final GoF = 1.179, R1 = 0.1100, wR2 = 0.2717, R indices based on 1429 reflections with I > 2σ(I) (redefinition on F2), 129 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.283 mm−1. Crystal data for 25a: C13H12O3S, M = 210.28, 0.30 × 0.20 mm, monochromatic, space group P21/n (no. 14), cell parameters: a = 6.6000(5), b = 6.0000(5), c = 11.4544(8) Å, β = 91.308(5)°, V = 517.97(7) Å3, Z = 2, Dcalcd = 1.348 g cm−3, Fcalcd = 224, Nonius Kappa CCD, MoKα radiation, λ = 0.71073 Å, θ = 120(2) K, 2θmax = 50.0°, 1518 reflections collected, 1518 unique (Rexp = 0.0000). Final GoF = 1.179, R1 = 0.1100, wR2 = 0.2717, R indices based on 1429 reflections with I > 2σ(I) (redefinition on F2), 129 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.283 mm−1. Crystal data for 25b: C13H12O3S, M = 210.28, 0.30 × 0.20 mm, monochromatic, space group P21/n (no. 14), cell parameters: a = 6.6000(5), b = 6.0000(5), c = 11.4544(8) Å, β = 91.308(5)°, V = 517.97(7) Å3, Z = 2, Dcalcd = 1.348 g cm−3, Fcalcd = 224, Nonius Kappa CCD, MoKα radiation, λ = 0.71073 Å, θ = 120(2) K, 2θmax = 50.0°, 1518 reflections collected, 1518 unique (Rexp = 0.0000). Final GoF = 1.179, R1 = 0.1100, wR2 = 0.2717, R indices based on 1429 reflections with I > 2σ(I) (redefinition on F2), 129 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.283 mm−1. Crystal data for 26a: C12H12O3S, M = 210.28, 0.30 × 0.20 mm, monochromatic, space group P21/n (no. 14), cell parameters: a = 6.6000(5), b = 6.0000(5), c = 11.4544(8) Å, β = 91.308(5)°, V = 517.97(7) Å3, Z = 2, Dcalcd = 1.348 g cm−3, Fcalcd = 224, Nonius Kappa CCD, MoKα radiation, λ = 0.71073 Å, θ = 120(2) K, 2θmax = 50.0°, 1518 reflections collected, 1518 unique (Rexp = 0.0000). Final GoF = 1.179, R1 = 0.1100, wR2 = 0.2717, R indices based on 1429 reflections with I > 2σ(I) (redefinition on F2), 129 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.283 mm−1.


5. The intramolecular addition of the sulfenic acid 10 to the diene is a reversible process, and the ratio of 6:7 we believe is a reflection of their relative thermodynamic stability.


9. All chiral compounds used in this study are racemic.


11. No change was observed in the ‘H NMR of 24a or 25a upon cooling to −60°C.
