Design and Synthesis of Stable α-Diazo-β-oxo sulfoxides

Stuart G. Collins, a,b Orlagh C. M. O’Sullivan, b Patrick G. Kelleher b and Anita R. Maguire a

a Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland. Fax: +353(0)214274097; Tel: +353(0)214901694; E-mail: a.maguire@ucc.ie
b Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland. E-mail: stuart.collins@ucc.ie

Contents: 1H NMR spectra of bicyclic and monocyclic sulfides, sulfoxides and α-diazosulfoxides.

1H and 13C NMR spectra of monocyclic and bicyclic lactone sulfides Pg 2-8

1H and 13C NMR spectra of monocyclic and bicyclic lactone and lactam sulfoxides Pg 9-19

1H and 13C NMR spectra of monocyclic and bicyclic lactone and lactam α-diazosulfoxides Pg 20-32

Discussion on the synthesis of monocyclic and bicyclic lactone sulfides Pg 33-36

All 1H and 13C NMR spectra were recorded in CDCl3
$^1$H and $^{13}$C NMR spectra of monocyclic and bicyclic lactone sulfides
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2013
$^1$H and $^{13}$C NMR spectra of monocyclic and bicyclic lactone and lactam sulfoxides
$^1$H and $^{13}$C NMR spectra of monocyclic and bicyclic lactone and lactam $\alpha$-diazosulfoxides
Minor EtOAc solvent peaks removed for clarity of $\text{CHS}$ signal for 73
Bicyclic and monocyclic lactone sulfides

Koskimies has described the synthesis of the bicyclic sulfide 19 from cyclohexene oxide by ring opening with thioglycolate anion followed by lactonization.\textsuperscript{34} This approach was successfully employed for the synthesis of the series of bicyclic and monocyclic sulfides 19-28 as summarized in Table 1. Thus, treatment of the appropriately substituted epoxide with thioglycolic acid dianion in methanol leads to the hydroxy acids with some lactonization occurring during the acidification in certain cases, Subsequent acid catalysed lactonization of the hydroxy acids led efficiently to the sulfides 19-28 (Table 1). Trans stereochemistry was assigned due to the mechanism of the nucleophilic ring opening of the epoxide and also by comparing the spectral data to that in the literature.\textsuperscript{34-36a}

The bicyclic sulfide 19 (Table 1, entry 1)\textsuperscript{34} was isolated following recrystallization in 97\% yield over the two steps. Starting from 1-methylcyclohexene oxide the \textit{trans}-sulfide 20 bearing a bridgehead methyl group was isolated as a colourless oil in 62\% yield (Table 1, entry 2). Use of cyclopentene oxide and cycloheptene oxide led to the 5,6 and 7,6-fused bicyclic sulfides 21 and 22 respectively (Table 1, entries 3 and 4). A number of points can be made about the synthesis of the sulfide 21 and its very poor isolated yield. Conditions for the epoxide ring opening and lactonization in this instance must be carefully controlled and, furthermore, the sulfide 21 is relatively unstable and degrades on storage in a freezer for 1-2 days. Also it was noted that in some instances shorter lactonization times (3-4 hours) led to the isolation of better quality crude product 21 in higher yields. On oxidation to the analogous sulfoxide, stability is no longer an issue and therefore oxidation is undertaken immediately following synthesis of the sulfide 21. In the case of the cycloheptyl fused sulfide 22, a
reduced yield of 47% is associated with partial ring opening during the work-up on washing with aqueous sodium bicarbonate (Table 1, entry 4).

The monocyclic sulfides were next explored for the synthesis of a new range of monocyclic α-diazosulfoxide precursors which are less rigid and less conformationally constrained than the corresponding bicyclic analogues. Thus, the diphenyl lactone sulfides 25 and 26 \(^{33,41}\) were prepared from trans- and cis-stilbene oxide respectively (Table 1, entries 7-8). At the outset of this project it was anticipated that monocyclic α-diazosulfoxides were likely to be unstable and fragment; therefore use of the stilbene-derived sulfides was selected for the initial study as recovery of degradation products such as stilbene would be much easier than smaller volatile fragments lacking the aryl rings.

In the event, diazo transfer to the sulfoxides derived from 25 and 26 proved possible and therefore the series of monocyclic sulfides was expanded to include the novel compounds cis-5,6-dimethyl-[1,4]oxathian-2-one 23 and trans-5,6-dimethyl-[1,4]oxathian-2-one 24 generated from trans and cis-butene oxide respectively (Table 1, entries 5-6). The relative yields of the cis- and trans-sulfides in the monocyclic series are interesting, with lower yields of the trans-sulfides recovered following chromatography; possibly indicating partial degradation on silica gel.

It was decided to extend the monocyclic series to a six-membered lactone bearing unsymmetrical substituents (phenyl and methyl groups) at the C-5 and C-6 positions, cis-6-methyl-5-phenyl-[1,4]oxathian-2-one (27), to explore the influence of substituents on the stability of the resulting α-diazosulfoxide (Table 1, entry 9). As expected, ring opening of the epoxide 17 by thioglycolate occurred selectively at the benzylic position. The trisubstituted sulfide 5,6,6-trimethyl-[1,4]-oxathian-2-one 28 was synthesized from 2,3-epoxy-2-methylbutane 18 in 50% yield over two steps. While nucleophilic attack of the thioglycolate anion occurred predominately at the
less substituted carbon, trace amounts of the regioisomeric sulfide were observed in
the $^1$H NMR spectrum of the crude material.

Koskimies has carried out a study on the conformational properties of 1,4-oxathian-2-
one using $^1$H NMR and $^{13}$C NMR data.$^{34,35}$ Using chemical shift, geminal coupling
constant and long range coupling constant evidence he has concluded that the
probable conformation of these systems is either the classical boat or the half-chair
conformation due to the planar ester functionality and the puckered C-S-C-C part of
the ring, with ring inversion possible in both types (Figure 2).

**Figure 2** Conformations of 1,4-oxathian-2-ones

From this work Koskimies has also been able to distinguish between the C-3 protons
with the equatorial hydrogen $H_{3e}$ being assigned as the proton at $\delta_H$ 3.23 and the axial
hydrogen $H_{3a}$ appearing at $\delta_H$ 3.69 in the $^1$H NMR.

**Table 1: Synthesis of bicyclic and monocyclic lactone sulfides**

<table>
<thead>
<tr>
<th>entry</th>
<th>epoxide</th>
<th>R'</th>
<th>R''</th>
<th>R'''</th>
<th>Sulfide</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>—(CH$_2$)$_4$—</td>
<td>—</td>
<td>—</td>
<td>19</td>
<td>97</td>
</tr>
<tr>
<td>cis$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>—(CH$_2$)$_4$—</td>
<td>—</td>
<td>CH$_3$</td>
<td>20</td>
<td>62$^a$</td>
</tr>
</tbody>
</table>
(a) *Cis* and *trans* refers to the relationship between R\(^1\) and R\(^2\). Refer to Figure 1 for structures of the sulfoxide series of these compounds. (b) Product decomposed to complex mixture of unidentifiable products after 24 h. (c) Product isolated from reaction mixture was pure by \(^1\)H NMR spectroscopy.

For the lactam series *cis*- and *trans*-5,6-diphenyl-thiomorpholin-3-one (30) and (31) were synthesised according to the procedure described by Garcia Ruano\(^41\) to explore the influence of the lactam substituent relative to the lactone (Table 2, entries 12 and 13).

<table>
<thead>
<tr>
<th></th>
<th>cis</th>
<th>trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>11</td>
<td>(CH(_2))(_3) -</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>(CH(_2))(_6) -</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>CH(_3)</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>CH(_3)</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>Ph</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>Ph</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>CH(_3)</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>CH(_3)</td>
</tr>
</tbody>
</table>

 Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2013