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Synthesis of 1,4-oxathian-2-ones by triton B-catalyzed one-pot reaction of epoxides with ethyl mercaptoacetate

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Abstract: A rapid one-pot reaction of epoxides with ethyl mercaptoacetate furnishing 1,4-oxathian-2-ones in the presence of a catalytic amount of eco-friendly triton B is reported. High regioselectivity is due to the nucleophilic attack on the less sterically hindered carbon atom of the aliphatic unsymmetrical epoxide.

Keywords: 1,4-oxathian-2-ones; eco-friendly; epoxide; ethyl mercaptoacetate; intramolecular transesterification; triton B.

Introduction

Benzyltrimethylammonium hydroxide (triton B) is an eco-friendly basic phase-transfer catalyst employed in many chemical reactions [1–3]. The recent increasing interest in this catalyst is due to its physical and chemical properties, ecological effect, availability and low cost [4].

1,4-Oxathian-2-ones are an important class of heterocyclic compounds [5] with many applications in medicinal chemistry [6–8] and industrial fields [9]. The increasing interest in these compounds has led to the development of many synthetic methods using different substrates [10] and catalysts [4]. 1,4-Oxathian-2-one derivatives can be synthesized by many methods [11–16] including transformation of epoxides [17–19]. Many synthetic protocols involve opening of epoxides into the corresponding β-hydroxy sulfides [20–25].

As part of our work on the use of triton B as a catalyst for diverse organic transformations [3], we report in this paper, a new method for the synthesis of 1,4-oxathian-2-one derivatives by a one-pot reaction of epoxides with ethyl mercaptoacetate using, for the first time, triton B as a commercially available and inexpensive base catalyst.

Results and discussion

The reaction of equimolar amounts of epoxide 1 and ethyl 2-mercaptoproacetate 2 in the presence of triton B (2.5%) was carried out at 25°C for 10 min and afforded a mixture of β-hydroxythioacetate 3 and 1,4-oxathian-2-one 4 in good yield with predominance of compound 3. This result is consistent with the ring opening reaction of the epoxide, leading to 3, while the cyclic compound 4 is formed via the partial lactonization of the intermediate product 3 (Scheme 1).

Previously, the Lewis acid LiBr has been used as a catalyst in the reaction of thio acids with epoxides to yield the corresponding α-mercapto carboxylic acids through attack of the thiol on the more substituted carbon atom of the epoxide ring [8]. In our case, the β-hydroxythioacetates 3b–g were formed through the nucleophilic attack of the thiolate anion on the less substituted epoxide 1. Generation of thiolate is facilitated in the presence of basic triton B. The thiolate attacks the less substituted epoxide carbon atom, via an S_N2 mechanism. In the case of epichlorohydrin 1e bearing both epoxide and alkyl halide moieties, the reaction is regio- and chemo-selective affording exclusively the corresponding β-hydroxythioacetate 3e, and no chloride substitution product is observed [3, 22]. The reaction of the styrene oxide 1g gave a mixture of two regioisomers 3g and 3g′, which results from competitive nucleophilic attacks on carbon atoms β and α of the epoxide, respectively (Scheme 1). Compound 3g is the major product resulting from the nucleophilic attack on the less sterically hindered carbon atom β. The two regioisomers 3g and 3g′ undergo cyclization yielding the corresponding 1,4-oxathian-2-ones 4g (13%) and 4g′ (9%), respectively. It
appears that the intramolecular transesterification reaction is not complete at room temperature and reaches a dynamic equilibrium, as the ratio of $3/4$ does not change even after extending the reaction time from 10 min to 24 h.

The lactonization/transesterification reaction was also studied in the presence of NEt$_3$ as a base (Table 1). In the first attempts, under solvent-free conditions, the reaction of ethyl 2-mercaptoacetate 2 (1 equiv) with the symmetrical epoxide 1a (1 equiv) in the presence of Et$_3$N (2 equiv) was investigated at room temperature and at 100°C. In these cases, the uncyclized compound 3a was obtained exclusively after 24 h in 75% and 67% yields, respectively (Table 1, entries 1 and 2). Under similar conditions, but in refluxing toluene using a Dean-Stark apparatus, 1,4-oxathian-2-one 4a was the only isolated product after 18 h (Table 1, entry 3). The yield was 60% in both cases. On the other hand, under solvent-free conditions, the reaction of ethyl 2-mercaptoacetate 2 (1 equiv) with epoxide 1a (1 equiv) in the presence of a catalytic amount (2.5%) of triton B both at room temperature and at 100°C, afforded after 10 min a mixture of compounds 3a and 4a in excellent yields in ratios of $3a/4a=57/43$ and $3a/4a=54/46$, respectively (Table 1, entries 4 and 5).

Interestingly, in the presence of triton B in refluxing toluene using a Dean-Stark apparatus, the reaction was clean and rapid, affording exclusively 1,4-oxathian-2-one 4a within 10 min in 97% yield (Table 1, entry 6).

After the successful one-pot conversion of epoxide 1a into 1,4-oxathian-2-one 4a in the presence of triton B as catalyst at refluxing toluene (Table 1), the scope of the reaction with epoxides 1b–g was explored (Scheme 2). Thus, the use of triton B as a catalyst allows the one-pot synthesis of lactones 4b–g in short reaction times (10 min) and in excellent yields.

Products 3 and 4 were characterized using proton nuclear magnetic resonance ($^1$H NMR), carbon-13 nuclear magnetic resonance ($^{13}$C NMR) and elemental analysis or high resolution mass spectrometry (HRMS). All results are in agreement with the previous spectral studies of 1,4-oxathian-2-ones [26]. In particular, in $^1$H NMR spectra, the protons of the S-CH$_2$C=O group in compounds 3 and 4 show different patterns. In the acyclic compounds 3, the two protons are magnetically equivalent and give a singlet. In thiolactones 4, these two equatorial/axial protons are no longer magnetically equivalent and appear as an $AB$ system with a coupling constant $J_{HH}=15$ Hz.

### Table 1 Base-catalyzed reaction with epoxide 1a with ethyl 2-mercaptoacetate 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Time, min (h)</th>
<th>Ratio 3a/4a (%)$^a$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N (2 eq)</td>
<td>rt</td>
<td>Neat</td>
<td>(24)</td>
<td>100/0</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$N (2 eq)</td>
<td>100</td>
<td>Neat</td>
<td>(24)</td>
<td>100/0</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N (2 eq)</td>
<td>110</td>
<td>Toluene</td>
<td>(18)</td>
<td>0/100</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Triton B (2.5%)</td>
<td>rt</td>
<td>Neat</td>
<td>10</td>
<td>57/43</td>
<td>95$^b$</td>
</tr>
<tr>
<td>5</td>
<td>Triton B (2.5%)</td>
<td>100</td>
<td>Neat</td>
<td>10</td>
<td>54/46</td>
<td>90$^b$</td>
</tr>
<tr>
<td>6</td>
<td>Triton B (2.5%)</td>
<td>110</td>
<td>Toluene</td>
<td>10</td>
<td>0/100</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$The ratios were determined by $^1$H NMR; $^b$total yield of products.
Conclusion

A new eco-friendly and time-efficient one-pot protocol for the preparation of 1,4-oxathian-2-ones involves ring opening of epoxides by the reaction with ethyl mercaptoacetate followed by intramolecular transesterification of the intermediate products. The synthesis of 1,4-oxathian-2-ones via an epoxide ring-opening-ring-closing reaction cascade was carried out for the first time in the presence of eco-friendly and inexpensive triton B as a base catalyst.

Experimental

1H and 13C NMR spectra were recorded on a Bruker AC 300 spectrometer in CDCl3, at 300 MHz and 75 MHz, respectively. HRMS spectra were recorded on a Finnigan MAT 95 mass spectrometer operating in chemical ionization mode (CI).

Synthesis of hydroxythioacetates 3

Ethyl 2-mercaptoacetate (2) (1.80 g, 15 mmol) was added dropwise over a 10 min period to a stirred mixture of epoxide 1a–g (15 mmol) and 2.5 mol% of triton B at room temperature. The consumption of the epoxide was monitored using thin layer chromatography (TLC). The crude products were purified by distillation excepting 2f and 2e which were isolated by column chromatography on silica gel eluting with hexane/ethyl acetate, 60:40.

Ethyl 2-(2-hydroxyethylthio)acetate (3a) Colorless viscous oil; yield 95%; bp 150°C/0.1 mm Hg; 1H NMR: δ 6.71 (t, J = 7.2 Hz, 2H, CH2), 2.82–3.02 (m, 2H, CH2), 3.16 (s, 2H, OCH2), 3.33 (s, 2H, CH2CO), 4.03–4.17 (m, 3H, CH2CH2OPh), 6.90–7.32 (m, 5H, HAr); 13C NMR: δ 14.1, 34.0, 42.1, 61.6, 72.4, 125.8, 127.8, 128.5, 146.2, 170.9. Anal. Calcd for C10H18O4S: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.81; H, 6.76; S, 11.89.

Ethyl 2-(2-hydroxy-1-phenylethylthio)acetate (3g′) Colorless viscous oil; yield 76%; bp 150°C/0.1 mm Hg; 1H NMR: δ 6.18 (t, J = 7.1 Hz, 2H, CH2), 2.80–3.01 (m, 2H, CH2), 3.26 (s, 2H, CH2CO), 4.19 (q, J = 7.1 Hz, 2H, CH2O), 4.77–4.82 (m, 1H, HAr); 13C NMR: δ 14.1, 34.0, 42.1, 61.6, 72.4, 125.8, 127.8, 128.5, 146.2, 170.9. Anal. Calcd for C10H18O4S: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.81; H, 6.76; S, 11.89.

Synthesis of 1,4-oxathian-2-ones 4

A mixture of epoxide 1 (15 mmol), ethyl 2-mercaptoacetate 2 (1.80 g, 15 mmol) and triton B (2.5 mol%) in toluene (50 mL) was heated to 110°C in a two-neck flask equipped with a condenser to remove ethanol. After completion of the reaction, as indicated by TLC analysis, the mixture was cooled, and the toluene was removed. The residue was subjected to column chromatography on silica gel eluting with hexane/ethyl acetate (60:40) to give pure 1,4-oxathian-2-one 4.

Scheme 2
Hexahydrobenzo[θ][1,4]-oxathiin-2(3H)-one (4a) White solid; mp 88–89°C (lit. [26] mp 87–88°C); yield 97%; 1H NMR: δ 1.22–2.26 [m, (CH3)2], 3.00 (dd, J = 12.2, 12.0, 6.2 Hz, 1H, CHS); 3.22 (d, J = 15.0 Hz, 1H, CH), 3.68 (d, J = 15.0 Hz, 1H, CH, CO), 4.17 (ddd, J = 12.2, 12.0, 4.2 Hz, 1H, CHO). 13C NMR: δ 23.8, 25.1, 26.8, 32.2, 32.6, 43.1, 81.7, 168.1; MS: m/z 172.245 (M+). Anal. Calcd for C8H14O2S: C, 55.78; H, 7.02. Found: C, 55.56; H, 7.22.

6-Ethyl-1,4-oxathian-2-one (4b) Colorless viscous oil; yield 90%; 1H NMR: δ 1.04 (t, J = 7.5 Hz, 3H, CH3), 1.70–1.90 (m, 2H, MeCH2), 2.74–2.97 (m, 2H, SCH2), 2.90 (d, J = 15.0 Hz, 1H, CH, CO), 4.35–4.43 (m, 1H, CH-O). 13C NMR: δ 55.01; H, 8.18.

Colorless viscous oil; yield 90%; 1H NMR: δ 1.05 (t, J = 7.0 Hz, 3H, CH3), 1.23–1.88 (m, 6H, CH2); 2.75–2.94 (m, 2H, SCH2); 2.90 (d, J = 15.0 Hz, 1H, CH, CO), 4.61–4.68 (m, 1H, CH). 13C NMR: δ 20.9, 25.7, 30.7, 75.5, 168.3. HRMS. Calcd for C7H14O2SCl: m/z 165.98553. Found: m/z 165.98635.

6-Butyl-1,4-oxathian-2-one (4c) Colorless viscous oil; yield 92%; 1H NMR: δ 1.04 (t, J = 7.5 Hz, 3H, CH3), 1.70–1.90 (m, 2H, MeCH2), 2.74–2.94 (m, 2H, SCH2); 5.21 (m, 1H, CH). 13C NMR: δ 29.3, 34.7, 79.2, 168.4. HRMS. Calcd for C5H7O2SCl: m/z 194.03963. Found: m/z 194.03961.

Colorless viscous oil; yield 92%; 1H NMR: δ 1.04 (t, J = 7.0 Hz, 3H, CH3), 1.23–1.88 (m, 6H, CH2); 2.75–2.94 (m, 2H, SCH2); 5.21 (m, 1H, CH). 13C NMR: δ 29.3, 34.7, 79.2, 168.4. HRMS. Calcd for C5H7O2SCl: m/z 194.03963. Found: m/z 194.03961.

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