

Lewis Acid-induced Rearrangement of 2,3-Epoxy Sulfides: Regiospecific Nucleophilic Trapping of Thiiranium Ion Intermediates with Nitrogen Nucleophiles

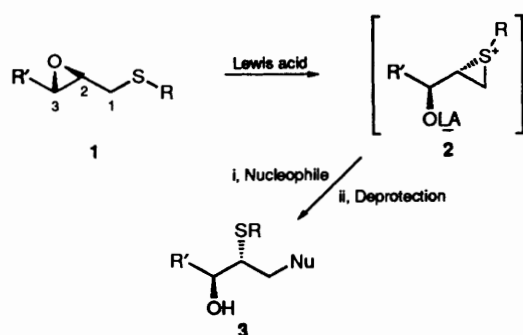
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The Lewis acid-induced isomerisation of 2,3-epoxy sulfides into the corresponding 3-trimethylsilyloxy-1,2-thiiranium ions is described. Such intermediates react with nitrogen nucleophiles regiospecifically to form 1-substituted 3-hydroxy 2-thioethers in good to moderate yields with full stereochemical control.

The ability of the Sharpless asymmetric epoxidation¹ to produce a wide variety of optically active 2,3-epoxy alcohols has led to their exploitation as valuable synthetic intermediates.² The corresponding 2,3-epoxy sulfides **1**, which may be readily prepared from epoxy alcohols have, however, been little investigated and represent a new, readily available, optically active building block for use in synthesis.^{3,4} As part of a general investigation in this area, we wished to explore the feasibility of formation of a thiiranium ion (episulfonium ion) **2** by the Lewis acid-catalysed isomerisation of a 2,3-epoxy sulfide (Scheme 1).



Scheme 1

Thiiranium ions are interesting⁵ and synthetically useful intermediates.⁶ Their formation from β -hydroxy sulfides has been investigated by a number of groups, in particular Warren⁷ and others,⁸ however the use of epoxides for this type of reaction has not been reported to any significant degree.⁹ The isomerisation **1**→**2** is related to the known Payne rearrangement of 2,3-epoxy alcohols¹⁰ which is particularly useful if selective nucleophilic trapping of the more reactive intermediate (in this case **2**) can be achieved.¹¹ We herein report a preliminary account of our results in this area.

For our initial studies we chose the previously reported *trans*-2,3-epoxy sulfides **4** and **5**,³ the *cis*-2,3-epoxy sulfides **6** and **7**,[†] and the benzyl thioether **8** as representative substrates. Treatment of these with Lewis acids failed to produce a characterisable thiiranium ion, however if trimethylsilyl trifluoromethanesulfonate (TMSOTf) is added to the epoxy sulfide at low temperature (-78°C) in dichloromethane, a rapid disappearance of starting material can be detected by TLC. Addition of a variety of nitrogen nucleophiles, warming to 0°C and stirring for up to 3 days gives the trimethylsilyl ethers

[†] Prepared from *cis*-hex-2-en-1-ol by an analogous route to that reported.³

which can be readily deprotected (K_2CO_3 , MeOH) to give good to moderate overall yields of the desired products (Table 1).

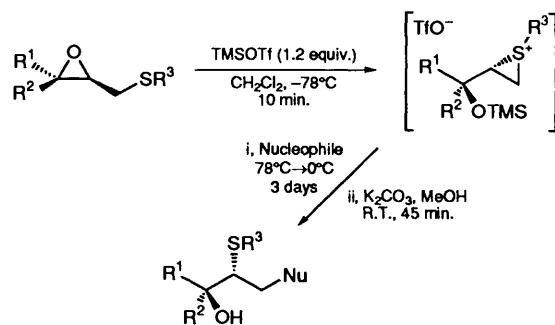
There are a number of important points to note. Firstly, the reaction is successful for a range of epoxy sulfide substrates, including *cis* and *trans* isomers, and methyl, phenyl and benzyl thioethers. Although in some cases yields are only moderate, they correspond to pure products after chromatography, and are overall yields for the three-step sequence of thiiranium ion generation, nucleophilic trapping and deprotection. Secondly, when homochiral 2,3-epoxy sulfide substrates are used, the products retain their optical activity (entries 6 and 11), and in all cases are single diastereoisomers as determined by ^{13}C NMR. Thirdly, variation of Lewis acid can, in some cases, lead to an improvement in yield (entries 17 and 18). Finally, the nucleophile is introduced regiospecifically at position 1, which is consistent with the intermediacy of episulfonium ion **2** or an equivalent thereof.^{12,13}

In summary, this new powerful methodology provides access to a range of functionalised 1-amino-3-hydroxy 2-thioethers with full control of absolute and relative stereochemistry. Further investigations into the versatility of this reaction, and the nature of the reactive intermediates involved, are currently underway in our laboratories.

Experimental

Typical Procedure (Entry 8).—Trimethylsilyl trifluoromethanesulfonate (0.411 mmol) was added to a solution of 1-methylthio-2,3-epoxyhexane **4** (0.342 mmol) in dichloromethane (2 cm^3) at -78°C under nitrogen. After 10 min, bis(trimethylsilyl)acetamide (0.684 mmol) was added to the solution which was then allowed to warm to 0°C over 30 min; it was stirred at this temperature for a further 56 h. Methanol (2 cm^3) and potassium carbonate (1.03 mmol) were added to the mixture which was then allowed to warm to room temperature. After 45 min solvent was removed under reduced pressure and dichloromethane (10 cm^3) added to the residue. The resultant solution was washed with water ($2 \times 2\text{ cm}^3$) which was back-extracted with dichloromethane ($3 \times 5\text{ cm}^3$) and the combined organic extracts were dried (MgSO_4), filtered and concentrated under reduced pressure. Purification of the residue by chromatography on TLC grade Florisil [74% ethyl acetate, 1% ethanol, 25% light petroleum (b.p. $40\text{--}60^\circ\text{C}$)] gave the product (0.220 mmol, 54% yield) as a colourless oil.[‡]

[‡] All new compounds were characterised by ^1H and ^{13}C NMR, IR, and mass spectra, and gave satisfactory elemental analyses and/or accurate mass spectra.



4, R¹ = Bu, R² = H, R³ = Me; 5, R¹ = Bu, R² = H, R³ = Ph; 6, R¹ = H, R² = Bu, R³ = Me; 7, R¹ = H, R² = Bu, R³ = Ph; 8, R¹ = Bu, R² = H, R³ = CH₂Ph

Table 1 Results of nucleophilic trapping experiments

Entry ^a	Substrate	Nucleophile	Product	Yield (%)
1	4			85
2	5			81
3	4			81
4	5			75
5	6			68
6	7 ^d			55 ^e
7	8			53
8	4			54 ^b
9	5			58
10	6			44
11	7 ^d			40
12	8			51
13	4			44
14	5			55
15	4			33
16	5			39 (83 ^g)
17	4			47 (37 ^g)
18	5			40 (23 ^g)
19	4			44 ^g
20	4			37 ^g
21	5			33 ^g

^a All compounds used as racemates unless otherwise stated. ^b LiAlH₄ reduction of the product gives the *N*-ethylamine consistent with *N*-alkylation. ^c Yield based on recovered starting material. ^d Homochiral (>96% e.e.) 2,3-epoxy sulfide used. ^e [α]_D²⁵ +36.6 (*c* 1.18 in EtOH). ^f [α]_D²⁵ +47.6 (*c* 0.97 in EtOH). ^g BF₃·OEt₂ used rather than TMSOTf (yield in parentheses, when given, is for TMSOTf).

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