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Lewis Acid Induced Rearrangement of 2,3-Epoxy Amines; Characterisation of Aziridinium Ion Intermediates and Regiospecific Ring Opening with Nitrogen Nucleophiles

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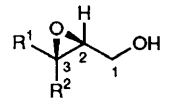
The Lewis acid induced isomerisation of 2,3-epoxy amines into the corresponding 2-trimethylsiloxymethylaziridinium ions is described; such intermediates have been characterised by ^{1}H NMR spectroscopy, and react with nitrogen nucleophiles regiospecifically to form 1-substituted 2,3-diamino alcohols in good to excellent yields and with full stereochemical control.

The ability of the Sharpless asymmetric epoxidation[1] to produce a wide variety of optically active 2,3-epoxy alcohols **1** has led to their exploitation as valuable synthetic intermediates.[2] We have recently shown that 2,3-epoxy sulfides **2**, which may be readily prepared from epoxy alcohols, are a new, readily available, optically active building block for use in synthesis.[3,4] We now describe some preliminary results of our studies using the corresponding 2,3-epoxy amines **3** which provide access to 3-hydroxy-1,2-diamines, which have potential as chiral ligands in asymmetric synthesis,[5] as novel biologically active compounds[6] and as new systems capable of self-organisation *via* hydrogen bonding.[7]



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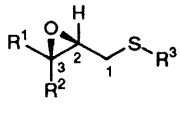

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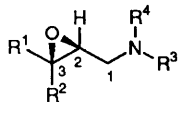

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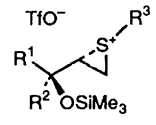
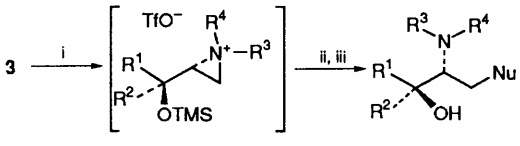


4

We have recently reported the Lewis acid catalysed isomerisation of 2,3-epoxy sulfides **2** into the corresponding 2-trimethylsiloxymethylthiiranium trifluoromethanesulfonates **4**, which were regiospecifically trapped at the least hindered position (C-1) with a variety of nucleophiles.[3] We now report the analogous reaction of 2,3-epoxy amines **3** to give the corresponding 2-trimethylsiloxymethylaziridinium trifluoromethanesulfonates **5** which, when treated with nucleophiles, give 1-substituted 2,3-diamino alcohols **6** in an enantiomerically and diastereomerically pure form (Scheme 1).

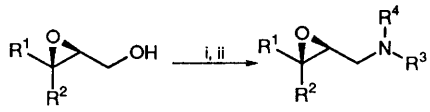


5 **6**

Scheme 1 *Reagents and conditions:* i, TMSOTf, −78 °C, $CHCl_2$; ii, nucleophile, −78 °C–room temp.; iii, deprotection

Aziridines are readily accessible synthetic intermediates[8] but are underused in synthesis, particularly when compared with epoxides. This is probably due to their relatively low reactivity, often requiring a strong electron withdrawing group on the nitrogen atom to promote ring opening with nucleophiles.[9] Examples where aziridinium salts have been used in synthesis are also relatively rare,[10] however their enhanced reactivity, particularly when compared to aziridines, make them potentially extremely useful electrophiles, particularly for reaction with relatively weak nucleophiles.

For our initial studies we chose the simple *trans*-2,3-epoxy amines **7**, **8** and **9**[3] as representative substrates. These are readily prepared in two steps from 2,3-epoxy alcohols in good overall yield by potassium iodide catalysed displacement of toluene-*p*-sulfonate by the required amine (Scheme 2).† Note



1

7 R^1 = Pr, R^2 = H, R^3, R^4 = $[CH_2]_5$
8 R^1 = Pr, R^2 = H, R^3 = R^4 = CH_2Ph
9 R^1 = Pr, R^2 = H, R^3 = R^4 = allyl

Scheme 2 *Reagents and conditions:* i, TsCl, pyridine; ii, R^3R^4NH (2 equiv.), KI, DMF, room temp., 73–83%

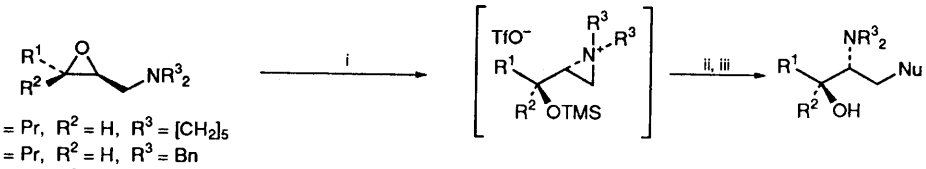
that tertiary amines are required for aziridinium salt formation, and that the diallyl- and dibenzyl-amines are of particular importance as they will allow ready deprotection[11]‡ to the corresponding primary amines, which are in many cases our desired target molecule.

With our substrates in hand, we began to investigate aziridinium salt formation. The 2,3-epoxy amine **8**, derived from dibenzylamine, was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in $CDCl_3$ at −40 °C and the reaction mixture allowed to warm to room temperature (Scheme 3). The ^{1}H NMR spectrum of the resulting solution clearly showed clean formation of the aziridinium salt **12**, which was stable for a number of days at room temperature.[12] In many previous examples where aziridinium salts have been used, they have been present only in small equilibrium concentrations.[10] It is clear that in this case we have essentially irreversible aziridinium salt formation, which is a considerable advantage in that it prevents formation of piperazinium dimers,

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

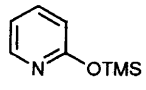
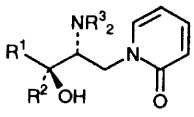
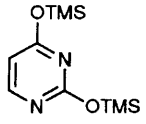
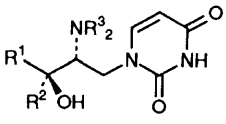
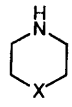
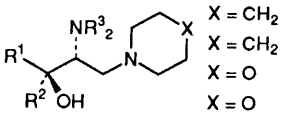
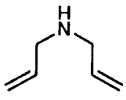
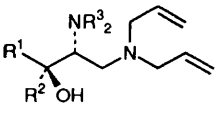
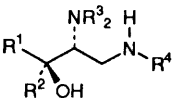
‡ ^{1}H NMR of **10**, δ_H(300 MHz, $CDCl_3$, *J*/Hz) 0.11 (9 H, s, $SiMe_3$), 0.92 (3 H, t, *J* 9, CH_3), 1.23–1.44 (2 H, m, CH_2CH_2), 1.69–1.80 (2 H, m, CH_2CH_2), 3.23 (1 H, dd, *J* 8.4, 2.7, one of aziridinium CH_2), 3.32 (1 H, dd, *J* 2.7, 7.4, one of aziridinium CH_2), 3.64 (1 H, t, *J* 8.0, aziridinium CH), 4.27 (1 H, d, *J* 13.2, benzylic CH_2), 4.43 (1 H, d, *J* 14.1, benzylic CH_2), 4.60 (2 H, d, *J* 13.5, benzylic CH_2), 4.70 (1 H, dt, *J* 2.8, 3.5, CHO) and 7.30–7.53 (10 H, m, ArH).

Table 1 Results of nucleophilic trapping of aziridinium salts

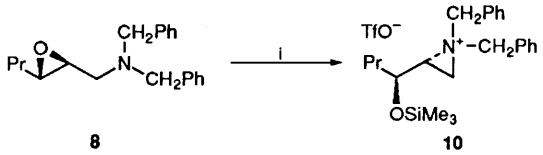


7 R^1 = Pr, R^2 = H, R^3 = $[CH_2]_5$
8 R^1 = Pr, R^2 = H, R^3 = Bn
9 R^1 = Pr, R^2 = H, R^3 = allyl

Reagents and conditions: i, TMSOTf (1.2 equiv.), CH_2Cl_2, −78 °C, 10 min; ii, nucleophile, −78 °C–room temp., 3–5 days

Entry	Substrate[a]	Nucleophile	Product	Yield (%)
1	**8**			93
2	**9**			83
3	**8**			90
4	**9**			86[b]
5	**7**		**11**	79
6	**8**			60
7	**9**			67
8	**8**			92
9	**9**			90
10	**8**			67
11	**9**			88
12	**8**	$BuNH_2$		44
13	**8**	Pr^iNH_2		47

[a] All compounds used as racemates unless otherwise stated. [b] Homochiral (> 96% e.e.) (2*S*,3*S*)-epoxy amine used, **9** $[\alpha]_D^{18}$ −28.6 (*c* 1.02, EtOH); **11** R^1 = Pr, R^2 = H, R^3 = allyl, $[\alpha]_D^{18}$ +46.5 (*c* 0.99, EtOH).



8 **10**

Scheme 3 *Reagents and conditions:* i, TMSOTf, $CDCl_3$, −40 °C–room temp.

which are often side products when aziridinium salts are generated from β-halogenoamines.[13] This dimerisation has been shown to be the dominant reaction even in the presence of nucleophiles including amines and amino acids, however we have not observed such dimerisation in any of our reactions (*vide infra*).

The isomerisation **8**→**10** is related to the known Payne rearrangement of 2,3-epoxy alcohols[13] which is particularly useful if selective nucleophilic trapping of the more reactive intermediate (in this case **10**) can be achieved.[14] A recent paper has described a related isomerisation of a primary 2,3-epoxy amine to the corresponding aziridin-2-ylmethanol using trimethylaluminium as catalyst.[15] Similarly, 2,3-epoxy sulfonamides are reported to rearrange to the *N*-tosylaziridin-2-ylmethanols under basic conditions.[16]

The real advantage of our procedure is if the aziridinium intermediates can be efficiently trapped with nucleophiles, particularly poor nucleophiles which have proved problematic previously. The results of our preliminary investigations are shown in Table 1.

Treatment of the 2,3-epoxy amine with TMSOTf at −78 °C in dichloromethane, followed by addition of an appropriate nucleophile, warming to room temperature, and stirring for up to 5 days gives good to excellent yields of our desired products. In general, the initially formed trimethylsilyl ethers were deprotected without isolation, and quoted yields are for the three step process of aziridinium salt formation, nucleophilic trapping and deprotection. Of particular importance is the high regioselectivity of the reaction, which results in introduction of the nucleophile exclusively at the less hindered terminal carbon (C-1). The reaction is successful for all the 2,3-epoxy amine substrates so far investigated, and is also stereospecific. Optical activity is retained in the products as would be expected from the intermediacy of the aziridinium salt (entry 5).

In summary, this powerful new methodology provides access

to a range of 1-substituted 2,3-diamino alcohols with full control of absolute and relative stereochemistry. We are currently applying this new methodology to the synthesis of new chiral ligands for asymmetric catalysis, novel biologically active compounds, and new systems capable of self-organisation *via* hydrogen bonding. The results of these studies will be reported in due course.

Experimental

Typical Procedure (*Table* 1, *entry* 7).—Trimethylsilyl trifluoromethanesulfonate (0.29 g, 0.25 cm^3, 1.3 mmol) was added to a solution of *trans*-diallyl(2,3-epoxyhexyl)amine (0.21 g, 1.1 mmol) in dichloromethane (6 cm^3) at −78 °C under nitrogen. After 10 min, piperidine (0.18 g, 0.21 cm^3, 2.15 mmol) was added to the solution which was then allowed to warm to room temperature and stirred for 120 h. Methanol (10 cm^3) and potassium carbonate (1 g) were added to it and the mixture stirred for a further 12 h. The solvent was then removed under reduced pressure and the residue purified by column chromatography on flash silica [50% ethyl acetate, 50% light petroleum (b.p. range 40–60 °C)] to give the product (0.20 g, 0.71 mmol, 67% yield) as a pale yellow oil.

Acknowledgements

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