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Rearrangement of Primary 2,3-Epoxy Amines into 1,2-Aziridinyl 3-Ols.

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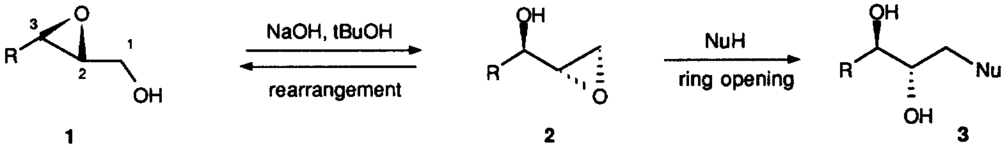
Abstract - Conditions were found to transform primary 2,3-epoxy amines into 1,2-aziridinyl 3-ols which involve an intramolecular opening of the epoxide ring mediated by trimethylaluminum.

Key words : 2,3-epoxy amines, 1,2-aziridinyl 3-ols, intramolecular ring opening, trimethylaluminum, rearrangement.

The Payne rearrangement [1] of 2,3-epoxy alcohols involves the equilibration of the epoxy alcohol **1** with the isomeric 1,2-epoxy 3-ol **2** as shown in scheme I and usually produces mixtures of **1** and **2**.

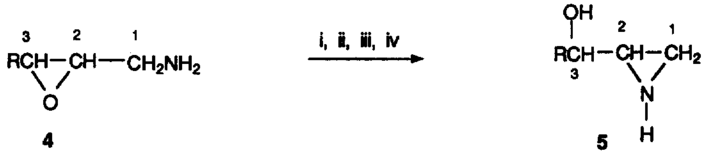


Scheme 1

It was therefore of limited preparative value until Sharpless and Masamune [2] realized that a nucleophile introduced into an equilibrating mixture may react selectively with one of the epoxy alcohols, e.g. **2**, giving the corresponding ring opening product **3**. This and our own studies on the synthesis and reactivity of epoxy azides and amines [3] raised the question whether or not primary 2,3-epoxy amines **4** would rearrange to 1,2-aziridinyl 3-ols **5** (scheme 2) and what would be the conditions for such a rearrangement.

Epoxy amines **4** were easily prepared by a chemoselective reduction of the corresponding azides using Ph_3P in THF in the presence of water [4]. Compounds 4 were purified by bulb to bulb distillation and obtained in good yields (**4a** : R = Me, 69 %, trans ; **4b** : R = nBu, 58 %, trans ; **4'b** : R = nBu, 50 %, cis ; **4c** : R = Ph, 91 %, trans ; **4'c** : R = Ph, 77 %, cis). They are relatively thermally stable. For example, **4c** was stable in boiling toluene for 18 hours whereas **4a**, under the same conditions gave tars without any detectable **5a**. Moreover, under Payne rearrangement conditions, i.e. 1 : 1 tBuOH - 0,5 M NaOH, 70°C, 24 hours, **4c** did not rearrange to **5c** but gave tars. The impossibility for the epoxy amines 4 to give 5 via an intramolecular 3-exo-tetragonal process [5] which is usually a favorable one seems surprising although a similar observation was recently reported. The rearrangement of N-tosyl-oxirane methylamines being observed and explained by the so-called gem-dialkyl effect [6].

Efficient reactions conditions were found to transform **4** into **5** according to the following scheme :

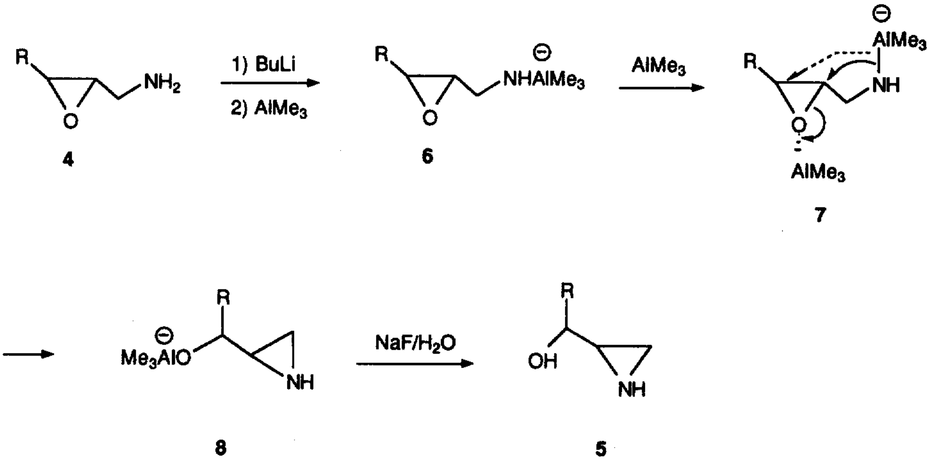


Reaction conditions and reagents : i BuLi, -80°C, THF. ii $AlMe_3$, toluene, -80°C.
iii Δ : $-80 \rightarrow$ 0°C. iv NaF, H_2O.

Scheme 2

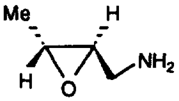
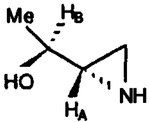
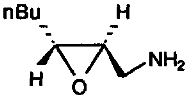
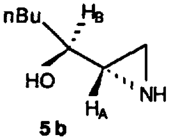
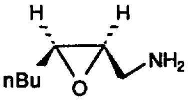
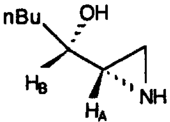
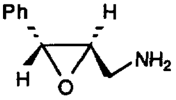
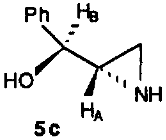
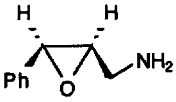
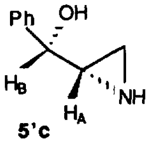
1.5 equivalents of nBuLi were added to a THF solution of **4** at -78°C followed by the addition of 1.5 equivalents of $AlMe_3$ in toluene. The reaction mixture was allowed to warm up to 0°C and quenched with NaF before hydrolysis. Aziridinols **5** were purified by bulb to bulb distillation (table I).

The rearrangement of 2,3-epoxyamines **4** occured under mild conditions and gave exclusively the 1,2-aziridinyl 3-ols **5** arising from a 3-exo-tetragonal process. No azetidinols which could have arised from a 4-endo-tetragonal cyclization were detected. Erythro and threo aziridinols which stereochemistry was assigned according to the $^3JH_AH_B$ values (see table I) in agreement with literature data [7] were obtained respectively from trans and cis epoxydes. This result is indicative of a clean SN2 attack at C_2 by the nitrogen nucleophile. It is also interesting to note that the use of BuLi without $AlMe_3$ and $AlMe_3$ without BuLi did not give any rearrangement products but respectively the starting material and tars. A tentative mechanism may be as follows : the aminoalanate **6** may rearrange to **8** via a complex like **7** (scheme 3).



Scheme 3

Table I - Rearrangement of 2,3-epoxy amines **4** to 1,2-aziridinyl 3-ols **5**.

Substrate [b]	Product [a,b]	J_{AB} (Hz)	yield % [c]
 **4a**	 **5a**	4.0 (erythro)	69
 **4b**	 **5b**	3.6 (erythro)	72
 **4'b**	 **5'b**	6.0 (threo)	75
 **4c**	 **5c**	3.8 (erythro)	73
 **4'c**	 **5'c**	6.4 (threo)	78

[a] All new compounds gave satisfactory elemental analysis and show spectroscopic data in agreement with the given structures.

[b] Only one enantiomer is represented.

c Yields are for isolated, pure products.

A typical procedure for the rearrangement of **4c** is as follows : to a stirred solution of the 2,3-epoxy amine **4c** (0.30 g, 2.2 mmol) in anhydrous THF (20 ml) at -80°C was slowly added n-BuLi (2.1 ml of a 1.6 M solution in hexane, 3.3 mmol) via syringe. After 15 minutes were added 1.65 ml of a 2 M solution of Me_3Al in toluene (3.3 mmol) and the reaction mixture allowed to warm up to 0°C. 0.5 g of NaF were then added. After stirring for 1 hr, 0.5 ml of water were added and the reaction mixture stirred a further hour at room temperature, filtered over celite, washed with ether (20 ml) and the solvents removed under vacuum. The residue was recrystallized from ether to afford 0.20 g (73 %) of **5c**, m.p. 70-71°C. ^{1}H NMR (300 MHz), $CDCl_3$, δ_{ppm}/TMS : 1.54 (d, 1H, J = 5.8 Hz) ; 1.70 (d, 1H, J = 3.6 Hz) ; 2.13 (ddd, H_A, J = 3.6, 3.8, 5.8) ; 2.6 (br.s, 2H) ; 4.56 (d, H_B, J = 3.8 Hz) ; 7.1 - 7.6 (m, 5H). ^{13}C NMR (75.5 MHz), $CDCl_3$, δ_{ppm}/TMS : 21.3 (tm, $^1J_{CH}$ = 171 Hz) ; 35.1 (dm, $^1J_{CH}$ = 168 Hz) ; 71.2 (dm, $^1J_{CH}$ = 144 Hz) ; 126.3 ; 127.8 ; 128.5 ; 142.6 (6 aromatic carbons).

In conclusion, simple 2,3-epoxyamines **4** did not rearrange either spontaneously nor under thermal and Payne rearrangement conditions. Simple and efficient conditions were found involving aminoalanates to promote the rearrangement of 2,3-epoxyamines into the valuable 1,2-aziridinyl 3-ol [8].

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