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Substituent Control in the Synthesis of Azetidines and Pyrrolidines by *N*-Tosyl-Oxiraneethylamines Base-Mediated Cyclization.

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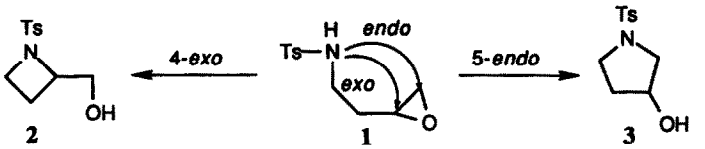
Key Words: Oxiraneethylamines; Azetidinemethanols; Pyrrolidinols; Rearrangement; Epoxide ring opening.

Abstract: *N-tosyl-oxiraneethylamines undergo cyclization upon treatment with aqueous sodium hydroxide to afford either N-tosyl-azetidinemethanols or N-tosyl-pyrrolidin-3-ols in high yields. The change in regioselectivity of this cyclization process is quite dependent on the location of a pentamethylene substitution in the chain connecting the nitrogen with the oxirane ring.*

The intramolecular cyclization of epoxy-amines is a powerful tool for the synthesis of nitrogen heterocycles.[1,3] Thus, this cyclization strategy has been applied successfully to the preparation of pyrrolidine and piperidine alkaloids.[2,3] However, very few examples exist for the construction of azetidines using this method.[4]

We have previously reported the base-induced cyclization of *N*-tosyl-oxiranemethylamines[5] and *N*-tosyl-oxiranepropylamines,[6] generating aziridines and pyrrolidines respectively. With hopes of expanding the scope of this methodology to include the preparation of the four-membered rings, we targeted a series of *N*-tosyl-oxiraneethylamines **1**. Such substrates are susceptible to two distinct cyclization pathways (Scheme 1); 4-*exo* attack of the nitrogen atom on the epoxide would lead to azetidinemethanol **2**, while 5-*endo* attack would provide pyrrolidin-3-ol **3**.

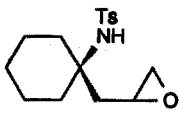
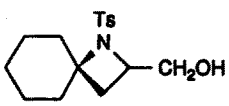
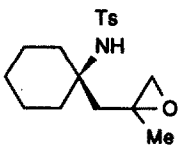
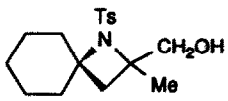
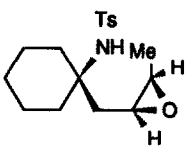
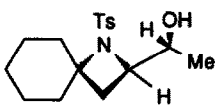
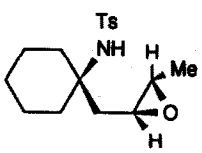
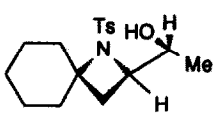
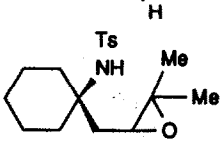
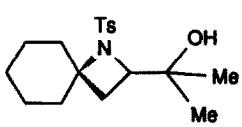
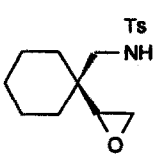
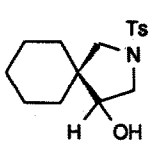
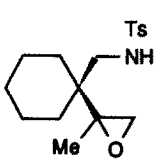
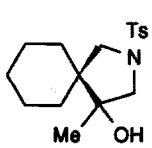
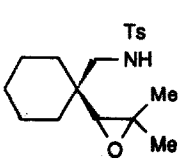
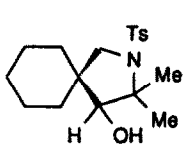


Scheme 1

The epoxy-tosylamines required for this study are readily prepared by epoxidation (mCPBA / $CHCl_3$) of the *N*-tosyl-homoallylic amines obtained by standard methods. Cyclization is effected by aqueous sodium hydroxide at 100°C, following our published protocol;[6] Table I summarizes the results.

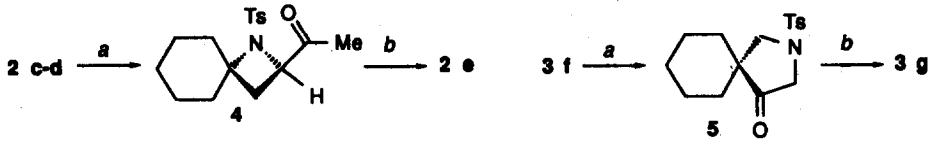
Structural assignments are based mainly on ^{1}H-NMR data.[7] It is noteworthy that in all cases but **1c-d**, the hydroxyl groups are of a different type in each of the cyclized compounds (see Scheme 1: a primary hydroxyl in **2** and a secondary hydroxyl in **3**). Hence, the determination of the hydroxyl group type, through the multiplicity of the related NMR signal under slow exchange conditions,[8] allows the definition of the nitrogen ring. Additional evidence comes from resonances due to hydroxymethylene and hydroxymethine protons. Both cyclized

Table I. Cyclization of oxiraneethylamines

Substrate	Product [a]	Yield % [b]
1 a 	2 a 	95
1 b 	2 b 	95
1 c[c] 	2 c[c] 	80
1 d[c] 	2 d[c] 	95
1 e 	2 e 	90
1 f 	3 f 	80
1 g 	3 g 	92
1 h 	3 h 	91

[a] All new compounds gave satisfactory elemental analysis.
[b] Yields reported are for isolated, purified products.
[c] Only one enantiomer is represented.

compounds **2c** and **2d** give the same methyl ketone **4** upon chromic oxidation,[9] indicating the correctness of the assigned structures.[10] As an ultimate verification, we have achieved some internal chemical correlations (Scheme 2).



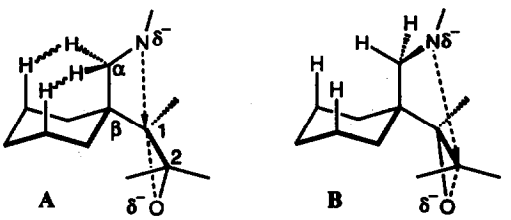
(a) $Na_2Cr_2O_7$ / H_2SO_4 / H_2O / Et_2O; *(b)* MeMgI ; H_2O

Scheme 2

The stereochemical assignments of **2c** and **2d** are consistent with our earlier observations i.e. inversion of configuration at the site of nitrogen attack.[5,6]

The exclusive production, in high yields, of azetidinemethanols from **1a-e** is in line with the preeminence of the 4-*exo* route previously seen in base-induced ring closure of δ-epoxynitriles,[11] γ-iodoepoxides[12] and oxiraneethanols.[13] It is noticeable that neither the alkyl substitution pattern nor the stereochemistry about the epoxide group appear to be critical for regiocontrol of cyclization. Conversely, the epoxy-tosylamines **1f-h** lead, in excellent yields, to pyrrolidinols **3f-h** as the sole products. Since **1f**, **1g** and **1h** respectively differ from **1a**, **1b** and **1c** only by the location of the cyclohexane moiety, it is obvious that the change in regiochemistry is connected with the moving of the pentamethylene group from the "α" to the "β" carbon atom with respect to nitrogen.

The preference for four- vs. five-membered rings is currently ascribed to the greater ease with which the necessary colinear arrangement of nucleophile, epoxide carbon and oxide leaving group is attained.[11,14] For substrates **1f-h** whose favored conformation is expected to be the one where the aminomethyl group is axial, the destabilization of transition state **A** in relation to transition state **B** (Scheme 3) is not of obvious origin. By analogy with intramolecular cyclization of oxiraneethanols,[15] it appears that a roughly 3 kcal / mol stabilization of **B** over **A** suffices to force the reaction to occur via the 5-*endo* mode. Such an energy difference can arise from the 1,3-diaxial relationships of the aminomethyl group, and / or the neopentylic nature[16] of the "1" carbon atom being attacked by a hydrated nitrogen anion in **A**.



Scheme 3

In conclusion, the base-induced cyclization of *N*-tosyl-oxiraneethylamines has proved valuable for building azetidine rings. Nevertheless, in some cases, pyrrolidines are instead obtained with complete selectivity. This change of cyclization mode (5-*endo* rather than 4-*exo*) is closely related to the substitution pattern of the chain connecting the nitrogen with the oxirane ring. We believe that this methodology has considerable potential in the synthesis of functionalized nitrogen heterocycles.

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7. *Selected data* [mp °C; ^{1}H-NMR (200 MHz, $CDCl_3$, TMS)] **2 a**: 102°C; δ 1.03-2.00 (*m*, 12H), 2.45 (*s*, 3H), 3.22 (*br. s*, 1H, OH), 3.71-3.77 (*m*, 2H), 4.06-4.18 (*m*, 1H), 7.32-7.80 (AA'BB' syst., 4H); **2 b**: 96°C; δ 1.08-2.12 (*m*, 10H), 1.26 (*s*, 3H), 1.69-2.13 (AB syst., J_{AB}=10.8 Hz, 2H), 2.42 (*s*, 3H), 3.00 (*br. s*, 1H, OH), 3.50-3.64 (AB syst., J_{AB}=12.2 Hz, 2H), 7.25-7.81 (AA'BB' syst., 4H); **2 c**: 146°C; δ 1.06 (*d*, J=6.3 Hz, 3H), 1.11-2.00 (*m*, 12H), 2.43 (*s*, 3H), 3.72 (*dt*, J=7.1 and 8.6 Hz, 1H), 3.92-4.06 (*dq*, J=6.3 and 8.6 Hz, 1H), 4.38 (*s*, 1H, OH), 7.29-7.78 (AA'BB' syst., 4H); **2 d**: 109°C; δ 1.10 (*d*, J=6.4 Hz, 3H), 1.15-2.02 (*m*, 12H), 2.43 (*s*, 3H), 2.65 (*br. s*, 1H, OH), 3.93-4.06 (*m*, 2H), 7.31-7.77 (AA'BB' syst., 4H); **2 e**: 142°C; δ 1.06 (*s*, 3H), 1.11-1.94 (*m*, 12H), 1.45 (*s*, 3H), 2.43 (*s*, 3H), 3.93-4.02 (X part of ABX syst., 1H), 3.96 (*br. s*, 1H, OH), 7.29-7.81 (AA'BB' syst., 4H); **3 f**: 112°C; δ 1.08-1.59 (*m*, 10H), 2.44 (*s*, 3H), 3.09-3.27 (AB syst., J_{AB}=9.8 Hz, 2H), 3.17-3.24 (*dd*, J=11 and 2.5 Hz, 1H), 3.50-3.58 (*dd*, J=11 and 4.8 Hz, 1H), 3.70 (*br. s*, 1H, OH), 3.80-3.83 (*dd*, J=4.8 and 2.5 Hz, 1H), 7.30-7.75 (AA'BB' syst., 4H); **3 g**: 122°C; δ 0.99-1.67 (*m*, 10H), 1.10 (*s*, 3H), 1.21 (*br. s*, 1H, OH), 2.43 (*s*, 3H), 3.14-3.19 (*d*, J=9.9 Hz, 1H), 3.22-3.33 (AB syst., J_{AB}=10.6 Hz, 2H), 3.50-3.55 (*d*, J=9.9 Hz, 1H), 7.30-7.77 (AA'BB' syst., 4H); **3 h**: 154°C; δ 1.13-1.61 (*m*, 10H), 1.35 (*s*, 3H), 1.43 (*s*, 3H), 1.67 (*br. s*, 1H, OH), 2.43 (*s*, 3H), 2.87-2.92 (*d*, J=10 Hz, 1H), 3.36 (*s*, 1H), 3.44-3.49 (*d*, J=10 Hz, 1H), 7.26-7.76 (AA'BB' syst., 4H).
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10. $\nu_{(C=O)}$, (KBr) : **4** , 1707 cm^{-1}; **5** , 1755 cm^{-1}.
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16. We are indebted to a referee for this suggestion.

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