Use of Dioxiranes for the Chemoselective Oxidation of Tertiary Amines bearing Alkene Moieties

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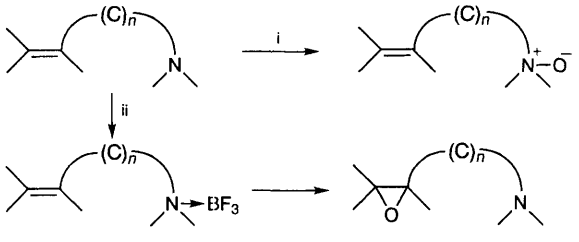
A neat and high yield chemoselective epoxidation of alkene moieties present in tertiary amines is accomplished by treatment of the corresponding amine–boron trifluoride adduct with dimethyldioxirane or methyl(trifluoromethyl)dioxirane.

The advantages offered by dimethyldioxirane (DMD)[1] and methyl(trifluoromethyl)dioxirane (TFMD)[2], *i.e.* their high ability to transfer oxygen atoms, ease of manipulation, possibility of working under mild reaction conditions and simple treatment of crude reaction mixtures, justify the numerous applications that these reagents have found in recent years. Among these applications, the epoxidation of C=C double bonds, the oxidation of heteroatoms (N, S, P) or the insertion into C–H bonds are prominent examples.[3–5]

Epoxidation of C=C double bonds in molecules bearing amino groups is troublesome due to the high tendency of the nitrogen atom to undergo preferential oxidation. This is true when conventional oxidation methods, for instance peroxyacids, are used, but it is also observed in the case of dioxiranes. In this context, Reetz and Lauterbach reported the epoxidation of γ-amino unsaturated esters by using *tert*-butyl hydroperoxide anion,[6] and Boyd *et al.* described the epoxidation of dihydroquinoline derivatives by means of sodium hypochlorite under phase-transfer conditions.[7] On the other hand, Asensio *et al.* reported recently an elegant method for the hydroxylation of amino derivatives with TFMD by performing the reaction in a protic acid medium. By this procedure, the amino group was protected from oxidation and the oxygen insertion could take place at a C–H bond.[8] In the case of epoxidations, however, this procedure cannot be used due to the sensitivity of epoxides to the acid medium. We envisaged that quaternisation of the amino moiety by formation of an adduct with a non-protic Lewis acid could circumvent the above problem (Scheme 1). In the present communication, our preliminary results on this approach are presented. It is worth noting that double-bond epoxidation of aminoalkenes such as those studied in this work is of interest for the generation of suitable intermediates for the preparation of natural products, such as indole alkaloids.[9] In these strategies, the poor results obtained by carrying out the epoxidation with conventional peroxyacids is also documented.[10,11]

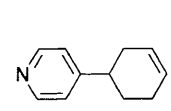
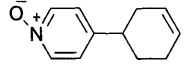
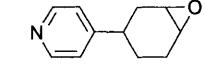
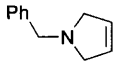
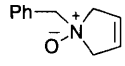
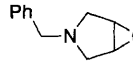
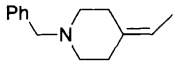
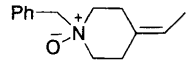
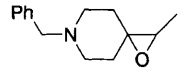
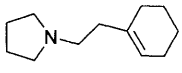
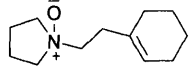
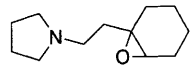
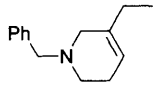
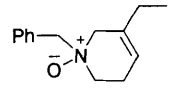
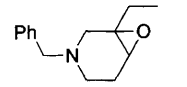
As shown in Table 1 (Method A), reaction of selected tertiary amines with DMD[12] at 0 °C led to the quantitative formation of the corresponding *N*-oxide derivatives. Nevertheless, the pyridine derivative (Table 1, entry 1) constituted the only case where the *N*-oxide could be epoxidised by further treatment with excess DMD. In all the other cases studied, the epoxidation of the *N*-oxide was not observed even by using either MCPBA or the more powerful TFMD reagent.†

The epoxidation of the alkene moieties present in the selected tertiary amines was carried out by using the method B shown in Table 1. Thus, treatment of the amine with an equimolecular amount of boron trifluoride in diethyl ether at −70 °C led to the precipitation of the corresponding adduct. This compound was thoroughly dried under vacuum to avoid the presence of residual diethyl ether,‡ before it was allowed to react with DMD or TFMD under mild neutral conditions. When the epoxidation was completed, the solvents were removed under vacuum, the residue was redissolved in the minimum amount of acetone and the free base containing the epoxy moiety was released and



Scheme 1 *Reagents and conditions* i, DMD–acetone, 0 °C; ii, BF_3·Et_2O, −70 °C then DMD or TFMD, CH_2Cl_2–acetone, 0 °C then $KHCO_3$

Table 1 Oxidation of tertiary amines containing alkene moieties by using dioxiranes

Entry	Substrate	Method[a]	Oxidation reagent	Product[b]	Isolated yield (%)
1		A	DMD		
		B	DMD		> 95[c]
2		A	DMD		
		B	TFMD		82
3		A	DMD		
		B	TFMD		70
4		A	DMD		
		B	DMD		85
5		A	DMD		
		B	TFMD		97

[a] Method A: DMD–acetone, 0 °C. Method B: i, BF_3·Et_2O, 70 °C; ii, Removal of Et_2O under vacuum; iii, DMD or TFMD, CH_2Cl_2–acetone, 0 °C; iv, $KHCO_3$. [b] Conversion into the *N*-oxides was quantitative. The *N*-oxide derived from entry 1 was the only one that could be converted into the corresponding epoxy derivative by treatment with excess DMD. [c] This epoxide was formed in near quantitative yield as determined by GC and ^1H NMR in the presence of an internal standard. However, although stable in solution, partial decomposition of this compound was observed throughout the different isolation procedures assayed, which lowered the yield of pure product to 30–45%.

recovered by partition of this solution with 1 mol dm^{-3} $KHCO_3$ and an organic solvent. By this procedure, good to excellent overall yields of the expected epoxides were obtained.§ In fact, only the epoxide derived from the pyridine analogue (Table 1, entry 1) showed high sensitivity to this work-up procedure (see footnotes in Table 1).

The above epoxidation procedure deserves some additional comments. First, the convenience of using dioxiranes for this purpose was evidenced by observing that the epoxidation of the BF_3 adduct derived from the 1-benzyl-1,2,5,6-tetrahydropyridine derivative (Table 1, entry 5) with MCPBA was incomplete and only low yields of the corresponding epoxide could be isolated. On the other hand, and as expected from the different reactivities among both dioxiranes, epoxidations carried out with TFMD took place at higher rates and usually gave higher yields than those performed with DMD. However, there was one case, *i.e.* entry 3, where *only* TFMD was capable of epoxidising the double bond present in the corresponding BF_3 adduct. We rationalise this fact by the deactivating inductive effect of the quaternised nitrogen atom on the alkene moiety. Moreover, the slow reaction of the adduct derived from the tetrahydropyridine derivative (Table 1, entry 5) with DMD, which could be also circumvented by the alternative use of TFMD for performing this epoxidation, supports the above hypothesis.

In summary, we believe that the procedure reported herein might constitute a simple and valuable tool for the epoxidation of alkene moieties present in amino derivatives. Reactions involved are easy to perform, neat and the expected epoxides could be isolated in high conversion yields. The use of epoxy derivatives related to those depicted above as synthons for the construction of bioactive natural products is under investigation in our laboratories.

Financial support from CICYT-Generalitat de Catalunya (Grant QFN-92-4304) and from CICYT (Grant AGF 178/92) are acknowledged.

Received, 24th October 1994; Com. 4/06503D

Footnotes

† In fact, we noticed that these *N*-oxides caused the deactivation of the dioxirane reagent. Whether this process could be related to the well studied decomposition of TFMD induced by iodide[13] or to an alternative mechanism is under current investigation.

‡ The decomposition of dioxiranes promoted by simple dialkyl ethers has been recently reported by us.[14]

§ All new epoxides were characterised by spectral means (^1H and ^{13}C NMR, MS) and, whenever the stability of the compounds made it possible, elemental analysis.

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