Epoxidation with Pyridine–Trifluoroacetic Anhydride–Molecular Oxygen and Mechanistic Aspects

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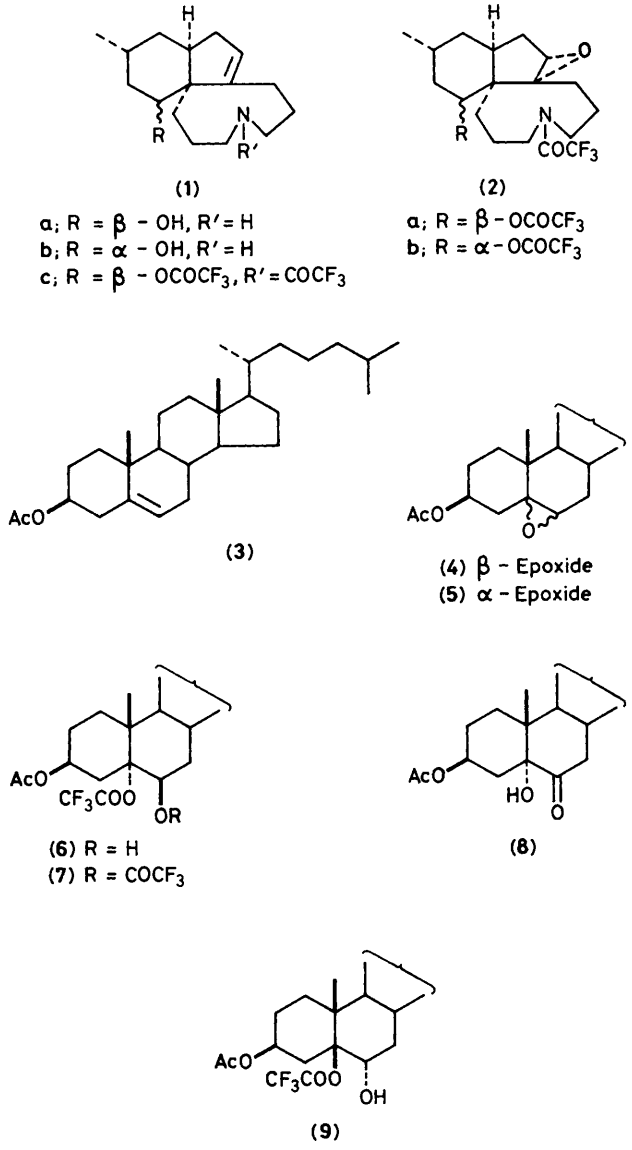
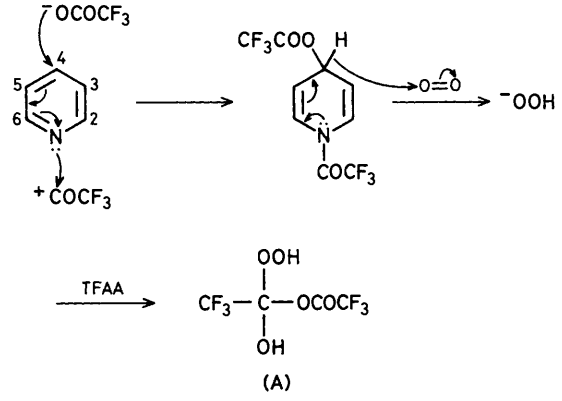
Epoxidation of cholesteryl acetate with pyridine–trifluoroacetic anhydride–molecular oxygen is described and one of the possible mechanisms is presented.

We have reported that reaction of the alkene (**1**) with pyridine (py)–trifluoroacetic anhydride (TFAA) overnight gave the epoxide (**2**) stereoselectively and was accelerated in an atmosphere of oxygen (O_2).[1] We describe herein epoxidation (oxidation) of cholesteryl acetate (**3**) by the present method (py–TFAA–O_2) and mechanistic aspects.

Oxidation of (**3**) with py–TFAA–O_2 at 35 °C for 4 h gave the β-epoxide (**4**)[2] (5.3%), α-epoxide (**5**)[2] (7.5%), hydroxy trifluoroacetate (**6**)† (65%), and bistrifluoroacetate (**7**) (11.5%), which was rapidly hydrolysed to (**6**) (83.3%) with sodium bicarbonate in methanol.‡ The β-epoxide (**4**) was treated with py–TFAA for 1 h at room temperature to give (**6**) (73.0%). Its ^{1}H n.m.r. spectrum showed the signals due to a proton *geminal* to a hydroxy group at δ 4.62 (1H, m, $w_{1/2}$ 8 Hz), suggesting that the newly introduced hydroxy group is *axial*. Oxidation of (**6**) with Jones' reagent, followed by aluminium oxide chromatography gave the hydrolysed product, hydroxy-ketone (**8**), m.p. 230—233 °C (81.0%).[3,4] On the other hand, (**5**) was treated with py–TFAA for 4 h at room temperature to give (**9**) (18.5%) along with the starting material (60.0%). The ^{1}H n.m.r. spectrum of (**9**) showed the signal due to a proton *geminal* to the hydroxy group at δ 4.80 (1H, m, $w_{1/2}$ 10 Hz), suggesting that the hydroxy group is *axial*. These results indicate that an initial epoxidation of (**3**) to (**4**) and (**5**) and a subsequent diaxial cleavage of the epoxide ring of the more reactive (**4**) afforded (**6**) and (**7**), and



† All new compounds gave satisfactory accurate mass and other spectral data (n.m.r. and i.r.).



Scheme 1

Table 1. The results of epoxidation of (**1c**) to (**2a**).[a]

Base	Yield of (**2a**)	Base	Yield of (**2a**)
Pyridine	58% (3 h)	2,6-Lutidine	—[b]
2-Picoline	—[b]	3,5,-Lutidine	trace[b]
3-Picoline	67% (120h)	Quinoline	—[b]
4-Picoline	—[b]	2,4,6-Collidine	—[b]
2,4-Lutidine	—[b]	3-Cyanopyridine[c]	—[b]

[a] Reactions were carried out with 15 mg of (**1c**), 3 ml of base, and 2 ml of TFAA under oxygen atmosphere for 24 h at room temperature, unless otherwise noted.
[b] The starting material was recovered in 75—83% yield.
[c] MeCN was used as solvent.

‡ A spot corresponding to (**9**) was observed on t.l.c. of reaction products, but could not be fully characterized. In this connection, exposure of several compounds containing a monosubstituted or disubstituted alkene to these reaction conditions resulted in the recovery of starting materials.

consequently epoxidation by the present method produced (**4**) preferentially [(**4**) : (**5**) 11 : 1] in comparison with epoxidation by *m*-chloroperbenzoic acid [(**4**) : (**5**) 3 : 7].[2]

In order to investigate the mechanism (active species) of this reaction, the effect of substituents on the pyridine ring in the epoxidation of (**1c**) to (**2a**) was investigated. The results are listed in Table 1. As can be seen from Table 1, pyridine itself is the most effective base for epoxidation, which is apparently influenced by the pattern of substitution on the pyridine ring. Since neither (**1c**) nor (**3**) was oxidized under conditions of TFAA–O_2 or py–O_2 then py, TFAA, and O_2 must be essential for this epoxidation and O_2 works as an indirect oxidant. Therefore, we present the mechanism shown in Scheme 1 as one possible mechanism, involving the hydroperoxide intermediate (A)[5,6] generated from TFAA and the hydroperoxide anion formed by reduction of O_2 *via* a process similar to NADH reduction.

Received, 18th February 1985; Com. 199

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