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Peracid oxidation of chiral isoxazolidines: developments and perspectives

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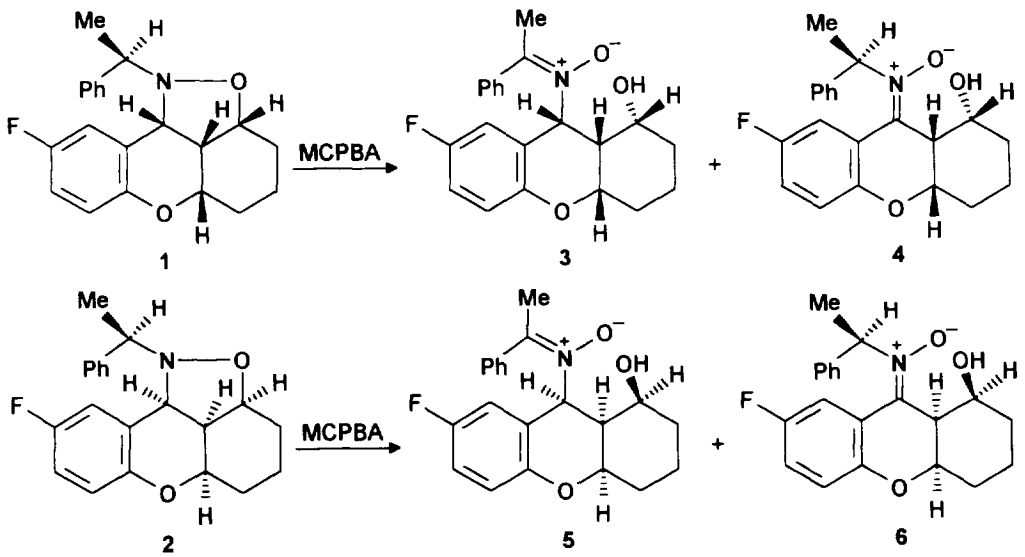
Abstract: Oxidative cleavage of chiral non-racemic isoxazolidines by 3-chloroperbenzoic acid leads to a pair of isomeric nitrone derivatives, both of which were isolated in enantiopure form. © 1997 Elsevier Science Ltd

The long-known isoxazolidines are receiving great attention as versatile intermediates in organic syntheses.[1,2] Their reaction with peracids was first reported some time ago[3] and has been later described in other papers.[4–9] However, in our opinion, neither stereochemical aspects nor the synthetic potential of this reaction have been explored exhaustively. Hence, we have undertaken a further investigation of the behaviour of isoxazolidines towards peracids by using the chiral non-racemic substrates **1** and **2**, the synthesis of which has been recently performed in our laboratory.[10]

Results and discussion

The diastereoisomeric substrates **1** and **2** were submitted to reaction with 3-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature. In each case, the reaction gave a pair of isomeric nitrone derivatives (Scheme 1).



Scheme 1.

All products **3–6** were isolated in the pure state and fully characterized. Their enantiomeric purity was monitored by ^{1}H-NMR at 300 MHz in the presence of Eu(hfc)$_3$

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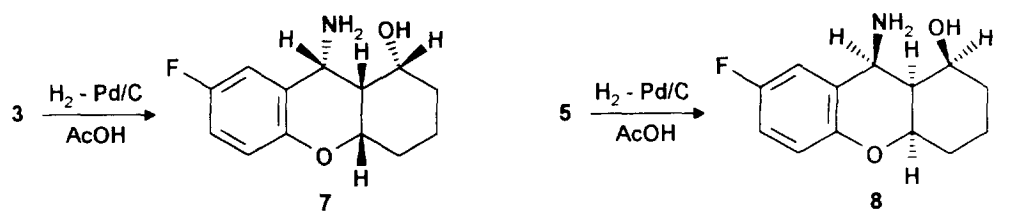
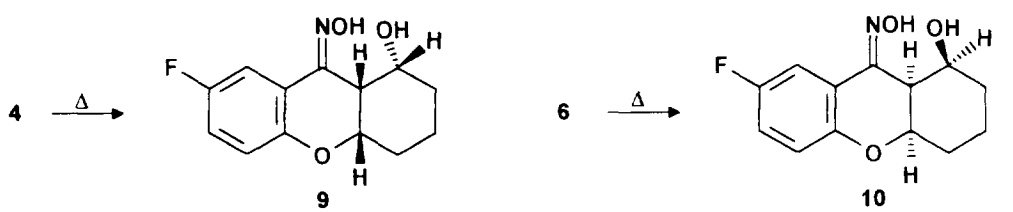
[tris{heptafluoropropylhydroxymethylene-(+)-camphorato}europium-(III)] and was found to be total within the experimental error limits.

Although the observed pattern of behaviour somewhat reflects the literature data,[4–9] a few points are worthy of note. In spite of the long reaction times, the room temperature and the stoicheiometric amount (rather than a large excess) of MCPBA were essential in order to prevent the decomposition of the nitrone species. Thus, a series of pure, optically active nitrones could be isolated. The second point is concerned with the modest degree of site-selectivity in relation to the migrating hydrogen. Previous evidence on this aspect reveals a wide variability,[3–9] which however finds rationalization on considering that methylenic hydrogens are more prone towards migration than methynic ones, but little discrimination can be operative when only one kind of hydrogen is available.

As illustrated in Scheme 2, the catalytic hydrogenation of the enantiomeric substrates **3** and **5** determined concomitant reduction of the nitrone functionality and removal of the benzyl-like pendant, so resulting in aminoalcohols **7** and **8**, which were proven enantiomerically pure by ^{1}H-NMR in the presence of (*R*)-*O*-acetylmandelic acid. Such hydrogenation seemed unreasonable in the case of **4** and **6** because a complex mixture of diastereoisomeric products could have been expected. On the other hand, the thermolysis of nitrones **4** and **6** gave the enantiomeric β-hydroxyketoximes **9** and **10** (Scheme 3), according to a precedented Cope-type elimination pattern.[11,12]



Scheme 2.



Scheme 3.

In the light of the results here presented, the oxidative cleavage of chiral non-racemic isoxazolidines by MCPBA can be devised as a source of optically active, highly functionalized intermediates of multiform reactivity.

Experimental section

Melting points were determined using a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin–Elmer 1725X spectrophotometer. ^{1}H-NMR spectra were obtained using a Bruker 300 MHz apparatus; chemical shifts are given in ppm from $SiMe_4$, with coupling constants in Hz. Mass spectra were obtained with a VG-70EQ apparatus. The optical rotations were measured using a Perkin–Elmer 241 polarimeter, with a 1 dm pathlength at 25°C.

*Reaction of isoxazolidine **1** with MCPBA*

A solution of **1** (0.40 g, 1.17 mmol) in dichloromethane (30 ml) was treated with MCPBA (0.22 g, 1.30 mmol) and stirred for 7 days at room temperature. The mixture was washed with 5% $NaHCO_3$

solution (50 ml), then with satured $Na_2S_2O_5$ (50 ml) and dried on Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel column with light petroleum/ethyl acetate 3:1 as eluent. The first fractions gave (−)-(αR,1R,4aS,9aR)-*N*-(7-fluoro-1,2,3,4,4a,9a-hexahydro-1-hydroxy-9*H*-xanthen-9-yliden)-α-phenylethanamine *N*-oxide **4** (100 mg, 23%). M.p. 153–154°C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.50–1.80 (2H, m), 1.86 (3H, d, *J*=6.5), 1.89–2.00 (4H, m), 2.25–2.35 (1H, m), 3.04 (1H, br s), 3.86–3.92 (1H, m), 4.37 (1H, br s), 5.63 (1H, q, *J*=6.5), 6.84 (1H, dd, *J*=5.0, 9.0), 7.00 (1H, ddd, *J*=3.1, 9.0, 9.0), 7.29–7.46 (5H, m), 9.64 (1H, dd, *J*=3.1, 12.0); $[\alpha]_D^{25}$=−37.1 (c=0.23 $CHCl_3$); IR (nujol): 3340 cm^{-1}; MS: *m/z*=355 (M^+); Anal. Calcd. for $C_{21}H_{22}FNO_3$: C, 70.95; H, 6.24; N, 3.94. Found: C, 70.91; H, 6.27; N, 3.87. The last fractions gave (−)-(1R,4aS,9R,9aR)-7-fluoro-1,2,3,4,4a,9a-hexahydro-1-hydroxy-*N*-(1-phenylethyliden)-9*H*-xanthen-9-amine *N*-oxide **3** (80 mg, 18%). M.p. 76–78°C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.40–1.60 (2H, m), 1.81–1.86 (1H, m), 2.06–2.20 (4H, m), 2.56 (3H, s), 4.02 (1H, br s), 4.22 (1H, br s), 5.15 (1H, br s), 5.77 (1H, d, *J*=7.6), 6.76 (2H, m), 6.86 (1H, ddd, *J*=3.1, 8.8, 8.8), 7.30–7.33 (2H, m), 7.46–7.52 (3H, m); $[\alpha]_D^{25}$=−2.5 (c=0.94 $CHCl_3$); IR (nujol): 3340 cm^{-1}; MS: *m/z*=355 (M^+); Anal. Calcd. for $C_{21}H_{22}FNO_3$: C, 70.95; H, 6.24; N, 3.94. Found: C, 71.01; H, 6.31; N, 3.99.

Reaction of isoxazolidine 2 with MCPBA

Compound **2** (0.46 g, 1.35 mmol) was treated with MCPBA (0.28 g, 1.62 mmol) as described in the preceding preparation. The crude product mixture was chromatographed on silica gel column with light petroleum/ethyl acetate 3:1 as eluent. The first fractions gave (+)-(αR,1S,4aR,9aS)-*N*-(7-fluoro-1,2,3,4,4a,9a-hexahydro-1-hydroxy-9*H*-xanthen-9-yliden)-α-phenylethanamine *N*-oxide **6** (70 mg, 14%). M.p. 161–162°C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.54–1.71 (2H, m), 1.84 (3H, d, *J*=6.6), 1.93–2.23 (5H, m), 2.95 (1H, dd, *J*=3.0, 3.0), 4.05–4.10 (1H, m), 4.28–4.33 (1H, m), 5.48 (1H, q, *J*=6.6), 6.83 (1H, dd, *J*=5.1, 8.9), 7.01 (1H, ddd, *J*=3.1, 8.9, 8.9), 7.27–7.44 (5H, m), 9.65 (1H, dd, *J*=3.1, 12.0); $[\alpha]_D^{25}$=+21.2 (c=0.28 $CHCl_3$); IR (nujol): 3350 cm^{-1}; MS: *m/z*=355 (M^+); Anal. Calcd. for $C_{21}H_{22}FNO_3$: C, 70.95; H, 6.24; N, 3.94. Found: C, 70.89; H, 6.31; N, 3.88. The last fractions gave **5** (140 mg, 35%). Physical and spectroscopic data were the same as for **3**. $[\alpha]_D^{25}$=+3.7 (c=0.27 $CHCl_3$).

Hydrogenation of nitrone 3

10% Pd/C (65 mg) was added to a solution of **3** (145 mg, 0.43 mmol) in AcOH (9 ml). The mixture was stirred under H_2 for 24 h. After filtration through celite, the solvent was evaporated under reduced pressure. The residue was treated with 0.5N NaOH and extracted with CH_2Cl_2. The organic phase was dried on Na_2SO_4 and evaporated to give pratically pure (−)-(1R,4aS,9R,9aR)-9-amino-7-fluoro-1,2,3,4,4a,9a-hexahydro-9*H*-xanthen-1-ol **7** (76 mg, 77%). M.p. 133–134°C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.50–1.65 (3H, m), 1.69 (3H, br s), 1.88–2.04 (3H, m), 2.14–2.23 (1H, m), 4.25 (1H, d, *J*=7.5), 4.33 (2H, overlapping), 6.70 (1H, dd, *J*=4.9, 8.8), 6.78 (1H, ddd, *J*=3.0, 8.8, 8.8), 7.18 (1H, dd, *J*=3.0, 8.8); $[\alpha]_D^{25}$=−77.6 (c=0.15 $CHCl_3$); IR (nujol): 3360, 3280 cm^{-1}; MS: *m/z*=237 (M^+); Anal. Calcd. for $C_{13}H_{16}FNO_2$: C, 65.79; H, 6.80; N, 5.91. Found: C, 65.72; H, 6.72; N, 5.85.

Hydrogenation of nitrone 5

According to the procedure described for **3**, compound **5** (170 mg, 0.48 mmol) gave pratically pure **8** (97 mg, 86%). Physical and spectroscopic data were the same as for **7**. $[\alpha]_D^{25}$=+80.0 (c=0.18 $CHCl_3$).

Thermolysis of nitrone 4

A solution of **4** (140 mg, 0.39 mmol) in toluene (50 ml) was refluxed for 21 h. After evaporation of the solvent, the residue was chromatographed on silica gel column with ethyl acetate as eluent to give (+)-(1R,4aS,9aR)-7-fluoro-1,2,3,4,4a,9a-hexahydro-9-hydroxyimino-9*H*-xanthen-1-ol **9** (0.50 g, 51%). M.p. 138–139°C (diisopropyl ether); ^{1}H-NMR ($CDCl_3$) δ 1.49–1.76 (3H, m), 1.94–2.05 (2H, m), 2.21–2.29 (1H, m), 3.32 (1H, dd, *J*=3.2, 3.2), 4.19–4.22 (1H, m), 4.40–4.48 (1H, m), 6.86 (1H, dd, *J*=4.8, 8.8), 6.95 (1H, ddd, *J*=3.1, 8.8, 8.8), 7.31 (1H, br s), 7.57 (1H, dd, *J*=3.1, 8.8); $[\alpha]_D^{25}$=+155.6

(c=0.21 $CHCl_3$); IR (nujol): 3590, 3420 cm^{-1}; MS: *m/z*=251 (M^+); Anal. Calcd. for $C_{13}H_{14}FNO_3$: C, 62.14; H, 5.62; N, 5.57. Found: C, 62.03; H, 5.72; N, 5.51.

Thermolysis of nitrone ***6***

According to the procedure described for **4**, compound **6** (120 mg, 0.34 mmol) gave **10** (40 mg, 47%). Physical and spectroscopic data were the same as for **9**. $[\alpha]_D^{25}=-153.0$ (c=0.20 $CHCl_3$).

Acknowledgements

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