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The Stereospecific Synthesis of a New Chiral Oxaziridinium Salt.

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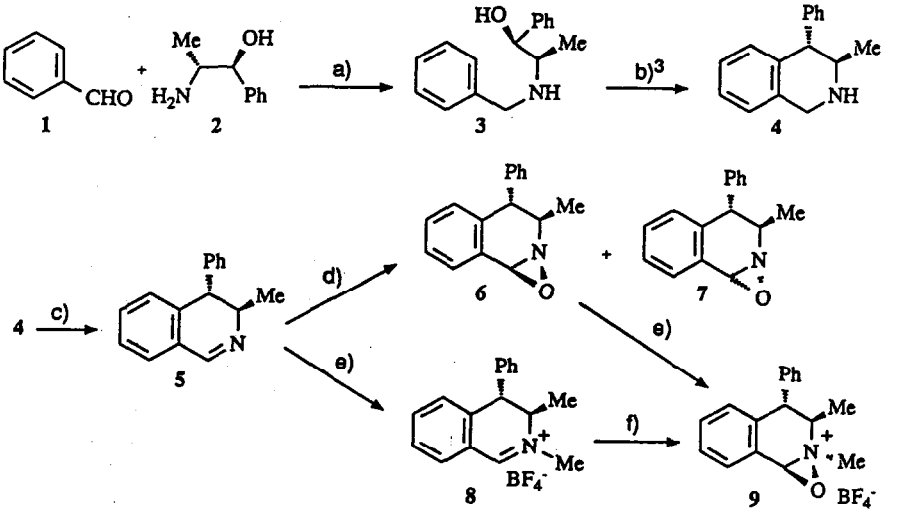
Abstract: A new chiral oxaziridinium salt has been prepared from (1S, 2R)-(+)-norephedrine. Enantioselective oxygen transfers to prochiral olefins and sulfides may be performed either stoichiometrically or in a catalytic cycle.

The fact that oxaziridinium salts are efficient electrophilic oxygen-atom transfer reagents either onto olefins[1a] or onto sulfides[1b] and that such reactions can be performed by *in situ* generated oxaziridinium salts from a catalytic amount of iminium salts and oxone[2], incited us to search for an oxaziridinium salt which may be stereospecifically obtained by oxidation of the parent iminium salt. Such a reagent would allow to attempt enantioselective oxygen transfer reactions either stoichiometrically or better still in a catalytic cycle.

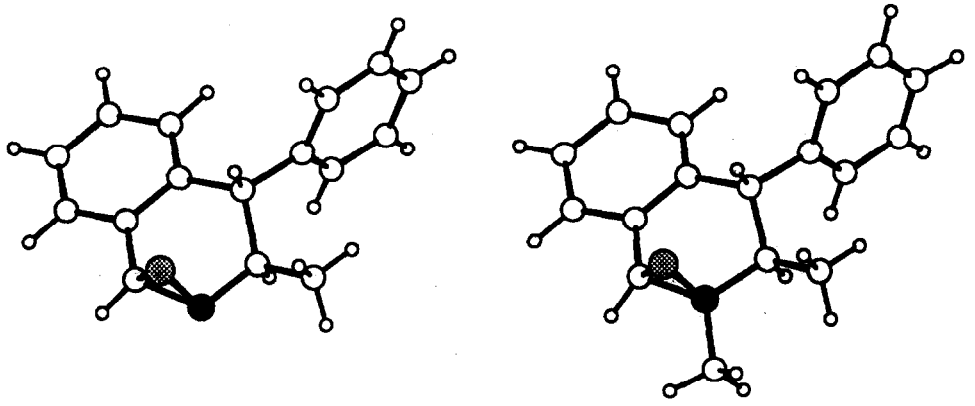
Thus, the enantiomerically pure oxaziridinium salt **9** has been prepared from (1S,2R)-(+)-norephedrine **2** as shown below, and we show that asymmetric epoxidations and oxidations of sulfides can indeed be performed with this reagent.



a) 1-$MgSO_4/CH_2Cl_2$; 2-$NaBH_4$/EtOH. b) CF_3CO_2H/SO_4H_2. c) 1-NaOCl ; 2-NaOMe. d) MCPBA/MeOH.
e) $Me_3O^+BF_4^-$/MeOH. f) p-nitrobenzoic acid (1.1 equiv) /$NaHCO_3$(0.1equiv.)

Two pathways leading to the oxaziridinium salt **9** can be followed from imine **5**. In the first (path **5** → **8** → **9**), the oxygen transfer from the peracid to the iminium salt **8** is stereospecific leading to the oxaziridinium salt **9** as a single product in high yield. In the second path (**5** → **6** → **9**), the peracidic oxidation of imine **5** is highly but not completely stereospecific leading to the oxaziridines **6** (main product) and **7** in the molar ratio 9/1. The two diastereoisomers have been isolated by column chromatography on silica gel.

Crystals of the oxaziridine **6**[4] [m.p. 89°C, $[\alpha]_D^{20}$ -14° (acetone)] and of the oxaziridinium **9**[4] [mp 124°C, $[\alpha]_D^{20}$ -60° (acetone)] have been obtained, and the structure of both compounds established by X-ray diffraction[5]. Both compounds show analogous conformations where the oxaziridine ring is axially oriented, being thus essentially perpendicular to the plane of the aromatic ring of the tetrahydroisoquinoline. The substituents 3-methyl and 4-phenyl are both equatorial. In the case of the oxaziridine **7**, the NMR spectra[4] show that the 3-methyl and the 4-phenyl are *trans* to each other and both are pseudoaxial, which is consistent with an oxaziridine ring also pseudoaxial as in compounds **6** and **9**.



6 **9**

Crystal structures of the oxaziridine **6** and of the oxaziridinium **9**.

Some preliminary experiments of oxygen transfer to prochiral substrates from compounds **6** and **9** have been performed. For example, an enantiomeric excess[8] of 33% was observed in the epoxidation of *trans*-stilbene with the oxaziridinium salt **9** either isolated or generated *in situ* from the iminium salt **8** in the catalytic conditions[7] previously described[2]. The enantiomeric excess[8] observed in the oxidation of methyl *p*-tolyl sulfide to sulfoxide was of 32% employing the oxaziridinium salt **9** as the oxygen transfer reagent and of 43% with the oxaziridine **6** in the presence

of trifluoroacetic acid under the conditions[8] which have been previously described[9].

These preliminary results demonstrate the possibility of performing enantioselective oxygen transfers employing an oxaziridinium salt. They are at present being completed by the oxidation of other prochiral model compounds and in addition the synthesis of other chiral oxaziridinium salts is under investigation.

On the other hand, to carry out enantioselective oxygen transfers via oxaziridinium salts generated in situ by oxidation of a catalytic amount of a chiral iminium salt, the oxygen transfer onto the iminium must be stereospecific. The knowledge of the factors that govern this stereospecificity can help the search for new chiral iminium reagents. Thus, the study of these factors seems relevant and is under progress.

References and notes

1. a) Hanquet G.; Lusinchi X.; Milliet P. *Tetrahedron Lett.* **1988**, *29*, 3941-3944.
   b) Hanquet G.; Lusinchi X.; *Tetrahedron Lett.* in press.

2. Hanquet G.; Lusinchi X.; Milliet P. *C.R.Acad.Sci.Paris* **1991**, *313*, *S.II*, 625-628.

3. The stereoselective cyclization reaction leading to amine **4** was carried out in the conditions described by Coote S.J. and Davies S.G. *J.Chem.Soc.,Chem.Commun.* **1988**, 648-649.

4. (1S,2R,3R,4S)-N-methyl-1,2-oxido-3-methyl-4-phenyl-1,2,3,4- tetrahydroisoquinolinium tetrafluoroborate **9**. m.p.=124°C (acetone/pentane), $[\alpha]_D^{20}$= -60° (c=0.1 acetone); MS(FAB) 252 (M^+·-tetrafluoroborate). ^{1}H NMR ($CDCl_3$, 200 MHz) : 1.53 (d 3H J=6 3-Me), 3.90 (s 3H N-Me), 3.98 (d 1H C_4-H J=10), 4.63 (dq 1H C_3-H J=6 J=10), 6.50 (s 1H C_1-H), 6.67 (m 1H arom.), 7.30 (m 3H arom.), 7.45 (m 4H arom.), 7.93 (m 1H arom.). ^{13}C NMR ($CDCl_3$, 50 MHz) : 14.14 (C_3-Me), 48.14 (C_3), 48.81 (C_4), 64.47 (N-Me), 87.81 (C_1),121.47, 128.77, 128.95, 129.40, 130.37, 130.57, 133.17, 134.05, 137.07, 137.65 (C arom.).

   Oxaziridine **6**: m.p.=89°C (pentane), $[\alpha]^D$= -14°. M.A.: Fd. C (81.07); H (6.29); N (5.58); O (6.65). Calcd. for ($C_{16}H_{17}NO$): C (80.98); H (6.37); N (5.90); O (6.70). ^{1}H NMR ($CDCl_3$, 200 MHz): 1.33 (d 3H, 3-Me J=6.5); 3.24 (dq 1H, C_3-H, J=6.5 J=9.8); 3.62 (d 1H, C_4-H, J=9.8); 5.13 (s 1H, C_1-H); 6.62 (m 1H, arom.); 7.15 (m 2H, arom.); 7.33 (6H, arom.); 7.60 (m 1H, arom.).
   Oxaziridine **7**: ^{1}H NMR ($CDCl_3$, 200 MHz): 1.20 (d 3H,3-Me,J=6.7); 4.05 (d 1H, C_4-H, J=1); 4.34 (dq 1H, C_3-H, J=1 J=6.7); 4.92 (s 1H, C_1-H); 6.94 (m 1H, arom.); 7.25 (m 4H, arom.); 7.47 (m 2H, arom.); 7.68 (m 1H, arom.).
   The C_3-H and C_4-H are weakly coupled (J=1Hz), which corresponds to an axial conformation for the 3-methyl, the 4-phenyl and the oxaziridine ring.

5. Riche C.; Chiaroni A.; Hanquet G.; Lusinchi M. To be published elsewhere.

6. *trans*-stilbene oxide: the e.e. was determined by comparing the optical rotation of the product with that reported in the literature[10] for pure R,R-(+)-*trans*-stilbene oxide, $[\alpha]_D^{20}$= +357° (c=0.59 benzene). In the stoichiometric epoxidation we found $[\alpha]_D^{20}$= +120° (c=0.87 benzene) for the product isolated in 76% yield. In the catalytic epoxidation we found $[\alpha]_D^{20}$= +117° (c=0.81 benzene) for the product isolated in 74% yield. The e.e. is thus 33% in both experiments. These equivalent results confirm that the epoxidazing agent under the catalytic conditions is the oxaziridinium salt.
   methyl *p*-tolyl sulfoxide: the e.e. was determined by integration of the two well resolved ($\Delta\delta$= 5Hz) S-methyl singlets observed in the ^{1}H NMR spectrum of the isolated sulfoxide (0.1 M in Cl_3CD, 400 Mz) when one equivalent of R-(+)-N-(3,5-dinitrobenzoyl)-α-phenethylamine[11] was added.

7. *trans*-stilbene (0.9g, 5mM); oxone (84% of "active oxygen" titrated by iodometry, 3.61g, 10mM); sodium bicarbonate (1.7g, 20mM), iminium salt **8** (0.08g, 0.25mM); acetonitrile (30ml); water (1ml).

8. methyl *p*-tolyl sulfide (52mg, 0.38mM); oxaziridine **6** (95mg, 0.38mg); trifluoroacetic acid (34µl, 0.45mM); chloroforme (8ml).

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