# Synthesis of Oxazolines from Epoxides

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Several epoxides have been converted into Δ^2-oxazolines by reaction with acetonitrile or benzonitrile in the presence of boron trifluoride–ether complex; yields are much higher than when reaction is brought about with sulphuric acid or tin(IV) chloride. The position of insertion of the nitrile and the stereochemistry of the ring enlargement are discussed.

SEVERAL substituted Δ^2-oxazolines possess valuable pharmaceutical properties.[1] This prompted us to explore the synthetic route from available alkenes, *via* their epoxides, and nitriles, shown in reaction (i), which is potentially attractive compared with the conventional, multi-stage methods.[1] Previous work has shown that the transformation in reaction (i) can be achieved in the presence of either concentrated sulphuric acid [2,3] or tin(IV) chloride.[4,5] However, the yields are usually low, in the range 10—40% under the latter conditions and not above 25% under the former. We have found, for a representative selection of epoxides with acetonitrile or in one case benzonitrile, that the use of the boron trifluoride–ether complex usually gives very high yields of the Δ^2-oxazoline.
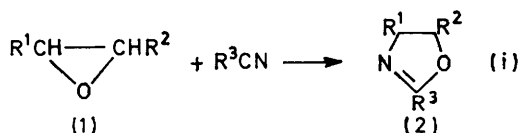
Reactions were carried out by stirring equimolar amounts of the epoxide and boron trifluoride–ether complex, with an excess of the nitrile as solvent, for 2 h at room temperature; yields are in the Table. The Δ^2-oxazolines were usually readily hydrolysed to the corresponding N-β-hydroxyethylcarboxamides, even just

when exposed to air for some weeks [reaction (ii)], and these solids provided appropriate derivatives for further characterisation in some cases.

$$(2) + H_2O \longrightarrow R^3CO \cdot NH \cdot CHR^1 \cdot CHR^2 \cdot OH \quad (ii)$$

Yields of Δ^2-oxazolines (2) from epoxides (1) and R^3CN

R^1	R^2	R^3	Yield (mol %)
Pr	Pr	Me	86 [a]
Ph	H	Me	45
H	4-MeC$_6$H$_4$·OCH$_2$	Me	77
[CH$_2$]$_4$ [b]		Me	77 [c]
[CH$_2$]$_4$ [b]		Ph	89

[a] *cis*-Configuration of propyl groups from corresponding *trans*-epoxide; see text. [b] Cyclohexene oxide as starting material. [c] *trans*-Derivative.

The position of the substituent in the oxazolines obtained from the monosubstituted alkenes with acetonitrile could be determined by n.m.r. spectroscopy, since the 2-methyl group gives a splitting of *ca.* 1·5 Hz with the proton(s) at C-4 but no detectable splitting with those at C-5.[3] Thus, the products from but-1-ene and styrene oxides gave doublet splittings (1·2 and 1·3 Hz, respectively), indicative of 4-substitution, whereas 3-(4-methylphenoxy)propene oxide gave a triplet (1·1 Hz), indicative of 5-substitution. Further, the oxazoline from styrene gave, on hydrolysis in air, CH$_2$(OH)·CHPh·NHAc and

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[2] R. Oda, M. Okano, S. Tokiura, and F. Misumi, *Bull. Chem. Soc. Japan*, 1962, **35**, 1219.

[3] R. A. Wohl and J. Cannie, *J. Org. Chem.*, 1973, **38**, 1787.

[4] T. I. Temnikova and V. N. Yandovskii, *Zhur. org. Khim.*, 1968, **4**, 178.

[5] Y. Hayashi, S. Ueda, and R. Oda, *J. Chem. Soc. Japan*, 1969, **90**, 946.

not PhCH(OH)·CH$_2$·NHAc, again consistent with its formulation as the 4-phenyl compound. In addition to the 4-ethyl-2-methyl-Δ^2-oxazoline from but-1-ene oxide, there was evidence (g.l.c.–mass spectrometry) for the formation of about 10% of the 5-ethyl isomer.

The n.m.r. spectrum of the oxazoline from *trans*-oct-4-ene oxide exhibited multiplets at low field for the H-4 and -5. When the sample was irradiated so as to decouple the methylene protons adjacent to those positions, the multiplets were resolved into an approximate AB quartet with $J_{4,5}$ 9 Hz, and the full spectrum was satisfactorily simulated on this basis. This coupling constant is in accord with a *cis*-disposition of the propyl groups in the oxazoline; were they *trans*, a value of *ca.* 6 Hz would be anticipated.[3,6] The oxazoline from cyclohexene oxide and acetonitrile was shown to have *trans*-stereochemistry by n.m.r. examination of the 2-acetoxycyclohexyl-ammonium salt obtained by treatment with hydrogen chloride; the spectrum showed couplings for each methine proton of 10, 10, and 5 Hz, consistent with each being axial and interacting, respectively, with the other methine proton and the axial and equatorial protons of the adjacent methylene group.

The stereospecificity shown by the formation of the *cis*-dipropyloxazoline from *trans*-oct-4-ene oxide and the *trans*-substituted oxazoline from cyclohexene oxide is consistent with a mechanism in which the complex (3) undergoes an S_N2 reaction with the nitrile to yield the species (4) and thence, after C–C rotation, the oxazoline (5) (*cf.* the mechanism suggested for the proton-catalysed reaction [3]). However, this would not be consistent with the preferred formation of the 4-ethyloxazoline from but-1-ene oxide; S_N2 displacement would be expected to occur preferentially at the unsubstituted carbon atom, to give the 5-ethyloxazoline. On the other hand, unimolecular ring opening of the complex (3) to yield a carbocation, although compatible with the behaviour of both but-1-ene and styrene oxides (*cf.* ref. 2), is not compatible with the observed stereochemistry. The

observations can be reconciled if ring opening occurs unimolecularly, the oxygen substituent then acting as a neighbouring group to maintain the stereochemistry, as represented by the structure (6), until reaction with the nitrile yields (4). However, the reaction is probably delicately balanced between the S_N1 and S_N2 limits; thus, 3-(4-methylphenoxy)propene oxide, the 4-MeC$_6$H$_4$·-OCH$_2$ substituent in which can be only weakly electron-attracting compared with ethyl, gives the 5-substituted oxazoline.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured for solutions in deuterio-chloroform (except where stated) on a Perkin-Elmer R10 or Varian A60 60 MHz spectrometer. Analytical and preparative g.l.c. were carried out on a Pye instrument (series 104, model 24) with 5 ft columns packed with 10% Apiezon L coated on Celite. Mass spectra were determined on an A.E.I. MS12 spectrometer which could be coupled *via* a heated capillary tube to the gas chromatograph.

trans-Oct-4-ene oxide was prepared from the alkene with peracetic acid in dichloromethane (*cf.* ref. 7) and had b.p.

(3)   (4)   (5)

(6)

SCHEME

43—44° at 14 mmHg (lit.,[8] 67° at 34 mmHg). All other materials were available commercially. Boron trifluoride-ether complex was distilled before use.

Procedure.—Equimolar amounts (typically 0·01 mol) of the epoxide and boron trifluoride–ether complex in the appropriate nitrile as solvent (typically 10—15 ml) were stirred at room temperature for 2 h. The mixture was poured into aqueous sodium hydrogen carbonate and the dichloromethane extract was washed, dried (MgSO$_4$), and evaporated to leave the oxazoline as a viscous oil. Pure samples were obtained by preparative g.l.c. and used to calibrate the analytical column, for which *p*-nitrotoluene was used as internal standard.

Reactions with acetonitrile. *trans*-Oct-4-ene oxide gave 2-methyl-*cis*-4,5-dipropyl-Δ^2-oxazoline (only one peak on g.l.c.); *m/e* 169 (M^+); τ 5·4—5·9 (1H, m), 6·0—6·4 (1H, m), 8·15 (3H, d, J 1·2 Hz, 2-Me), 8·25—8·9 (8H, m, CH$_2$), and 8·9—9·25 (6H, m, remaining Me); decoupling, by irradiation

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[8] D. E. Bissing and A. J. Speziale, *J. Amer. Chem. Soc.*, 1965, **87**, 2683.

at the frequency of the CH_2 groups adjacent to the ring, yielded an approximate ABq from the two resonances at lowest τ (J 9 Hz). When exposed to air for several weeks, this oxazoline yielded N-(2-*hydroxy*-1-*propylpentyl*)*acetamide*, m.p. 153—155° after sublimation (Found: C, 64·2; H, 11·1; N, 7·4. $C_{10}H_{21}NO_2$ requires C, 64·1; H, 11·3; N, 7·5%).

Styrene oxide gave 2-methyl-4-phenyl-Δ^2-oxazoline (only one peak on g.l.c.); m/e 161 (M^+); τ 2·8 (5H, s, ArH), 4·7—6·15 (3H, m, CH and CH_2), and 7·95 (3H, d, J 1·3 Hz, Me). In air this yielded N-(2-hydroxy-1-phenylethyl)-acetamide, m.p. 122—124° (from ethanol) (lit.,[9] 123—124°); on admixture with N-(2-hydroxy-2-phenylethyl)acetamide [prepared by reduction of the corresponding ketone with sodium borohydride;[10] m.p. 120—122° (lit.,[11] 120—122°)] the m.p. was depressed to 90—95°.

3-(4-Methylphenoxy)propene oxide gave 2-*methyl*-5-(4-*methylphenoxymethyl*)-Δ^2-oxazoline; m/e 205 (M^+); τ 3·15 (4H, q, ArH), 5·1—5·6 (1H, m, 5-H), 6·1 (2H, d, J 6·5 Hz, side-chain CH_2), 6·2—6·4 (2H, m, ring CH_2), 7·7 (3H, s, Me on phenoxy), and 8·1 (3H, t, J 1·1 Hz, 2-Me). In air this gave N-[2-*hydroxy*-3-(4-*methylphenoxy*)*propyl*]*acetamide*, m.p. 94·5—95·5° (from ethyl acetate) (Found: C, 64·5; H, 7·6; N, 6·2. $C_{12}H_{17}NO_3$ requires C, 64·6; H, 7·7; N, 6·3%).

Cyclohexene oxide gave 3a,4,5,6,7,7a-hexahydro-2-methylbenzoxazole (only one peak on g.l.c.); m/e 139 (M^+);

τ 5·9—7·3 (2H, m, 3a- and 7a-H), 8·05 (3H, d, J 1·6 Hz, Me), and 7·6—9·2 (8H, m, CH_2). Hydrogen chloride was bubbled through a solution of this oxazoline in ethyl acetate to give, after evaporation and sublimation at 181° at 18 mmHg, trans-2-*acetoxycyclohexylammonium chloride*, m.p. 218—220° (decomp.) (lit.,[12] 213—213·5° for *cis*-isomer); τ 5·25 and 6·7 (each 1H, d of d of d, J 10, 10, and 5 Hz), 7·85 (3H, s, Me), and 7·7—9·1 (8H, m, CH_2) (Found: C, 49·2; H, 8·2; N, 7·05. $C_8H_{16}ClNO_2$ requires C, 49·6; H, 8·3; N, 7·2%).

But-1-ene oxide gave 4-ethyl-2-methyl-Δ^2-oxazoline (containing *ca.* 10% of the 5-ethyl isomer as estimated by g.l.c.); τ 5·6—6·8 (3H, m, 4- and 5-H), 8·1 (3H, d, J 1·2 Hz, 2-Me), 8·2—8·8 (2H, m, CH_2), and 9·05 (3H, t, J 7 Hz, other Me).

Reaction with benzonitrile. Cyclohexene oxide gave 3a,4,5,6,7,7a-hexahydro-2-phenylbenzoxazole (only one peak on g.l.c.); m/e 201 (M^+). This was dissolved in ether and treated with hydrogen chloride in ether to precipitate the *hydrochloride*, m.p. 175—177° after sublimation; τ 1·7—2·8 (5H, m, ArH), 5·1 (1H, s, NH), 5·1—6·2 (2H, m, 3a- and 7a-H), and 7·3—8·8 (8H, m, CH_2) (Found: C, 65·45; H, 6·8; N, 5·9. $C_{13}H_{16}ClNO$ requires C, 65·7; H, 6·8; N, 5·9%).

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