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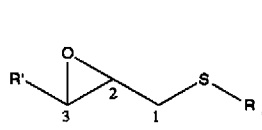
Lewis Acid Induced Reaction of 2,3-Epoxy Phenylsulphoxides.

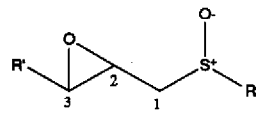
Christopher M. Rayner* and Andrew D. Westwell
School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K..

Abstract: The regio- and stereocontrolled hydrolysis of diastereomerically pure 2,3-epoxy phenylsulphoxides *via* novel sulphoxonium salts generated under Lewis acidic conditions is described.

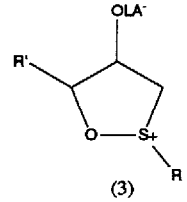
The ability of the Sharpless asymmetric epoxidation[1] to produce a wide variety of optically active 2,3-epoxy alcohols has lead to their exploitation as valuable synthetic intermediates.[2] The readily prepared 2,3-epoxy sulphides (1), have however been little investigated.[3] The control of regioselectivity in the epoxide opening reaction is a particularly important aspect of the chemistry of these substrates, often a mixture of products resulting from nucleophilic attack at C-2 and C-3 being observed.[2b] As part of a general investigation in this area, we wish to report some novel chemistry of 2,3-epoxy sulphoxides (2) including the regiospecific hydrolysis at C-3.



(1)



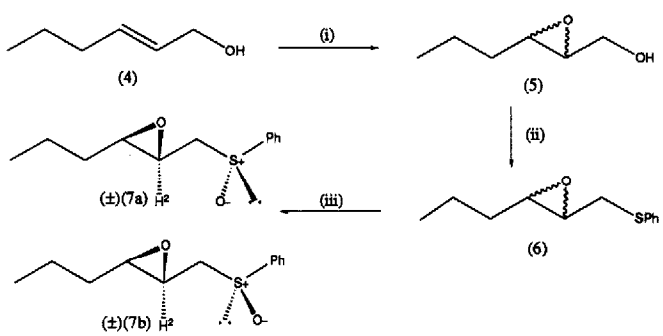
(2)



(3)

It is well known that sulphoxides may participate as neighbouring groups in a number of reactions.[4] We wished to investigate the feasibility of formation of sulphoxonium salts of the type (3) by intramolecular nucleophilic ring opening of the epoxide by the sulphoxide oxygen in the presence of a Lewis acid (LA). Subsequent reaction of these salts with nucleophiles (e.g. H_2O) would then be expected to occur at the sulphur atom, proceeding with inversion of configuration according to literature precedent.[5a]

The 2,3-epoxy sulphoxide precursors were synthesised as shown in scheme 1.

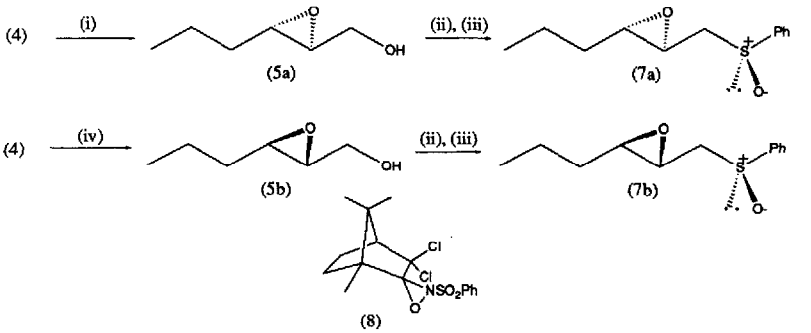


Reagents: i, $VO(acac)_2$, CH_2Cl_2, ^tBuOOH, 86% yield; ii, PhSSPh, PBu_3, Pyridine, 87% yield; iii, $VO(acac)_2$, CH_2Cl_2, ^tBuOOH, 4 days, -40°C, 84% yield.

Scheme 1.

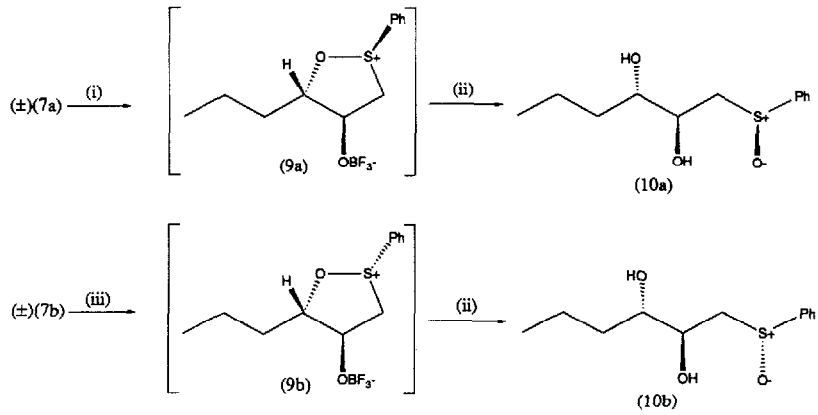
Epoxidation of commercially available allylic alcohol (4) gave the racemic 2,3-epoxy alcohol (5). Formation of the phenyl thioether (6)[6] followed by oxidation gave the racemic 2,3-epoxy sulphoxides (7a) and (7b) as a 1:1 mixture. These were readily separable by column chromatography [SiO_2, 30% ethyl acetate/petrol(b.p. 40-60°C) eluant] and their stereochemistry assigned as shown in scheme 1, initially on the basis of their 300MHz ^1H NMR spectra.[7]

Of particular importance for this were the signals due to H-2. In the case of (7a), in its lowest energy conformer H-2 (δ 3.12 ppm) is in an approximately 1,3-parallel orientation with the sulphoxide group. Although the molecule would be rather flexible, on average this would result in a deshielding of this hydrogen due to the known anisotropy of the sulphoxide group.[8] In the case of (7b) however, much smaller effects would be expected for H-2 and this is reflected in its chemical shift (δ 2.83 ppm). This assignment is also consistent with the chemical reactivities of (7a) and (7b) (*vide infra*). In order to confirm this stereochemical assignment, the individual diastereoisomers were synthesised by a double enantioselective oxidation route (scheme 2).



Reagents: i, $Ti(O^iPr)_4$, CH_2Cl_2, ^{t}BuOOH, L-(+)-DET, 69% yield; ii, PhSSPh, PBu_3, pyridine; iii, (8), CCl_4, 0°C; iv, $Ti(O^iPr)_4$, CH_2Cl_2, ^{t}BuOOH, D-(-)-DET, 63% yield.

Scheme 2.



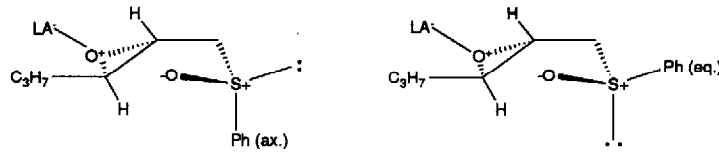
Reagents: i, $BF_3.Et_2O$, Et_2O, -78°C→room temperature, 16 hours; ii, $NaHCO_3$ (aq.); iii, $BF_3.Et_2O$, Et_2O, -78°C→room temperature, 40 mins..

Scheme 3.

Asymmetric epoxidation of (4) using L-(+)-Diethyl tartrate (DET) as the chiral auxiliary[1] gave (5a)[>96%e.e.#], conversion to the phenyl thioether as before, and oxidation with (-) α,α-dichlorocamphorsulphonyloxaziridine[9] gave optically active (7a)(64% yield after purification, ratio 7a:7b, 13:1) as the major product in accord with the known enantioselectivity of the two oxidation systems. Similarly, asymmetric epoxidation using the enantiomeric tartrate [D-(-)-DET] gave (5b) [>96% e.e.#] which was converted into the alternative diastereoisomer (7b)(59% yield after purification, ratio 7a:7b,1:7) as above. Treatment of the separated racemic diastereoisomers with a Lewis acid ($BF_3.OEt_2$) followed by aqueous base was then carried out (scheme 3).

Thus (7a) underwent slow conversion (>5 hours) to the sulphonium salt (9a) on warming to room temperature as determined by tlc analysis. Hydrolysis gave the 2,3-dihydroxy sulphoxide (10a) as a single diastereoisomer (99% yield from (7a)). Similarly, treatment of (7b) under identical conditions gave a relatively rapid conversion (<40 min. at room temperature) to (9b) and hydrolysis as before gave (10b) as a single diastereoisomer (93% yield).

The relative rates of these processes may be rationalised by consideration of the necessary conformations for reaction (figure 1).

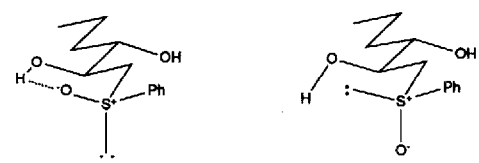


Reactive conformer for (7a) Reactive conformer for (7b)

Figure 1.

In the case of (7a), for the molecule to adopt the necessary alignment of the sulphoxide oxygen with the breaking C-O epoxide bond, the phenyl group on the sulphur atom must adopt a relatively high energy pseudoaxial orientation. However for (7b), the phenyl group is in a pseudoequatorial orientation. This results in a lower energy transition state for (7b) and hence a faster reaction. This is in full accord with our initial stereochemical assignments.

The products of these reactions also show properties consistent with the predicted stereochemical pathway for the reaction. From earlier work on β-hydroxy sulphoxides by Brunet *et. al.*[10], the hydrogen bonding properties of these molecules would depend on the relative stereochemistry of the β-hydroxyl group and the sulphoxide. Figure 2 shows likely conformations of (10a) and (10b)[8c].



Conformation of (10a) Conformation of (10b)

Figure 2.

In the case of (10a), hydrogen bonding between the sulphoxide group and the β–hydroxyl group would be expected to occur. Physical and spectroscopic data are consistent with this.[10-13] Further proof was obtained by X-ray crystallographic analysis of (10b) (figure 3).

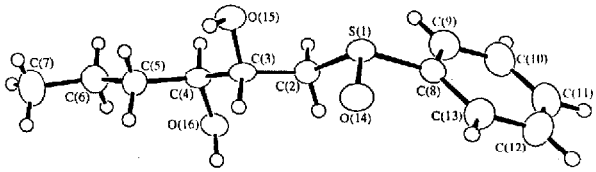


Figure 3. X-ray structure of (10b).

The observed stereochemical outcome of the reaction is good evidence for the intermediacy of the sulphoxonium salts (9) with hydrolysis occurring at the sulphur atom with inversion of configuration. Further investigations into the reactions of such intermediates are currently underway.[14]

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7. ^{1}H NMR ($CDCl_3$, 300MHz); (7a) δ 0.88 (3H, t, J 7.0Hz, CH_3), 1.30-1.50 (4H, m, CH_2CH_2), 2.69 (1H, dt, J 5.0, 2.1Hz, H-3), 2.90, 2.93 and 3.12 (3H, ABX system, J 13.9, 4.9, 6.7Hz, CH_2-1, CH-2 respectively), 7.43-7.56 (3H, m, ArH), 7.60 (2H, dd, J 7.5, 1.9Hz, ArH); (7b) δ 0.93 (3H, t, J 7.0Hz, CH_3), 1.35-1.60 (4H, m, CH_2CH_2), 2.83 (1H, dt, J 5.4, 2.4Hz, H-2), 2.87 (1H, dt, J 4.2, 2.4Hz, H-3), 3.01 (1H, dd, J 13.5, 5.1Hz, one of CH_2-1), 3.12 (1H, dd, J 13.5, 5.9Hz, remaining CH_2-1), 7.50-7.60 (3H, m, ArH), 7.67 (2H, dd, J 2.0, 7.4Hz, ArH).
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12. ^{1}H NMR ($CDCl_3$, 300MHz); (10a) δ 0.95 (3H, t, J 7.1Hz, CH_3), 1.2-1.7 (4H, m, CH_2CH_2), 2.63 (1H, d, J 4.9Hz, HO-CH-3), 2.90 (1H, dd, J 13.5,2.5Hz, one of CH_2-1), 3.10 (1H, dd, J 13.5, 8.2Hz, remaining CH_2-1), 3.73-3.76 (1H, m, CH-3), 4.03 (1H, d, J 2.6Hz, HO-CH-2), 4.20-4.26 (1H, m, CH-2), 7.50-7.70 (5H, m, ArH); m.p. 66-67.5°C (EtOAc/light pertrol); (10b) δ 0.85 (3H, t, J 7.1Hz, CH_3), 1.10-1.50 (4H, m, CH_2CH_2), 2.23 (1H, d, J 3.7Hz, HO-CH-3), 2.60 (1H, dd, J 13.8, 1.5Hz, one of CH_2-1), 3.30 (1H, dd, J 10.0, 13.9Hz, remaining CH_2-1), 3.61-3.72 (1H, m, CH-3), 3.95-4.05 (1H, m, CH-2), 4.15 (1H, d, J 2.8Hz, HO-CH-2), 7.48-7.72 (5H, m, ArH), m.p. 96-97.5°C, (benzene).
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14. All new compounds were characterised by ^{1}H and ^{13}C NMR, IR, and mass spectra, and gave satisfactory elemental analysis and/or accurate mass spectra.
Enantiomeric excess determined by ^{1}H NMR using $Eu(hfc)_3$ on the corresponding acetate.

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