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# DIASTEREOCONTROLLED SYNTHESIS OF CYCLOPROPANE PHENYL SULFOXIDES.

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Abstract. Good diastereocontrol of three stereocentres is obtained in the synthesis of cyclopropane phenyl sulfoxides.



We recently reported[1] that in the dealkoxycarbonylation of dimethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate, 3-alkylthio or 3-arylthio substituents induce moderate diastereoselection leading to mixtures of the isomeric monoesters in the average trans-cis ratio of 2:1. Analogous sulfonyl derivatives led in excellent yields to the trans derivatives with pratically 100 % of E diastereoselectivity. These results prompted us to examine the reaction of decarbalkoxylation of the dimethyl 2,2-dimethylcyclopropane-3-phenylsulfinyl-1,1-dicarboxylate 2a, 3a with the aim of controlling the

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stereochemistry of the three diastereocentres present in 4 and 5 (Scheme).

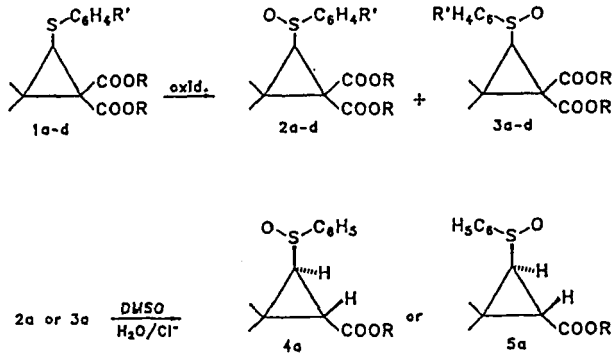
To achieve this goal it was essential to control the oxidation step as it was immediately realized that the decarboxylation of a mixture of isomers 2a, 3a took place with E diastereoselectivity better than 97-98%.

Directing effects in the oxidation of sulfides to sulfoxides by hydroxyl[2] and amino[3] groups have previously been reported, as well as by carboxylic acid groups and their amide derivatives.[4,5]

The reasons for this specificity are not completely clear and most often hydrogen bonding effects are invoked, although steric control[6] has also been considered to be important. In this paper we report that one can easily control the diastereoselectivity of the oxidation of the sulfur atom of derivatives 1 by a careful choice of the oxidizing agent and the nature of the substituents R and R'.

Oxidation of 1a (Scheme) with one equivalent of hydrogen peroxide in methanol in the presence of a catalytic amount of ammonium molybdate afforded a 95% yield of a mixture of two diastereoisomeric sulfoxides in the relative percentage of 70:30. Structural assignment was initially made on the basis of the NMR chemical shifts ($CDCl_3$) of the methyl and the methoxyl groups. It is well established[7] that protons lying in the vicinity of an S-O bond are normally deshielded,

SCHEME

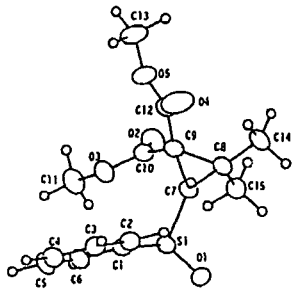



a : R = $CH_3$; R'= H ; c : R = $CH_3$; R' = 2-$COOCH_3$

b : R = R'= H ; d : R = $CH_3$; R' = 2-COOH

and we therefore tentatively assigned the configuration 2a to the isomer present in higher concentration(70%) and the configuration 3a to the other. As a matter of fact 2a exhibits two methyl signals both at lower fields (δ 1.36 and δ 1.64) than the corresponding signals of the isomer 3a (δ 1.06 and δ 1.42 ). Furthermore the methoxy signals of 2a are both at higher fields (δ 3.62 and δ 3.78 ) than the analogous signals of 3a (δ 3.68 and δ 3.84 ) as expected . The isomers 2a and 3a were isolated pure as solids by chromatography on a silica gel column using a mixture of diethyl ether-light petroleum 1:1 as eluent.The structure of 2a, unambiguosly determined by X-ray crystallographic analysis, was in perfect agreement

FIGURE




ORTEP Stereoview of the sulfoxide 2a



with the attribution we have made on the basis of NMR analysis.

The compound crystallizes in the orthorhombic spacegroup $Pna2_1$ with a=12.309 (3)A°, b=13.086 (3)A° , c=19.470 (5)A° and Z=8. The non hydrogen atoms were located by direct methods. Full matrix least-squares refinement led to a conventional R=0.056 after several cycles of anisotropic refinement. An ORTEP view of the molecule is shown in the figure. The diastereoselectivity obtained in the oxidation of 1a with the system $H_2O_2$-ammonium molybdate in methanol is very likely dependent on steric reasons. When the same reaction was carried out using one equivalent of m-chloroperoxybezoic acid in methylene chloride at -8°C the same diastereoisomeric mixture of sulfoxides was obtained but this time 3a was the major product (70%) (Table ). This inversion of diastereoselection could

TABLE

| Sulfide | Sulfoxide | Method | Ratio 2:3 | Yield[a] % |
|---|---|---|---|---|
| 1a | 2a-3a | B | 30:70 | 95 |
| 1a | 2a-3a | B[b] | 60:40 | 94 |
| 1a | 2a-3a | c | 70-30 | 55 |
| 1a | 2a-3a | A | 80-20[d] | 94 |
| 1b | 2b-3b | A | 40-60[e] | 77 |
| 1b | 2b-3b | B | 30-70[e] | 67 |
| 1c | 2c-3c | A | 98-2 | 98 |
| 1c | 2c-3c | B | 60-40 | 70 |
| 1d | 2d-3d | A | 98:2 | 98 |
| 1d | 2d-3d | B | 60-40 | 80 |

a)Isolated yields of mixture of isomers.

b)Methanol as a solvent.

c)Hydrogen peroxide (1 equiv.) in acetic acid at R.T. for 20 h.

d)Chromatography of 2 g of the mixture of sulfoxides on a silica gel column using diethyl ether-light petroleum(1:1) as eluent afforded 1g (62% yield) of 2a and 0.12g (30% yield) of 3a.

e)2b and 3b were prepared as pure samples in 70% yield by basic hydrolysis of pure 2a and 3a following experimental conditions of ref.1.

suggest that when m-chloroperoxybenzoic acid is used the oxygen atom is delivered on the same side of the ester group,despite the higher steric hindrance, as a consequence of hydrogen bonding between the peracid hydrogen atom with one or both the ester groups.

If the oxidation is carried out with m-ClPBA in methanol or with $H_2O_2$-$CH_3COOH$ the composition of the diastereoisomeric mixture is again inverted, with 2a the isomer present in higher percentage. In both methanol and acetic acid hydrogen bondings between the solvent and the peracid are strongly competitive with hydrogen bonding between 1a and the peracid, thus reducing the level of diastereocontrol induced by the ester groups. As a consequence, the diastereoselection is again controlled by steric factors and the oxygen atom is delivered preferentially by the same side of the methyl groups. The importance of the steric factors is further strengthened by the diastereoselection[8] obtained (100%) in the oxidation of 1c and 1d with $H_2O_2$/ammonium molybdate-methanol. Again, performing the oxidation with mCPBA in methylene chloride gives a mixture of isomers probably as a consequence of the ester groups ability to hydrogen bond with the peracid. The oxidation of 1b, easily obtained[1] by basic hydrolysis of 1a, leads to mixtures, difficult to separate, of the two possible sulfoxides of which 3b

is the major component. By repeated crystallizations from methanol-water small quantities of the two isomers have been obtained in poor yields (see table for an alternative synthesis of 2b and 3b by hydrolizing the esters 2a and 3a ).

Finally, decarbalkoxylation in DMSO/$H_2O$/NaCl of 2a and 3a, separated[9] by column chromatography, occurs with remarkable 100 % E diastereoselectivity leading cleanly to good yields of 4a and 5a (Scheme) to which the trans geometry has been assigned on the basis of the vicinal protons coupling constants[10].

The sequence of reactions gives access to a set of sulfoxides with remarkable control of the geometry of compounds with two or three diastereocenters. Easy manipulation of the ester function should give access to families of cyclopropyl sulfoxides of known configuration.

## EXPERIMENTAL

General.I.R. spectra were recorded on a Perkin Elmer spectrometer and $^1$H-NMR spectra on a Varian FT-80A spectrometer. Elemental analysis were carried out on a Carlo Erba model 1106 Element analyzer. All melting points are uncorrected.Products 1a-d have been previously described.[1]

General oxidation procedures of cyclopropanes 1a-d

Method A : To a stirred solution of derivatives 1a-d (6 mmol) in MeOH (10 ml) at -8/-10 °C, in the presence of ammonium molybdate[11] (10 mg), 35% $H_2O_2$ (6mmol) is slowly added. The mixture is kept at this temperature for 2h and then stirred for 15h at room temperature.

It is then poured into brine (30 ml) and extracted with chloroform (3x30 ml). The organic layer is dried over anhydrous sodium sulfate. Filtration and evaporation gave the crude sulfoxides which are purified by column chromatography ( silica gel, diethyl ether - light petroleum 1:1 ) and crystallized from an appropriate solvent.

Method B: To a stirred solution of 1a-d (6 mmol) in $CH_2Cl_2$ (10 ml) at -8 °C, MCPBA (6 mmol) is added portionwise. Stirring is continued for 20 h at room temperature. After washing with 10% $NaHCO_3$ (2x25 ml), the solution is dried over sodium sulfate and evaporated. The crude sulfoxides are purified as in method A. In the case of 1b and 1d the relative sulfoxides are filtered after spontaneous precipitation from the reaction mixture.

Decarbalkoxylation of 2a and 3a.

A mixture of the pure sulfoxide 2a or 3a (10 mmol), NaCl (10 mmol), DMSO (25 ml) and $H_2O$ (1,8 ml) is refluxed for 4h until the end of $CO_2$ evolution. It is

then poured onto brine (50 ml) and extracted with diethyl ether (3x50 ml). The organic solution, after drying ($Na_2SO_4$) and evaporation afforded 1,7g of the crude product 4a or 5a (70 %). Chromatography on a silica gel column using diethyl ether light petroleum (1:1) afforded 4a or 5a in a pure state.

Spectral data of compounds 2a-d,3a-d,4a,5a

2a m.p.77-78° (Hexane-aceton); IR(nujol) 1730, 1750, 1045 $cm^{-1}$; NMR($CDCl_3$) δ 1.36 (s,3H), 1.64 (s,3H), 3.05 (s,1H), 3.62 (s,3H), 3.78 (s,3H), 7.55 (m,5H). Anal. Calcd. for $C_{15}H_{18}O_5S$: C 58,06; H 5.80. Found:C 58.15; H 5.87.

2b m.p. 184° (Methanol-water); IR ( nujol ) 1702, 1722, 945, NMR ($CDCl_3$) δ 1.23 (s,3H), 1.53 (s,3H), 2.76 (s,1H), 7.65 (m,5H), 11.10 (broad signal, 2H, $D_2O$ exchangeable). Anal. Calcd. for $C_{13}H_{14}O_5S$: C 55.32;H 5.00. Found: C 55.29; H 5.00.

2c m.p.104° (Aceton-light petroleum); IR (nujol) 1720, 1750, 1760, 1040 $cm^{-1}$; NMR ($CDCl_3$) δ 1.08 (s,3H), 1.67 (s,3H), 3.09 (s,1H), 3.70 (s,3H), 3.82 (s,3H), 3.88 (s,3H), 7.90 (m,4H). Anal. Calcd. for $C_{17}H_{20}O_7S$: C 55.43; H 5.47. Found: C 54.95; H 5.56.

2d m.p. 165-167° (Ethanol-water); IR(nujol) 1710, 1730, 1750, 1050 $cm^{-1}$; NMR δ ($CDCl_3$) 1.17 (s,3H), 1.66 (s, 3H), 3.27 (s, 1H), 3.67 (s, 3H), 3.76 (s, 3H), 7.40 (s, 1H, $D_2O$ exchangeable), 7.77 (m, 4H). Anal. Calcd.

for $C_{16}H_{18}O_7C$ 54.24; H 5.21. Found: C54.05; H 5.10.

3a m.p. 59 °C ( Hexane - aceton ) ; IR (nujol ) 1730, 1750, 1040; NMR ($CDCl_3$) δ 1.06 (s,3H); 1.42 (s,3H); 2.95 (s,1H); 3.68 (s,3H); 3.84 (s,3H); 7.55 (m,5H).

3b m.p. 178 °C ( methanol - water ); NMR ($CDCl_3$) δ 0,95 (s,3H); 1.35 (s,3H); 2.70 (s,3H); 7.65 (m,5H); 11.10 (broad signal, 2H, $D_2O$ exchangeable). Anal. Calcd. for $C_{13}H_{14}O_5$ S: C 55.32; H 5.00. Found: C 55.35; H 5.10.

3c[12] NMR ($CDCl_3$) δ 1.10 (s,3H); 1.75 (s,3H); 3.08 (s,1H); 3.65 (s,3H); 3.81 (s,3H); 3.99 (s,3H); 7.90 (m,4H).

3d[12] NMR ($CDCl_3$) δ 1.11 (s,3H), 1.75 (s,3H), 3.14 (s,1H), 3.60 (s,3H), 3.76 (s,3H), 7.50 (broad signal, $D_2O$ exchangeable, 1H), 7.70 (m,4H).

4a m.p.92° (Ethanol-water); IR (nujol) 1745, 1045 $cm^{-1}$; NMR ($CDCl_3$) δ 1.26 (s,3H), 1.56 (s.3H), 2.03 (d,1H, J=5.5 Hz), 2.80 (d, 1H, J=5.5 Hz), 3.55 (s,3H), 7.52(m,5H). Anal. Calcd. for $C_{13}H_{16}O_3S$: C 61.89, H 6.39. Found: C 61.46, H 6.43.

5a m.p. 48-50° ( Ethanol- water ); IR ( nujol ) 1750, 1040 $cm^{-1}$. NMR ( $CDCl_3$ ) δ 1.18 (s,3H), 1.48 (s,3H), 2.42 (d, 1H, J=5.5 Hz), 2.70 (d, 1H, J=5.5 Hz), 3.60 (s,3H), 7.55 (m,5H). Anal. Calcd. for $C_{13}H_{16}O_3S$: C 61.89, H 6.39. Found: C 61.55, H 6.35.

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11) In the case of 1b oxidation is carried out in the absence of ammonium molybdate.

12) Data worked out from unseparated mixtures of isomers.

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