

Asymmetric Induction in the Reduction of β -Oxosulphoximides by Sodium Borohydride

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Optically active β -oxosulphoximides have been prepared by reaction of optically active α -metallated *NS*-dimethyl-*S*-phenylsulphoximide with carboxylic esters. Their reduction by sodium borohydride is stereoselective, the extent of asymmetric synthesis (up to 50%) depending on steric factors.

TRANSMISSION of chirality from sulphur to carbon is a rapidly expanding research topic.¹ In our efforts to develop new methods of obtaining various kinds of optically active compounds, such as amines² and alcohols,³ starting from easily accessible sulphur derivatives, we were faced with a lack of knowledge of the factors which affect the extent of chiral discrimination. The nature of the asymmetric sulphur moiety should play a very important role; indeed *e.g.* kinetic resolution of unsaturated sulphoximides *via* addition of chiral amines is much more effective than that of the corresponding sulphoxides.⁴ To investigate this point further, we prepared a series of β -oxosulphoximides and examined their reduction by metal hydrides. The results were compared with those previously found in the asymmetric reduction of β -oxosulphoxides.³

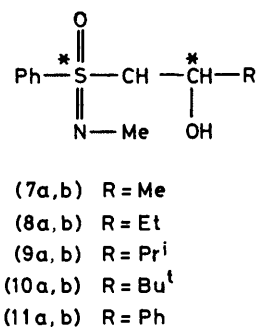
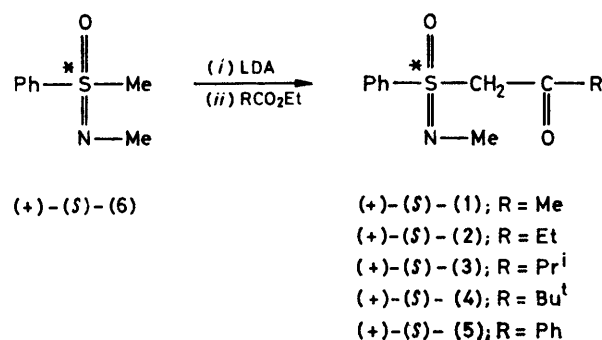
RESULTS AND DISCUSSION

Only one example of a β -oxosulphoximide has been reported,^{5,6} namely 1-phenyl-2-[*N*-(*p*-tolylsulphonyl)-methylsulphonimidoyl]ethanone, obtained by reaction of α -metallated, *SS*-dimethyl-*N*-(*p*-tolylsulphonyl)sulphoximide with benzonitrile and subsequent hydrolysis of the resulting enamine.⁶

We prepared a series of β -oxosulphoximides (1)–(5) in 50–70% yield by condensation of *N*-methylphenylsulphonimidoylmethyl-lithium with carboxylic esters (see Experimental section).

Starting from optically active (+)-(*S*)-*NS*-dimethyl-*S*-phenylsulphoximide (6), optically active derivatives (1)–(5) were obtained. Their (+)-(*S*)-absolute con-

shift-reagents, were unsuccessful, it can be assumed that it is very high, as previously observed³ in similar reactions involving different sulphur moieties.



The β -oxosulphoximides (1)–(5) on treatment with sodium borohydride afford the corresponding β -hydroxy-

TABLE I
Synthesis of optically active β -oxosulphoximides (1)–(5)

| Oxosulphoximide | [α] _D ²⁵ (°) ^a | n_D ²⁵ | Yield (%) | Found (%) | | | Formula | Requires (%) | | |
|-----------------|-------------------------------------------------------------|---------------------|--------------|-----------|-----|-----|---------------------------------------------------|--------------|------|------|
| | | | | C | H | N | | C | H | N |
| (1) | +143.4 | 1.5616 | 56 | 56.9 | 6.2 | 6.7 | C ₁₀ H ₁₃ NO ₂ S | 56.9 | 6.15 | 6.65 |
| (2) | +117.8 | 1.5507 | 67 | 58.7 | 6.7 | 6.2 | C ₁₁ H ₁₅ NO ₂ S | 58.6 | 6.7 | 6.2 |
| (3) | +156.9 | 1.5461 | 69 | 60.4 | 7.0 | 5.9 | C ₁₂ H ₁₇ NO ₂ S | 60.25 | 7.1 | 5.85 |
| (4) | +195.6 | 1.5378 | 49 | 61.6 | 7.6 | 5.5 | C ₁₃ H ₁₉ NO ₂ S | 61.65 | 7.5 | 5.55 |
| (5) | +131.7 | <i>b</i> | 50 | 65.9 | 5.5 | 5.1 | C ₁₅ H ₁₉ NO ₂ S | 65.95 | 5.5 | 5.15 |

^a *c* 2 in acetone. ^b M.p. 87 °C, from di-isopropyl ether.

figuration can directly be inferred from that of (6), since the chirality at sulphur is not affected in the reaction. Optical rotations, yields, and physical properties are reported in Table I. Although all attempts to determine the optical purity of (1)–(5), *e.g.* by using europium

sulphoximides (7a, b)–(11a, b) in almost quantitative yield. The reaction is stereoselective, the diastereoisomeric alcohols (7a, b)–(11a, b) generally being produced in unequal amounts (see Table 2). This indicates that [1,3] asymmetric induction from sulphur to carbon

is at work. Starting from the optically active derivatives (1)–(5), optically active compounds (7)–(11) were obtained. The degree of stereoselection was determined by ^1H n.m.r. analysis; the results are reported in Table 2. Conversion of β -oxosulphoximides into the corresponding hydroxy-derivative can also be effected with sodium borohydride adsorbed on alumina; the reaction is faster, but the diastereoisomeric ratios of the products do not change to any appreciable extent with respect to those observed in homogeneous conditions.

asymmetric carbon atom in the predominant diastereoisomers.

Two features of the present work deserve attention: (i) the nature of the chiral sulphur moiety exerts a leading role in determining the extent of asymmetric synthesis, as indicated by the comparison among β -oxosulphoximides and β -oxosulphoxides, the final outcome depending on a delicate balance of interactions with the other groups present in the molecule (see above); (ii) the sequence outlined above constitutes a simple

TABLE 2
Reduction of the β -oxosulphoximides (1)–(5) by NaBH_4 at -78°C ^a

| Oxosulphoximide | Product | $[\alpha]_D^{25}$ ($^\circ$) ^b | M.p. ($^\circ\text{C}$) (n_D^{25}) | Diastereoisomeric ratio ^{c,d} | Found (%) | | | Formula | Requires (%) | | |
|-----------------|---------|------------------------------------------------|---------------------------------------------|-------------------------------------------|-----------|-----|------|-------------------------------------------------|--------------|-----|-----|
| | | | | | C | H | N | | C | H | N |
| (1) | (7) | +103.9 $^\circ$ | (1.6628) | 50 : 50 | 56.0 | 7.1 | 6.5 | $\text{C}_{10}\text{H}_{15}\text{NO}_2\text{S}$ | 56.3 | 7.0 | 6.6 |
| (2) | (8a,b) | +144.5 $^\circ$ | (1.5463) | 44 : 56 | 58.2 | 7.6 | 6.2 | $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{S}$ | 58.15 | 7.5 | 6.2 |
| (3) | (9a,b) | +91.8 $^\circ$ | 101–102 | 40 : 60 | 59.7 | 7.9 | 5.75 | $\text{C}_{12}\text{H}_{19}\text{NO}_2\text{S}$ | 59.75 | 7.9 | 5.8 |
| (4) | (10a,b) | +81.3 $^\circ$ | 61–62 | 25 : 75 | 61.0 | 8.1 | 5.5 | $\text{C}_{13}\text{H}_{21}\text{NO}_2\text{S}$ | 61.2 | 8.2 | 5.5 |
| (5) | (11a,b) | +32.5 $^\circ$ | 95–96 | 30 : 70 | 65.3 | 6.3 | 5.05 | $\text{C}_{15}\text{H}_{17}\text{NO}_2\text{S}$ | 65.45 | 6.2 | 5.1 |

^a The reaction were carried on starting from 90% enantiomerically-enriched sulphoximides. ^b c 1 in acetone. ^c By ^1H n.m.r. spectroscopy. ^d Identical diastereoisomeric ratios were observed starting from racemic β -oxosulphoximides.

In the hydride reduction of (1)–(5) the transfer of chirality from sulphur to carbon depends on steric factors. It increases with increasing bulkiness of the substituent bonded to the carbonyl group along the series $\text{Me} < \text{Et} < \text{Pr}^i < \text{Ph} < \text{Bu}^t$. A different situation was previously encountered in the borohydride reduction of β -oxosulphoxides,³ the highest value of asymmetric induction (58%) being found in the case of the ethyl derivative *p*- $\text{MeC}_6\text{H}_4\text{SOCH}_2\text{COEt}$ and the lowest (20%) for the phenyl analogue *p*- $\text{MeC}_6\text{H}_4\text{SOCH}_2\text{COPh}$. Thus an appropriate selection of the inducing centre leads to higher values of chiral recognition with either more bulky or less bulky substituents.

Another striking difference is that lithium aluminium hydride, which constantly affords higher values of chiral recognition in the reduction of β -oxosulphoxides with respect to sodium borohydride, does not reduce β -oxosulphoximides. This is related to the fact that in the latter the keto-enol equilibrium is largely shifted toward the enol form, as indicated by their spectral properties (^1H n.m.r., i.r.).

(*SS*)-*N*-Methyl-*S*-(2-hydroxy-2-phenylethyl)-*S*-phenylsulphoximide (11a), $[\alpha]_D^{25} +43.3^\circ$ (c 1, acetone), was previously obtained by Johnson⁷ by reaction of (*S*)-(6) with benzaldehyde and fractional crystallization of the (40 : 60) diastereoisomeric mixture. This same compound is the predominant epimer obtained *via* reduction of (*S*)-(5). The (*SS*) absolute configuration can also tentatively be assigned to the predominant β -hydroxy-sulphoximides (7)–(10), on the basis of the constant pattern observed in the ^1H n.m.r. spectra of the products obtained by borohydride reduction of (1)–(5). Thus the major diastereoisomer always shows an upfield signal for the hydrogen α to the hydroxy group and a downfield signal for the *N*-methyl group with respect to the minor epimer. These data probably indicate a common magnetic environment for the ligands at the

synthesis of optically active β -hydroxysulphoximides, which can be used as ligands for asymmetric synthesis,⁸ or can be cleaved to optically active alcohols with aluminium amalgam.^{7,9}

EXPERIMENTAL

General.—Light petroleum had b.p. 40–60 $^\circ\text{C}$. Ether was dried over sodium, and tetrahydrofuran was distilled from lithium aluminium hydride. Di-isopropylamine was distilled from potassium hydroxide; *n*-butyl-lithium was used as *ca.* 2M solutions in hexane. Extractions were performed with dichloromethane and extracts were dried over sodium sulphate. I.r. spectra were recorded on a Perkin-Elmer 377 spectrometer; ^1H and ^{13}C n.m.r. spectra were recorded on a Varian HA 100 or a Varian A 390 instrument, with CDCl_3 as solvent and SiMe_4 as internal standard. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

Synthesis of β -Oxosulphoximides.—*n*-Butyl-lithium (5 mmol) in *n*-hexane was added dropwise at -78°C to a stirred solution of di-isopropylamine (4 mmol) in tetrahydrofuran (10 ml). The mixture was kept for 30 min below 0 $^\circ\text{C}$, cooled to -78°C , and *NS*-dimethyl-*S*-phenylsulphoximide (2 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to reach room temperature, cooled again to -78°C , and the ester (3 mmol) in tetrahydrofuran (5 ml) was added in one portion. The mixture was allowed to reach room temperature, refluxed for 12–35 h, and quenched with saturated aqueous ammonium chloride. The organic layer was separated off and the aqueous layer extracted with dichloromethane. The combined organic phases were concentrated at reduced pressure, and the residue was chromatographed on silica with ether-light petroleum as eluant. The racemic β -oxosulphoximides were obtained in 50–70% yield. The methyl derivative had n_D^{25} 1.560 5; the ethyl derivative had n_D^{25} 1.550 7; the isopropyl derivative had n_D^{25} 1.540 7; the *t*-butyl derivative had n_D^{25} 1.538 7; the phenyl derivative had m.p. 64–66 $^\circ\text{C}$. By repeating the reaction on optically active (+)-(*S*)-(6), prepared according to the

literature,⁷ optically active derivatives were obtained. Yields, specific rotations, and physical and analytical data are reported in Table 1.

Reduction of β -Oxosulphoximides to β -Hydroxysulphoximides.—*Method A.* The β -oxosulphoximide (1 mmol) in absolute ethanol (5 ml) was added at -78°C under nitrogen to a stirred solution of sodium borohydride (1 mmol) in absolute ethanol (5 ml). The mixture was kept at -78°C for 6 h. Methanol (5 ml) was then added and the solvent evaporated off *in vacuo*. Water and dichloromethane were added to the residue; the organic phase was washed with water and dried over sodium sulphate. Evaporation gave the product. Yields, specific rotations, diastereoisomeric ratios, and physical and analytical data are reported in Table 2.

Method B. Sodium borohydride adsorbed on neutral alumina was prepared by the literature method.¹⁰ The β -oxosulphoximide (1 mmol) in absolute ethanol (5 ml) was added at -78°C under nitrogen to a stirred suspension of the reagent (1 mmol) (10% w/w $\text{NaBH}_4\text{-Al}_2\text{O}_3$) and absolute ethanol (10 ml). The mixture was kept at -78°C for 4 h. The solid was filtered off and washed with absolute ethanol.

The combined organic phase was evaporated off *in vacuo* to give the product in almost quantitative yield.

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