Asymmetric Induction in the Reduction of β -Oxosulphoxides by Metal Hydrides

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A series of optically active β -oxosulphoxides has been prepared and their reduction by metal hydrides examined; when lithium aluminium hydride is used, the extent of asymmetric synthesis is in the range 60–70%.

REACTIONS of optically active sulphur derivatives generally result in a high degree of asymmetric induction, and consequently efforts have recently been devoted to the use of chiral sulphur units as synthons for various kinds of optically active compounds.¹⁻⁹

Although β -oxosulphoxides are well known and widely used in organic synthesis, surprisingly, only one compound, namely $(+)-(R)-\alpha-(p-tolylsulphinyl)$ acetophenone (1),¹ has been prepared in optically active form,

$$p-\text{MeC}_{6}\text{H}_{4}^{*}\text{SOMe} \xrightarrow[i]{i, RCO_{2} \text{ Et}}_{ii, RCO_{2} \text{ Et}} p-\text{MeC}_{6}\text{H}_{4}^{*}\text{SOCH}_{2}\text{COR}$$

$$(+)-(R)-(5) \qquad (+)-(R)-(1)-(4)$$

$$(1) R = Ph$$

$$(2) R = Et$$

$$(3) R = Pr^{i}$$

$$(4) R = Bu^{t}$$

$$p-\text{MeC}_{6}\text{H}_{4}^{*}\text{SOCH}_{2}^{*}\text{CHR} \qquad p-\text{MeC}_{6}\text{H}_{4}\text{SO}_{2}\text{CH}_{2}^{*}\text{CHR}$$

$$(4) R = Bu^{t}$$

$$(4) R = Bu^{t}$$

$$(6a,b) R = Ph$$

$$(10) R = Ph$$

$$(10) R = Ph$$

$$(10) R = Ph$$

$$(11) R = Et$$

$$(8a,b) R = Pr^{i}$$

$$(12) R = Pr^{i}$$

$$(9a,b) R = Bu^{t}$$

$$(13) R = Bu^{t}$$

and only its reaction with alkyl Grignard reagents, leading to mixtures of the corresponding diastereoisomeric alcohols in a 7:3 ratio, has been studied.¹ We have prepared a series of optically active β -oxosulphoxides and examined their reduction by metal hydrides to β -hydroxysulphoxides. Optically active β -oxosulphoxides could, in principle, be prepared either by reaction of α -sulphinyl carbanions derived from optically active sulphoxides with carboxylic esters or by Claisen-type condensation of optically active sulphinate esters with ketone enolate anions. However only the former proved to be successful, the latter leading to practically racemic derivatives.

From (+)-(R)-methyl-p-tolyl sulphoxide (5), $[a]_{p}^{25}$ +189.2° (CHCl₃), compounds (1), $[a]_{p}^{25}$ +180.9° (CHCl₃); (2), $[a]_{p}^{25}$ +210.0° (CHCl₃); (3), $[a]_{p}^{25}$ +191.5° (CHCl₃); and (4), $[a]_{p}^{25}$ +162.3° (CHCl₃), were obtained in 60-85% yield. Since the chirality at sulphur is not involved in the reaction, the absolute configuration of (1)-(4) can be inferred from that of (5) and established as (+)-(R). The optical purity of (1)-(4) was shown by ¹H n.m.r. analysis with the aid of the chiral shift reagent Eu(tfc)₃ [tris(trifluorocamphorato)europium] to be $\geq 95\%$.

The β -oxosulphoxides (1)—(4) can easily be reduced to the corresponding β -hydroxy derivatives (6)—(9) by metal hydrides such as sodium borohydride or lithium aluminium hydride. The reaction is stereoselective, the diastereoisomeric alcohols (6a, b)—(9a, b) being produced in unequal amounts. The reductions with sodium borohydride and lithium aluminium hydride were carried out at low temperature (-70 °C), since preliminary experiments showed that higher selectivity is obtained by decreasing the temperature. Furthermore at -70 °C reduction of the sulphoxide group to sulphide is avoided.

Starting from the optically active sulphoxides (1)— (4), optically active hydroxysulphoxides were obtained, which were oxidized to the corresponding optically active sulphones (10)—(13) (see Table 1). The occurrence of 1,3-asymmetric induction was established by ¹H n.m.r. analysis, with the aid of the shift reagent Eu(tfc)₃. In the reduction with lithium aluminium hydride, the transfer of chirality from sulphur to carbon is very high, the enantiomeric purity of (10)—(13) being in the

				Hydroxysulphone			
	Reducing	Hydroxysu	ulphoxide		Enantiomeric	M.p.	
Oxosulphoxide	agent "	[α] _D ²⁵ (°) ^b	Yield (%)	$[\alpha]_{D}^{25}(\circ)^{b}$	purity (%)	(t/°Ĉ)	
(1)	NaBH	(6), +124.7	86	(10), -4.0	20	73 - 75	
(2)	$NaBH_{\bullet}$	(7), +241.4	97	(11), -12.5	58	С	
(3)	$NaBH_4$	(8), +183.0	90	(12), -10.4	50	d	
(4)	$NaBH_4$	(9), +208.3	80	(13), -14.5	40	56 - 58	
(1)	$LiAlH_4$	(6), +115.0	93	(10), -11.5	60	8183	
(2)	LiAlH	(7), +260.0	85	(11), -14.6	68		
(3)	$LiAlH_4$	(8), +161.0	93	(12), -13.3	66		
(4)	LiAlH ₄	(9), +209.3	90	(13), -23.7	63	59 - 61	

TABLE 1 Reductions of the β -oxosulphoxides (1)—(4) by NaBH₄ and LiAlH₄ at -70 °C

^a Reductions with NaBH₄ were carried out in ethanol and reductions with LiAlH₄ in diethyl ether-tetrahydrofuran. ^b c 2, in chloroform. ^c n^{20} 1.5355. ^d n_D^{23} 1.5315.

range 60-70%, while in the reduction with sodium borohydride asymmetric induction is always lower and depends to a larger extent on the nature of the substrate.*

The use of chiral and achiral alkoxy-lithium aluminium hydrides,¹⁰ in the reduction of oxosulphides was also investigated. With compounds (1)—(3) it resulted only in lowering of the stereoselectivity. A few representative examples are reported in Table 2. A more obtained by partial reduction of racemic sulphoxides with chiral hydrides.¹²

Optically active hydroxysulphoxides are useful intermediates for the production, *inter alia*, of optically active alcohols 1,2 and epoxides.⁹ Both enantiomers of the sulphoxide (5), and hence of the oxosulphoxides (1)---(4), are easily accessible. Transfer of chirality from sulphur to carbon in the reduction of (1)---(4)

TABLE 2	
Reduction of the β -oxosulphoxides (1)—(3) by complex hydrides at -70 °C in diethyl et	her-tetrahydrofuran

				Hydroxysulphones		
			Hydroxysulphoxides Yield		Enantiomeric excess	 M.p.
Oxosulphoxide	Reducing agent ^a	$[\alpha]_{D^{25}}(^{\circ})^{b}$	(%)	$[\alpha]_{\mathbf{D}^{25}}(^{\circ})^{b}$	(%)	$(n_D^{\hat{2}0})$
(2)	LiAlH ₃ (OBornyl)	(6), +114.0	80	(10), -11.7	60	80-82 °C
(2) (3)	LiAlH ₃ (OMenthyl)	(7), +173.8	83	(11), -9.6	42	(1.5355)
(3)	LiAlH ₃ (OMenthyl)	(8), +179.2	73	(12), -6.9	33	(1.5307)
(3)	LiAlH(OBu ^t) ₃	(8), +189.9	80	(12), -5.0	20	(1.5312)
		<i>c</i> 2, in a	chloroform.			. ,

interesting situation was encountered with the sulphoxide (4); the diastereoisomeric ratio of the alcohols (9a, b) depends markedly on the nature of the reducing agent, to the point that a large excess of either of the two diastereoisomers (9a) or (9b) can be obtained (Table 3).

TABLE 3

Reduction of the racemic β -oxosulphoxide (4) by lithium aluminium hydrides at -70 °C in diethyl ether-tetra-hydrofuran

1	Diastereo- isomeric ratio	
Reducing agent	(9a) : (9b)	$[\alpha]_{\mathrm{D}}^{25} a$
LiAlH	83:17	
LiAlH ₂ (OXylyl) ₂	76 : 24	
LiAlH _s (OBornyl)	70:30	-1.5°
LiAlH _s (OMenthyl)	55:45	0
LiAlH ₂ (OMenthyl) ₂	45:55	0
LiAlH(OMe) ₃	43:57	
LiAlH(N-Methylephedrinyl)(OXylyl) ^b	29:71	$+13.0^{\circ}$
LiAlH ₂ (Ephedrinyl)	29:71	$+1.5^{\circ}$
LiAlH(OBu ^t) ₃	26:74	

^a c 2, in chloroform. ^b Ephedrinyl = $2-(\beta-hydroxy-\alpha-methylphenethylamino)ethyl.$

The reduction of racemic oxosulphoxides by chiral hydrides can in principle lead to asymmetric induction and/or kinetic resolution. This possibility can easily be checked since either of the two chiral centres of hydroxy-sulphoxides can be selectively destroyed by oxidation with peroxy-acids (oxidation of the sulphur) or manganese dioxide (oxidation of the hydroxy function) according to literature methods.¹¹ Starting from racemic (4), reduction with chiral lithium aluminium hydrides, followed by oxidation to the sulphone (13) and to the oxosulphoxide (4) generally resulted in very low enantioselectivity, if any. This tallies with the low optical purity of optically active simple sulphoxides

affords hydroxy derivatives of high and known optical purity, whose chirality at carbon can be controlled by the appropriate choice of the chirality at sulphur in the starting sulphoxide (5) and, in some instances, also by the nature of the reducing agent.

EXPERIMENTAL

General.-Light petroleum had b.p. 40-60 °C. Ether was dried over sodium and tetrahydrofuran was distilled from lithium aluminium hydride. Diethylamine 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. Optical rotations were measured with a $\hat{P}erkin-Elmer$ 141 polarimeter. (-)-Menthol, $[\alpha]_{D}^{20} - 49.5^{\circ}$ (c 10 in EtOH), (-)-borneol, $[\alpha]_{D}^{25}$ -26.6° (c 5.3 in EtOH), and (-)-(1R,2S)-ephedrine, $[\alpha]_{\rm p}^{25}$ -35.0° (c 4 in H₂O-HCl), were commercial products; (-)-N-methylephedrine, prepared by literature methods,¹³ had $[\alpha]_{D}^{20} - 24^{\circ}$ (c l in EtOH). Methyl p-tolyl sulphoxide, prepared by literature methods,¹⁴ had m.p. 76 °C, $[\alpha]_{D}^{25}$ + 189.2° (c 1 in CHCl₃) {lit.,¹⁴ $[\alpha]_{p}^{25}$ + 189.2° (c 1 in CHCl₃)}. Synthesis of β-Oxosulphoxides.—n-Butyl lithium (4 mmol)

in n-hexane was added dropwise at -40 °C to a stirred solution of diethylamine (4 mmol) in tetrahydrofuran (10 ml). The mixture was kept for 30 min below 0 °C, cooled to -30 °C, and methyl *p*-tolyl sulphoxide (2 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to reach room temperature, cooled again to -40 °C, and the ester (3 mmol) in tetrahydrofuran (5 ml) added in one portion. The mixture was kept for 30 min at 0 °C, heated at reflux for the appropriate time and quenched with saturated aqueous ammonium chloride. The organic layer was separated off and the aqueous layer was acidified with dilute sulphuric acid to pH 3-4 and extracted with dichloromethane. The combined organic phases were concentrated on a rotary evaporator, and the residue was chromatographed on silica with ether-light petroleum as eluant. Yields, specific rotations, and physical and analytical data are reported in Table 4.

Reduction of β -Oxosulphoxides to β -Hydroxysulphoxides.— Method A. The β -oxosulphoxide (1 mmol) in absolute

^{* (+)-(} R_8 , R_c)-(6a) and (+)-(R_8 , S_c)-(6b) were previously obtained as a 1:1 diastereoisomeric mixture by reaction of benzaldehyde with the α -sulphinylcarbanion prepared from optically active (+)-(R)-(5), and separated by chromatography and fractional crystallization.²

TABLE 4

Data for the β -oxosulphones (+)-p-MeC₆H₄S(:O)CH₂C(:O)R

		M.p. (°C)	Reaction	Yield	Foun	id (%)		Requir	es (%)
R	$[\alpha]_{\mathbf{D}}^{25}$	(t/°C)	time/h	(%)	C	н	Formula	C	н
Ph	+ 180.9 ª + 265.0 ^b ,c	82 - 83.5	2.5	62					
Et	$+210.0^{a}$ +260.3 ^b	6970	2	60	62.6	6.6	$\mathrm{C_{13}H_{18}O_2S}$	62.8	6.7
\Pr^i	+200.3 + 191.3 a -255.2 b	5759	2.5	67	64.3	7.1	$\mathrm{C_{12}H_{16}O_2S}$	64.25	7.2
But	+162.0 a +241.8 b	108-108.7	4	82	65.8	7.6	$\mathrm{C_{11}H_{14}O_2S}$	65.5	7.6

^a c 1, in chloroform. ^b c 1, in acetone. ^c lit., ¹ $[\alpha]_D^{25} + 264.2$ (acetone).

ethanol (5 ml) was added at -70 °C to a stirred solution of sodium borohydride (1 mmol) in absolute ethanol (5 ml). The mixture was kept at -70 °C for 4 h. Methanol (5 ml) was then added and solvent evaporated off in vacuo. Water and dichloromethane were added to the residue; the organic phase was washed with 10% aqueous sodium hydroxide and dried over sodium sulphate. Evaporation gave the product. Yields and specified rotations are re-ported in Table 1. The diastereoisomeric mixture (6a, b) had m.p. 90–105 °C, (8a, b) n_D^{23} 1.545 5, and (9a, b) m.p. 90–125 °C; the mixture (7a, b) was isolated as waxy solid. Analytical data are reported in Table 5.

TABLE 5

Analytical data for compounds (7)-(13)

	Requires (%)				
Compound	C	н	Formula	C	н
(7)	62.4	7.7	$C_{11}H_{16}O_{2}S$	62.2	7.6
(8)	63.7	8.0	$C_{12}H_{18}O_{2}S$	63.6	8.0
(9)	65.1	8.4	$C_{13}H_{20}O_{2}S$	65.0	8.4
(10)	65.0	5.85	$C_{15}H_{16}O_3S$	65.2	5.85
(11)	57.7	7.1	$C_{11}H_{16}O_3S$	57.9	7.1
(12)	59.7	7.6	$C_{12}H_{18}O_{3}S$	59.5	7.5
(13)	60.7	7.85	$C_{13}H_{20}O_{3}S$	60.9	7.85

Method B. The β -oxosulphoxide (1 mmol) in tetrahydrofuran (5 ml) was added at -70 °C under nitrogen to a stirred solution of lithium aluminium hydride (1 mmol) in diethyl ether. The mixture was kept at -70 °C for 3-5 h. Saturated aqueous ammonium chloride (3 ml) was then added and the mixture allowed to reach room temperature. The organic layer was separated off, the aqueous layer washed twice with diethyl ether, and the combined organic phases were washed with dilute sodium hydroxide solution and dried. Evaporation gave 80-90% yields of product free from unchanged β -oxosulphoxide. Yields and specific rotations are reported in Table 1. The diastereoisomeric mixture (6a, b) had m.p. 95-105 °C, (8a, b) np²⁴ 1.546 l, and (9a, b) m.p. 78-122 °C; the mixture (7a, b) was isolated as waxy solid.

The alkoxylithium aluminium hydrides Method C. were prepared by literature methods.¹⁰ The reductions were carried out at -70 °C in diethyl ether-tetrahydrofuran as solvent with a 4:1 ratio between the active hydrogen of the reducing agent and the β -oxosulphoxides. After 3— 5 h, work-up as just described afforded the crude product which was chromatographed (silica; ether-light petroleum) to give 75-90% yields of product. Optical rotations are reported in Tables 2 and 3.

Oxidation of β -Hydroxysulphoxides to β -Hydroxysulphones.—The β -hydroxysulphoxides were oxidized with a stoicheiometric quantity of m-chloroperoxybenzoic acid at 20 °C for 24 h and purified by column chromatography (silica; light petroleum-ether 8:2). Yields were in the range 80-90%; physical properties and optical rotations are reported in Tables 1 and 2, and analytical data in Table 5. Starting from racemic (4), reduction with chiral lithium aluminium hydrides and subsequent oxidation afforded the β -hydroxysulphone (13) with an optical purity of $\leq 8\%$.

Oxidation of β -Hydroxysulphoxides to β -Oxosulphoxides.— The oxidations were performed with a large excess (15 mol. equiv.) of active manganese dioxide in dichloromethane solution (25 ml) at room temperature with vigorous stirring, following the methods described in the literature.¹¹ Starting from (6a, b), compound (1) was obtained in 90% yield after 2 h. Starting from (9a, b), $[\alpha]_D^{25} + 13.0^\circ$ (c 2 in CHCl₃), compound (4) was obtained in 43% yield after 60 h, $[\alpha]_{D}^{25} + 3.0^{\circ}$ (c 3 in CHCl₃), optical purity 1.8%.

Determination of the Enantiomeric Purity of Oxosulphoxides and Hydroxysulphones and of the Diastereoisomeric Ratio of Hydroxysulphoxides by ¹H N.m.r. Spectroscopy.-All spectra were recorded on a Varian HA 100 instrument in deuteriochloroform as solvent. ¹H N.m.r. spectra of the racemic oxosulphoxides (2)—(4) and of the hydroxysulphones (10)—(13) showed for the aromatic protons an AA'BB' system, centred at δ ca. 7.4, which revealed doubling of the lower field signals in the presence of the chiral shift reagent $Eu(tfc)_3$. For the racemic oxosulphoxide (1) the AB system centred at δ 4.4 (2 H, CH₂) showed a doubling in the presence of $Eu(tfc)_3$. The ratio of $Eu(tfc)_3$ to compounds (1)—(4) and (10)—(13) was 1:1. The enantiomeric purities of the optically active derivatives were determined under the aforementioned conditions. In the case of the hydroxysulphoxide (9a, b) the diastereoisomeric ratio was determined by the ratio of the intensities of the t-butyl proton resonances, singlets at δ 1.08 and 1.12, respectively.

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