Asymmetric Oxidation of Thioethers.[1]

Enantioselective Synthesis of β-Hydroxysulfoxides by Direct Oxidation.

Valeria Conte, Fulvio Di Furia, Giulia Licini and Giorgio Modena**
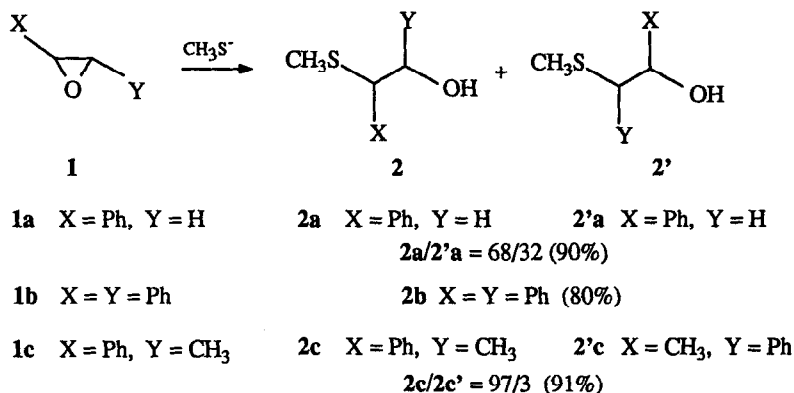
Centro di Studio sui Meccanismi di Reazioni Organiche del CNR, Dipartimento di Chimica Organica

dell'Università, Via Marzolo 1 I-35131 Padova, Italy

Summary:*S-methyl β-hydroxysulfoxides of fairly high optical purity (up to 80%) may be prepared by direct asymmetric oxidation [Bu^tO_2H, Ti(OPr^i)_4, (+)-DET] of acetylated or silylated S-methyl β-hydroxysulfides and subsequent deprotection. The upgrading of the optical purity from 78% up to >98% by simple crystallization has been obtained.*

Access to optically pure β-hydroxysulfoxides by direct asymmetric oxidation of the parent β-hydroxysulfides would be a significant synthetic achievement in view of their vast utilization in asymmetric transformations[2]. Unfortunately, the titanium-catalyzed procedure developed in our laboratory for the asymmetric oxidation of thioethers[3], while rather effective for some classes of substrates *e.g.* methylaryl sulfides[3] and 2-substituted-dithiolanes[4,5] (*e.e.* 70-98%), gives poor results in the oxidation of β-hydroxysulfides[6]. Unsatisfactory results have also been obtained when the Sharpless reagent[7] or the Kagan's procedure[8] were employed. We have recently reported[6] that the enantioselection in the oxidation of a series of β-hydroxysulfides (Ph-CH(OH)-CH_2-S-R; R=t-Butyl, o-Tolyl, Naphtyl; *e.e.* 20-47%) is lower than that attainable in the oxidation of structurally similar unfunctionalyzed sulfides. Therefore our data indicate that, at variance with the asymmetric epoxidation of allylic alcohols by the Sharpless reagent[7], in β-hydroxysulfide oxidations the hydroxy group plays a negative role as far as the enantioselection is concerned. At the same time we have critically examined all the data on sulfide asymmetric oxidations[9] reaching the conclusion that the simple steric differentiation of the two groups attached to the sulfur atom plays a dominant role in determining high enantioselections[9].

A series of S-methyl β-hydroxysulfides was, accordingly, synthesized by the stereospecific, though not

regiospecific, ring opening of racemic trans-styrene oxide,1a, trans-stilbene-oxide, 1b and trans-β-methyl-styrene oxide, 1c, all commercially available materials, by methyl thiolate in ethanol at reflux to obtain the isomeric β-hydroxysulfides 2 and 2'.
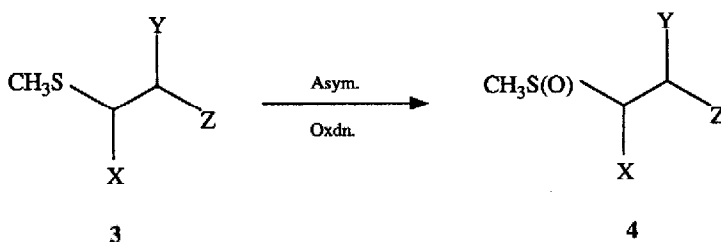

1a   X = Ph, Y = H

2a   X = Ph, Y = H   2'a X = Ph, Y = H
2a/2'a = 68/32 (90%)

1b   X = Y = Ph

2b X = Y = Ph (80%)

1c   X = Ph, Y = CH₃

2c   X = Ph, Y = CH₃   2'c X = CH₃, Y = Ph
2c/2c' = 97/3 (91%)

The isomeric mixtures of 2a,2'a and 2c,2'c were separated by flash chromatography (silica gel; light petroleum : Et$_2$O). The isolated β-hydroxysulfides with the exception of 2'c, obtained in too small amount, were then acetylated or silylated by standard procedures to the protected sulfides 3. The asymmetric oxidation[10] of 3a-k to the corresponding sulfoxides 4[11] amounts to the resolution of the racemic mixture by introduction of a new chiral center accompanied by a partial kinetic resolution. The absolute configuration of the three stereocenters of 4 has not yet been determined. The pertinent data are collected in the Table 1 where some data concerning the unprotected compounds are also reported for comparison purposes.

These results not only underline the highly beneficial effect of protecting the hydroxy group, but also confirm that S-methyl derivatives, where the difference in the size of the two substituents of the sulfur is maximized, are particularly suitable substrates for asymmetric oxidation. On the other hand, it is observed that the nature and the size of the protecting group play only a marginale role. However, in view of the easier deprotection procedure, silylation might be recommended. It is also whorthy of notice that the oxidation proceeds in fair chemical yields and that the diastereomeric ratios are usually favorable. Incidentally, the results with sulfides 3d and 3k confirm previous observations[12] that the use of cumyl hydroperoxide instead of t-butyl hydroperoxide leads to somewhat higher optical yields. Finally, the following result further demonstrates the significance of the procedure. Thus, when the diastereomeric mixture resulting from the oxidation of 3k was subjected to recrystallization (CH$_2$Cl$_2$-pentane), only the major diastereomer upgraded to >98% e.e. was obtained [α]$_D^{25}$ = +19.6 (c=1.1, CHCl$_3$)

Experiments aimed at enlarging the synthetic scope of the procedure reported above are now in progress in our laboratory.

TABLE 1

	X	Y	Z	yield[a], %	Diast.ratio[b]	e.e.%[c]	e.e.%[c]
					a:b	a	b
3a	H	Ph	OH	20	68:32	3	5
3b	H	Ph	OSiPh$_3$	78	56:44	70	64
3c	H	Ph	OSitBuPh$_2$	90	57:43	75	71
3d[d]	H	Ph	OSiPh$_3$	85	50:50	80	75
3e	Ph	H	OSitBuPh$_2$	90	87:13	74[e]	76
3f	Ph	Ph	OH	84	97:3	20	n.d.
3g	Ph	Ph	OSi(CH$_3$)$_2$tBu	82	89:11	20	60
3h	Ph	Ph	OCOCH$_3$	79	87:13	18	67
3i	Ph	CH$_3$	OH	22	100:0	18	--
3j	Ph	CH$_3$	OSiPh$_3$	90	88:12	70	n.d.
3k[d]	Ph	CH$_3$	OSiPh$_3$	91	91:9	78	70

a) isolated yields based on the oxidant, [substrate]:[oxidant] = 2:1. b) obtained by ^{1}H NMR (CDCl$_3$). c) obtained by ^{1}H NMR from the splitting of the CH$_3$-S(O)- signals in the presence of (+)-(S)-2,2,2-trifluoro-1-(9-anthryl) ethanol (Aldrich). d) obtained by using cumyl hydroperoxide. e) in the presence of (R)-(-)-N-(3,5-dinitro-benzoyl)-α-ethyl phenyl amine[13].

References and Notes

1. Part 5. Part 4: Di Furia, F.; Licini, G.; Modena, G.; De Lucchi, O. *Tetrahedron Lett.* **1989**, *30*, 2575.

2. See for example: Tanigaka, R.; Hamamura, K.; Kaji, A. *Chem. Lett.* **1988**, 977, and references therein.

3. Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325.

4. Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G.; Rossi, M. *Tetrahedron Lett.* **1986**, *27*, 6257.

5. Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G. in *The Role of Oxygen in Chemistry and Biochemistry*, vol. 33 of *Studies in Organic Chemistry*, Ando, W.; Moro-Oka, Y. eds.; Elsevier Science, Amsterdam, The Netherlands **1988**, p.193.

6. Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G. *Phosphorous & Sulfur* **1988**, *37*, 171.

7. Sharpless, K.B.; Woodard, S.S.; Finn, M.C. *Pure & Appl. Chem.* **1983**, *55*, 1823.

8. Pitchen, P.; Dunach, E.; Deshmukh, M.N.; Kagan, H.B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.

9. Bortolini, O.; Di Furia, F.; Licini, G.; Modena, G. in *Review on Heteroatom Chemistry* Oae, S. Ed.; MYU, Tokio, Japan **1988**, vol. 1, p.66.

10. A typical oxidation procedure is as follows: a solution of Ti(OiPr)$_4$ (1.0mL, 3.4mmol) in 15mL of dichloroethane (DCE) is added at r.t. to a solution of distilled ($[\alpha]_D^{25}$= +8.5) (+)-diethyltartrate (2.3mL, 6.7mmol) in 15mL of DCE and the mixture is stirred for 10min. To this yellow solution, cooled at -20°C, tBuOOH (0.66mL, 6.7mmol) and the sulfide (13.4mmol in 20mL of DCE) are subsequently added. The reaction mixture is stirred at -20°C until the oxidant is completely consumed (14-16hrs). The reaction is then quenched with 10mL of water and warmed at r.t. After 1h, the yellow gel is filtered over celite. The filtrate is extracted with CHCl$_3$, washed with 5% Na$_2$S$_2$O$_3$ (1x50mL), 5% NaOH, brine, dried over MgSO$_4$ and concentrated. The products are purified by flash- or low-pressure- (4-5atm) chromatography on silica-gel, eluent ethyl acetate:light petroleum.

11. All new compounds gave satisfactory spectral and elemental analyses.

12. Zhao, S.; Samuel,O.; Kagan,H.B. *Tetrahedron* **1987**, *43*, 5135.

13. Desmukh, M.; Dunach, E.; Juge,S.; Kagan, H.B. *Tetrahedron Lett.* **1985**, *26*, 402.