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TETRAHEDRON: *ASYMMETRY*

A facile stereospecific synthesis of chiral β-keto sulfoxides

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Abstract

A synthetic strategy has been devised for the preparation of chiral β-keto sulfoxides (actually, α-vinylsulfinyl ketones) starting from the readily available C-6 substituted 2,3-dihydro-1,4-oxathiines. The procedure, which is characterized by high yields and excellent enantiomeric excesses, represents an improvement in preparation methods for chiral β-keto sulfoxides. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Chiral β-keto sulfoxides have been extensively investigated and are commonly used in the synthesis of natural products and biologically active compounds.[1] Acyclic β-keto sulfoxides are generally prepared according to a procedure based on the reaction of α-sulfinyl anions with esters, as described by Corey.[2] Usually (+)-(*R*)-methyl *p*-tolyl sulfoxide, prepared by reaction of magnesium methyl iodide on a suitable chiral sulfinate ester, is converted by lithium diethylamide into its corresponding sulfinyl anion and the latter is then coupled with an ester.[3] Other methods include Claisen-type condensation of the optically active sulfinate ester with ketone enolate anions,[4] as well as the reaction of α-sulfinyl anions with cyclohexanones for the synthesis of chiral β-sulfinyl cyclohexanones.[5]

We wish to report in this paper a new procedure for the synthesis of chiral acyclic β-keto sulfoxides starting from chiral cyclic sulfoxides that in turn are prepared, with both *R* and *S* configurations, from C-6 substituted 2,3-dihydro-1,4-oxathiines. These starting compounds can be easily obtained from methyl ketones via their 1,3-oxathiolanes (overall yield range 85–92%), according to a procedure we have previously reported.[6]

The oxidation at the sulfur atom in the oxathiine ring is then performed under modified Sharpless conditions,[7,8] using cumene hydroperoxide (CHP) and Ti^{IV} isopropoxide in the presence of either L-(+) or D-(−) diethyl tartrate, in dry methylene chloride at −18°C, as shown in Scheme 1. The molar ratio of substrate and reagents is reported in Table 1. Other oxidation systems and substrate:reagent ratios were also tested, as shown in Table 1, although the results were definitely less satisfactory, in terms of both chemical yield and e.e.

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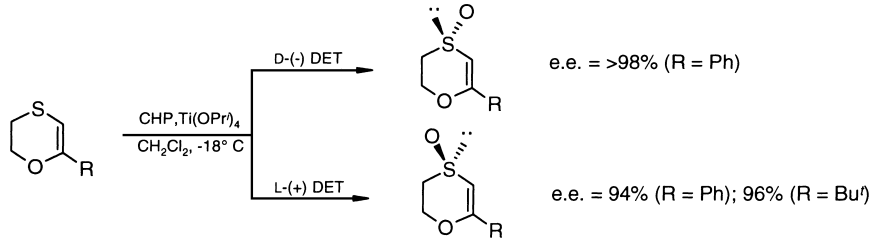


Scheme 1. Synthesis of the chiral cyclic sulfoxides

Table 1
Oxidation of 6-phenyl-2,3-dihydro-1,4-oxathiine under different conditions

Oxidizing System	Ratio [a]	Yield (%)	E.e. (%) [b]
Bu^{t}OOH, Ti^{IV}OPr^i, L-(+)-DIPT	2:2:4	65	65
Bu^{t}OOH, Ti^{IV}OPr^i, L-(+)-DET	2:2:4	70	68
” ” ”	1:2:4	90	70
CHP, Ti^{IV}OPr^i, L-(+)-DET	1.3:2:4	80	90
” ” ”	1:2:4	90	94

[a] Number of moles of the system components per substrate mole. [b] Determined by ^{1}H NMR analysis in the presence of (-)-quinine chiral shift reagent.

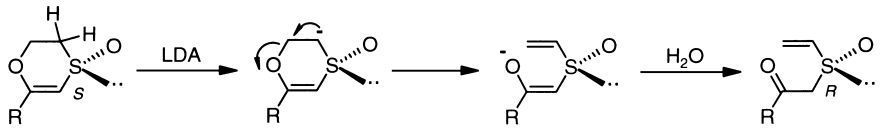
The C-6 substituted 2,3-dihydro-4-oxo-1,4-oxathiines prepared under our experimental conditions are reported in Table 2 with yields and e.e.s. Some preliminary results showed that the enantioselectivity of the sulfur oxidation decreases sharply when a second substituent is present at the C-5 position of the oxathiine ring.

Table 2
C-6 Substituted 2,3-dihydro-4-oxo-1,4-oxathiine

C-6 subst.	Chiral auxiliary	E.e. (%)	Assigned abs. config.	M.p. (°C)	$[\alpha]_D^{25}$ ($CHCl_3$)
Ph	L-(+)-DET	94 [a]	*R* [c]	104-105	+132 (c = 1.2)
”	D-(-)-DET	>98 [a]	*S*	104-105	-139 (c = 1.9)
Bu^t	L-(+)-DET	96 [b]	*R* [d]	86-87	+219 (c = 2.3)

[a,b] Determined by ^{1}H NMR analysis in the presence of (-)-quinine [a] or Pirkle's reagent [b]. [c] Assigned by X-ray crystal analysis: see Ref. 9. [d] Determined by ^{1}H NMR analysis according to Ref. 10.

The target compounds, chiral β-keto sulfoxides, were obtained by treatment of the parent 2,3-dihydro-4-oxo-1,4-oxathiines with lithium diisopropylamide in dry tetrahydrofuran at −78°C. Under these conditions they undergo a very clean and nearly quantitative (98% yield) ring cleavage affording the corresponding chiral α-vinylsulfinyl ketones (β-keto sulfoxides), as shown in Scheme 2. No evidence of the occurrence of isomerization at the stereogenic sulfur atom could be found.



Scheme 2. Conversion of the chiral cyclic sulfoxides into β-keto sulfoxides

To the best of our knowledge, α-vinylsulfinyl ketones have not been reported so far and, therefore, we tested their stereoselective reduction according to the procedures[11] previously reported for the reduction of α-alkyl (or phenyl) sulfinyl ketones: (*R*)-1-phenyl-2-(vinylsulfinyl)-1-ethanone [low-melting solid, $[\alpha]_D^{25}$ −194 (c=1.2 in $CHCl_3$)], from (*S*)-6-phenyl-2,3-dihydro-4-oxo-1,4-oxathiine, was in fact treated with DIBAL and led to a diastereomeric mixture of β-hydroxy sulfoxides [yield 95%, m.p. 126–128°C from hexane–ethanol, (1*S*,S*R*) d.e.=92%, $[\alpha]_D^{25}$ −89 (c=1.2 in CH_3OH)] which was separated by chromatography. The more abundant diastereomer was then desulfurized with Ra-Ni to give (1*R*)-phenylethanol (e.e.=98%).

When treated with DIBAL/$ZnCl_2$, (*R*)-1-phenyl-2-(vinylsulfinyl)-1-ethanone led again to a diastereomeric mixture [yield 87%, m.p. 76–78°C from hexane–ethanol, (1*R*,S*R*) d.e.=94%, $[\alpha]_D^{25}$ −125 (c=1.1 in CH_3OH)] and the desulfurization of the more abundant diasteromer by Ra-Ni gave (1*S*)-phenylethanol (e.e.=97%). Satisfactory C,H microanalyses were obtained for all the new compounds. ^{1}H NMR spectra[12] were consistent with the proposed structures.

These results match very well with that reported[11] for the stereoselective reduction of (*R*)-1-phenyl-2-(*p*-tolylsulfinyl)-1-ethanone. It is noteworthy that, in those instances where the sulfur moiety has to be removed after the reduction, the availability of the two chiral cyclic sulfoxides (and the β-keto sulfoxides therefrom) with opposite configuration, which can both be obtained under our conditions, affords a better chance to work with an enantiomerically pure starting β-keto sulfoxide.

Considering the final production of chiral 1-substituted ethanol, our procedure may be regarded as a formal stereoselective reduction of ethanones and differs from the already mentioned previous procedures[11] where the parent ethanone is produced by coupling of an α-sulfinyl anion with esters.

Acknowledgements

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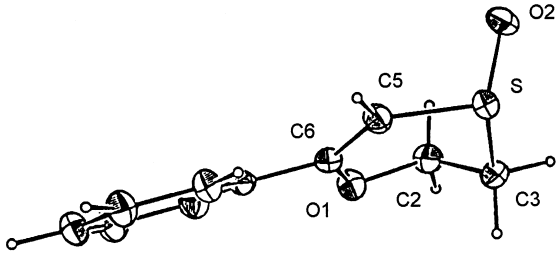
9. X-Ray: ($C_{10}H_{10}O_2S\cdot H_2O$; M_w=212.3); monoclinic system, space group $P2_1$, *a*=8.439(2) Å, *b*=5.326(1) Å, *c*=11.513(3) Å, β=98.87(1)° and Z=2. A total of 1175 independent reflections were collected at room temperature on an Enraf–Nonius CAD4-F diffractometer using Cu K_α radiation.



Least squares refinement of 1154 reflections with $I>3\sigma(I)$ converged upon the structure with R=0.033, Rw=0.041 and a goodness of fit=1.172. The inverted structure converged with the following values: R=0.037, Rw=0.046. Correspondence regarding the X-ray data should be addressed to F.G.

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12. (*S*)-6-Phenyl-2,3-dihydro-4-oxo-1,4-oxathiine (250 MHz, $CDCl_3$): δ 2.75–2.84 (*m*, 1H, Ha-3); 2.90–3.10 (*m*, 1H, Hb-3); 4.60–4.82 (*m*, 2H, H-2); 6.28 (*d*, 1H, *J*=2.1 Hz, H-5); 7.35–7.50 (*m*, 3H, H aromatic); 7.65 (*dd*, 2H, J_{ortho} =8.0 Hz, J_{meta}=1.8 Hz, H aromatic). (*R*)-6-*t*-Butyl-2,3-dihydro-4-oxo-1,4-oxathiine (200 MHz, $CDCl_3$): δ 1.15 (*s*, 9H, CMe_3); 2.51–2.69 (*m*, 1H, Ha-3); 2.81–2.93 (*m*, 1H, Hb-3); 4.38–4.62 (*m*, 2H, H-2); 5.74 (*d*, 1H, *J*=1.5 Hz, H-5). (*R*)-1-Phenyl-2-(vinylsulfinyl)-1-ethanone (400 MHz, $CDCl_3$): δ 4.32 (*d*, 1H, *J*=14.3 Hz, Ha-2); 4.48 (*d*, 1H, *J*=14.3 Hz, Hb-2); 6.01 (*d*, 1H, J_{cis}=9.8 Hz, Ha β-vinylic); 6.18 (*d*, 1H, J_{trans}=16.5 Hz, Hb β-vinylic); 6.89 (*dd*, 1H, J_{cis}=9.8 Hz, J_{trans}=16.5 Hz, H α-vinylic); 7.47–7.55 (*m*, 2H, H aromatic); 7.60–7.64 (*m*, 1H, H aromatic); 7.96 (*d*, 2H, J_{ortho}=8.5 Hz, H aromatic). (1*S*,S*R*)-1-Phenyl-2-(vinylsulfinyl)-1-ethanol (400 MHz, CD_3OD): δ 2.91 (*dd*, 1H, $J_{2a,1}$=2.5 Hz, $J_{2a,2b}$=14.0 Hz, Ha-2); 3.22 (*dd*, 1H, $J_{2b,1}$=11.0 Hz, $J_{2b,2a}$=14.0 Hz, Hb-2); 5.18 (*dd*, 1H, $J_{1,2a}$=2.5 Hz, $J_{1,2b}$=11.0 Hz, H-1); 6.05 (*d*, 1H, J_{cis}=9.8 Hz, Ha β-vinylic); 6.08 (*d*, 1H, J_{trans}=16.5 Hz, Hb β-vinylic); 6.93 (*dd*, 1H, J_{cis}=9.8 Hz, J_{trans}=16.5 Hz, H α-vinylic); 7.31–7.41 (*m*, 5H, H aromatic). (1*R*,S*R*)-1-Phenyl-2-(vinylsulfinyl)-1-ethanol (400 MHz, CD_3OD): δ 3.23 (*d*, 2H, $J_{2,1}$=6.6 Hz, H-2); 5.15 (*t*, 1H, $J_{1,2}$=6.6 Hz, H-1); 6.04 (*d*, 1H, J_{cis}=10.0 Hz, Ha β-vinylic); 6.07 (*d*, 1H, J_{trans}=16.6 Hz, Hb β-vinylic); 6.98 (*dd*, 1H, J_{cis}=9.7 Hz, J_{trans}=16.6 Hz, H α-vinylic); 7.31–7.46 (*m*, 5H, H aromatic).