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Enantio- or Diastereoselective Oxidation of (Methylthio)methylphosphonates as a Route to Precursors of Chiral Sulfoxides.

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Abstract:

The enantio- or diastereoselective oxidation of readily available (methylthio)methylphosphonates produces optically active (methylsulfinyl)methylphosphonates which can be used as direct precursors of chiral nonracemic methyl sulfoxides in a substitution reaction involving a carbanionic leaving group.

Keywords: enantioselection; sulfoxides; phosphorus compounds; carbanions.

Chiral nonracemic sulfoxides play a relevant role in organic chemistry and especially in asymmetric synthesis [1]. These compounds are usually prepared by the classical Andersen procedure, which involves the reaction of a menthyl sulfinate with organometallic reagents [2-3]. However, this method cannot be successfully used for the preparation of dialkyl sulfoxides.

Therefore, in order to overcome this difficulty, in the last decades various approaches have been elaborated. Significant progresses towards this direction have been made by the groups of Evans [4], Alcudia [5], and Whitesell [6], who have proposed the use of other chiral sulfinyl

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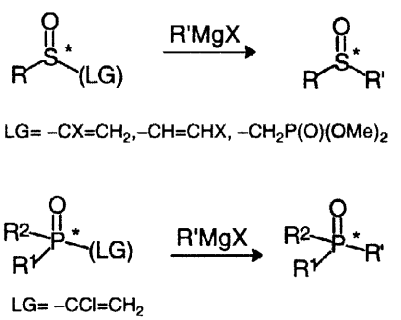
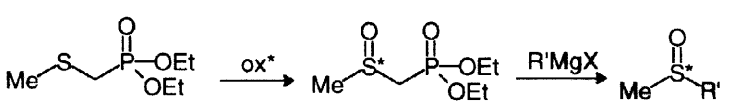
derivatives as starting materials in the reaction with organometallic reagents. A different approach has been introduced by Kagan and co-workers [7-8] who have performed a double substitution on a cyclic sulfite, obtaining some dialkyl sulfoxides with high e.e. values. Enantioselective oxidation of sulfides has been achieved by the groups of Modena and Di Furia [9-10], Kagan [7, 11-12], Uemura [13-14], and Davis [15], but this process is much more satisfactory for aryl alkyl sulfoxides than for dialkyl sulfoxides. Finally, biocatalyzed procedures have been also reported [16-17].

In previous works [18-22], we found that Grignard reagents could react with sulfoxides [18-19, 22] or phosphine oxides [20-21] bearing a halovinyl [18-21] or a methylphosphonyl group [22], which acted as carbon leaving groups in an enantiospecific displacement with inversion of configuration (Scheme 1).



Scheme 1

Thus, optically active sulfoxides or phosphine oxides bearing these carbon leaving groups are direct precursors of a variety of chiral nonracemic sulfoxides or phosphine oxides. Obviously, the synthetic validity of the procedure depends upon the availability of the starting sulfinyl or phosphinyl compounds. In this paper, we report the enantioselective oxidation of readily available (methylthio)methylphosphonates to obtain the corresponding (methylsulfinyl)methylphosphonates, which are able to undergo the replacement of the carbanionic leaving group by suitable organometallic reagents [22] (Scheme 2).



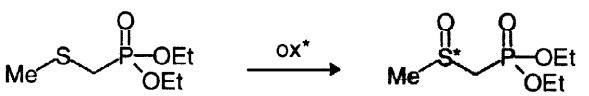
Scheme 2

Results and Discussion

Commercially available diethyl (methylthio)methylphosphonate **1** was oxidized by various procedures to the corresponding sulfoxide **2** [23]. At the outset, in order to evaluate the validity of the procedure envisaged, it was ascertained that, when reacted with Grignard reagents, the diethyl (methylsulfinyl)methylphosphonate behaved as the dimethyl (*p*-tolylsulfinyl)methylphosphonate (*i.e.* the replacement of the carbanionic leaving group occurred [22]).

Commercially available (+)-8,8-dichlorocamphorylsulfonyloxaziridine (DCSA) yielded sulfoxide **2** in good yields and with 59% e.e. (Table 1, entry 1).

Table 1: Enantioselective oxidation of diethyl (methylthio)methylphosphonate (1).



1 **2**

Entry	Oxidant	Oxidant equiv.	Reagent Ratios[a]	Solvent	Product Ratios[b] (Yield)	Time (h)	e.e. (%)[d] (config.)[e]
1	DCSA	1	—	CCl_4	0/100/0 (67[c])	20	59 (*S*)
2	CHP	2	1:2:1	CH_2Cl_2	0/48/52	20	62 (*R*)
3	CHP	1.1	1:2:1	CH_2Cl_2	18/82/0	4	60 (*R*)
4	CHP	2	1:2:0.5	CH_2Cl_2	0/18/82	4	78 (*R*)
5	CHP	1.3	1:2:0.5	CH_2Cl_2	0/80/20	4	80 (*R*)
6	CHP	1.1	1:2:0.5	CH_2Cl_2	18/82/0 (74[c])	4	76 (*R*)
7	CHP	0.7	1:2:0.5	CH_2Cl_2	67/33/0	15	71 (*R*)
8	CHP	0.7	1:2:0.5	CH_2Cl_2	58/42/0	24	70 (*R*)

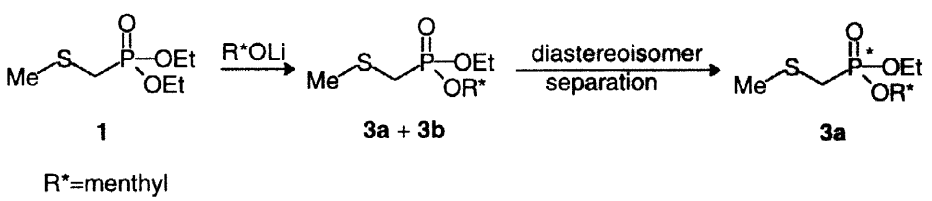
[a]Ratios between Ti(O-*i*-Pr)$_4$/(diethyl (*R,R*)-tartrate)/water. [b]GC ratios between (unreacted sulfide)/sulfoxide/sulfone. [c]Isolated yield of pure sulfoxide **2**, under the optimized conditions. [d]NMR determination by the addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide on the isolated sulfoxide. [e]In entry 6, the configuration was determined by obtaining predominantly (*S*) methyl *n*-octyl sulfoxide [4] in the reaction with *n*-octylmagnesium bromide (see Text). This result was also the basis for configuration assignment in the other cases.

The cumene hydroperoxide (CHP) oxidation of **1** in the presence of titanium/diethyl tartrate complexes (entries 2-8) yielded **2** in higher e.e. values. When 1 eq of water was added to the 1:2 complex between Ti(O-*i*-Pr)$_4$ and diethyl (*R,R*)-tartrate in the presence of 2 eq. of cumene hydroperoxide (entry 2) an extensive overoxidation of the produced sulfoxide to sulfone was

observed. The decrease in the amount of oxidant (entry 3) led to the recovery of a significant fraction of unreacted sulfide and to a moderate e.e. value (60%) in the oxidation. The use of a lower amount of added water represented a better choice (entries 4-8). When a large excess of CHP was used (entry 4), a large amount of sulfone was obtained. The reduction of the ratio between the oxidant and the metal to a 1.3:1 ratio, in the presence of 0.5 eq. of water (entry 5), yielded a 80:20 mixture of sulfoxide/sulfone, the sulfoxide being produced with 80% e.e. A further decrease in the added CHP (entry 6) produced a sulfoxide with a slightly lower (76%) e.e. value, but free from sulfone. Since the separation of the sulfoxide from the sulfide is by far easier than the separation of the sulfoxide from the sulfone, the reaction conditions of entry 6 seemed more favourable than those of entry 5, even if the e.e. value was slightly lower. A further decrease in the added oxidant (entries 7 and 8) gave unsatisfactory results, due to the high amounts of unreacted sulfide recovered.

The absolute configuration at the sulfur stereogenic centre of the sulfinyl derivative **2** was determined by reacting **2** (entry 6; 76% e.e.) with *n*-octylmagnesium bromide, and obtaining a predominantly (*S*) methyl *n*-octyl sulfoxide (77% e.e.) [4]. Since this type of reaction is known to be enantiospecific with inversion of configuration [22], **2** must then possess the (*R*) configuration.

Furthermore, **1** was subjected to a transesterification reaction with lithium menthoxide [24], to give the ethyl menthyl (methylthio)methylphosphonate **3** (Scheme 3).



1 **3a + 3b** **3a**

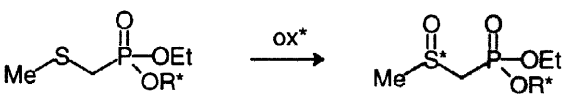
R*=menthyl

Scheme 3

Under the reaction conditions used (see Experimental), the ratio between the two possible diastereoisomers **3a** and **3b** with chirality at the phosphorus atom was found to be almost 4:1. These diastereoisomers were separated by column chromatography and the most abundant isomer **3a** was obtained free from the less abundant counterpart. Compound **3a** was then oxidized with sodium periodate or with chiral oxidants to obtain ethyl menthyl (methylsulfinyl)methylphosphonate **4** (Table 2) as two diastereoisomers **4a** and **4b**, which are epimers at the sulfur stereogenic centre. The diastereoisomeric excess, resulting from the

combined action of the chirality centres present on the substrate and on the catalyst, was comparable with the e.e. values previously obtained for the sulfinyl derivative **2**, but one crystallization of compound **4** allowed us to obtain the sulfur centre fully resolved. In particular, crystallization of the epimers **4**, produced with the oxidation system based upon the enantiomerically pure non-natural diethyl tartrate (entry 5), gave the pure stereoisomer **4a** (in a 38% overall isolated yield starting from **3a**).

Table 2: Diastereoselective oxidation of ethyl menthyl (methylthio)methylphosphonate (3a).



3a **4**

R*=menthyl

Entry	Oxidant	Solvent	Time (h)	Yield % [a] (main product)	d.e. (%)[b] (Config.)[c]
1	$NaIO_4$	CH_3OH/H_2O	12	64 (**4a**)	35 (*S*)
2	DCSA	CCl_4	20	52 (**4a**)	45 (*S*)
3	Ti(O-*i*-Pr)$_4$/(*R*,*R*)-DET/H_2O/CHP	CH_2Cl_2	4	90 (**4b**)	82 (*R*)
4	Ti(O-*i*-Pr)$_4$/(*S*,*S*)-DET/H_2O/CHP	CH_2Cl_2	4	81 (**4a**)	76 (*S*)
5	Ti(O-*i*-Pr)$_4$/(*S*,*S*)-DET/H_2O/CHP	CH_2Cl_2	4	81 (**4a**)	100 [d] (*S*)

[a]Isolated yields. [b]Determined by gas-chromatography. [c] In entry 4, the configuration at the sulfur stereogenic centre was determined by obtaining predominantly (*R*) methyl *n*-octyl sulfoxide [4] in the reaction with *n*-octylmagnesium bromide (see Text). This result was also the basis for configuration assignment in the other cases. [d] Determined after one crystallization.

The absolute configuration at the sulfur stereogenic centre of the resulting sulfoxide was determined by reacting the isolated epimer **4a**, obtained in the reaction conditions of entry 4 and crystallized, with *n*-octylmagnesium bromide. (*R*) Methyl *n*-octyl sulfoxide was produced. Therefore, **4a** must contain the (*S*) configuration at the sulfur stereogenic centre, and the epimer **4b** must possess the (*R*) configuration at the same centre.

Conclusion

The present work shows that the two-step procedure based upon an enantioselective oxidation of easily available (alkylthio)methylphosphonates and a subsequent reaction with Grignard reagents, with the release of a carbon leaving group, is a viable route leading to chiral nonracemic sulfoxides. Since these compounds present e.e. values equal to those of the precursor sulfinylmethylphosphonate, by resorting to a crystallization step e.e. values up to 100% can be reached. Furthermore, independently from the main scope of the present work (*i.e.* synthesis of precursors of dialkyl sulfoxides), compounds of type **4** appear by themselves of high synthetic interest, due to the simultaneous presence of resolved sulfur and phosphorus stereogenic centres.

Experimental

The purified reaction products were characterized by their ^{1}H- and ^{13}C-NMR spectra, recorded in $CDCl_3$ at 500 and 125 MHz respectively, and their mass spectra determined by GC/MS analysis (SE30, 30 m, capillary columns and Mass Selective Detector, 70 eV). The enantiomeric purity of compounds was determined by ^{1}H-NMR experiments with the addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide. The composition of the diastereoisomeric mixtures of compounds **3** and **4** was determined by GC analysis (capillary column, SE30).

Ethyl menthyl (methylthio)methylphosphonate (3). 1.2 mL of a solution of *n*-BuLi (2.5 M in hexane) were added at 0°C to a solution of 0.48 g (3 mmol) of (−)-menthol in 10 mL of anhydrous THF. After 10 min stirring, a solution of 0.3 g of **1** (1.5 mmol) in 4 mL of anhydrous THF was added. The mixture was stirred at rt for 24 h, and then quenched with a saturated NH_4Cl solution. The mixture was extracted with ethyl acetate and the extracts were dried and evaporated. The excess menthol was distilled off by a kugelrohr distillation (T=70-75°C, p= $7\cdot10^{-3}$ mbar). The residual menthyl esters (obtained in an overall yield of 71%) were separated by column chromatography (eluent petroleum ether/ethyl acetate 7:3). Anal. Calcd for $C_{14}H_{29}O_3PS$: C, 54.52; H, 9.48; S, 10.40. Found C, 54.52; H, 10.19; S, 10.41.

3a. (colourless oil) $[\alpha]_D$ = −38.5 (c=1, $CHCl_3$). MS 70 eV *m/e* (relative intensity) 308 (M^+, 5), 171 (39), 170 (54), 143 (23), 124 (100), 97 (30). ^{1}H-NMR δ 4.24-4.12 (m, 3 H), 2.65 (d, *J*=12.6 Hz, 2 H), 2.26 (s, 3H), 2.25-2.20 (m, 1 H), 2.12-2.09 (m, 1 H), 1.65-1.61 (m, 2 H), 1.47-1.38 (m, 2 H), 1.31 (t, *J*=7.0, 3 H), 1.13 (q, *J*= 12.0 Hz, 1 H), 0.99-0.96 (m, 1 H), 0.88 (d, *J*=7.1

Hz, 6 H), 0.86-0.80 (m, 1 H), 0.78 ppm (d, J=6.9 Hz, 3 H). ^{13}C-NMR δ 77.86 (d, J=7.8 Hz), 62.82 (d, J=6.6 Hz), 48.47 (d, J=5.9 Hz), 43.13, 34.00, 31.50, 28.41, (d, J=151.1 Hz), 25.46, 22.78, 21.91, 20.93, 17.37, 16.48 (d, J=6.2 Hz), 15.62 ppm.

Stereoselective oxidation of (methylthio)methylphosphonates. Oxidation by oxaziridines [15] or by sodium metaperiodate [3] was performed according to standard procedures, whereas the following protocol was followed for the oxidation with cumene hydroperoxide in the presence of titanium complexes. A solution of Ti(O-*i*-Pr)$_4$ (5 mmol) in 5 mL of anhydrous CH_2Cl_2 was added to a solution of diethyl tartrate (10 mmol) in 17 mL of anhydrous CH_2Cl_2. After 2 min, 45 μL of water were added. The mixture was stirred at rt for 20 min and then cooled to -20°C. After 20 min, 5 mmol of thioether in 15 mL of anhydrous CH_2Cl_2 and 5.5 mmol of CHP were added. The reaction mixture was stirred at –20 °C for the required time and quenched with water. The solids were removed by filtration, and the organic layer was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous sodium sulphate, and then evaporated *in vacuo*. The produced sulfinyl compound was separated by column chromatography (eluent petroleum ether/ethyl acetate/methanol 4:5:1).

Diethyl (methylsulfinyl)methylphosphonate (2). Spectroscopical data agreed with those reported [23]. $[\alpha]_D$ = +44.3 (c=1.6, $CHCl_3$) for an e.e. value of 80%.

Reaction of *n*-octylmagnesium bromide with diethyl (methylsulfinyl)methylphosphonate (2). A solution of 2.1 mmol of *n*-octylmagnesium bromide in THF was added to a solution of 1.4 mmol of sulfoxide **2** (Table 1, entry 6, e.e. 76%) in 20 mL of benzene at rt and under N_2. After 1.5 h, the reaction mixture was quenched with a saturated solution of NH_4Cl. After the usual work-up, the reaction mixture was purified by column chromatography (eluent petroleum ether/ethyl acetate 1:19). (*S*) Methyl *n*-octyl sulfoxide $[\alpha]_D$ = + 61 (c=1, acetone), e.e. value 77% (NMR, by the addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide). Isolated yield 50%. Spectroscopical data agreed with those reported [4].

Ethyl menthyl (methylsulfinyl)methylphosphonate (4a). White solid, mp 84-86 °C (hexane) $[\alpha]_D$ = –98.6 (c=1, $CHCl_3$). MS 70 eV *m/e* (relative intensity) 308 (1), 187 (100), 171 (16), 170 (18), 143 (12), 125 (33), 124 (66), 97 (64). ^{1}H-NMR δ 4.31-4.24 (m, 1 H), 4.20-4.11 (m, 2 H), 3.32 (ddd, J= 17.8, J= 14.3, J= 0.7 Hz, 1 H), 3.23 (t-like due to dd, J= 14.1 Hz, 1 H),

2.83 (d, *J*= 0.7 Hz, 3 H), 2.21-2.16 (m, 1 H), 2.07-2.04 (m, 1 H), 1.67-1.62 (m, 3 H), 1.44-1.41 (m, 1 H), 1.33 (dt, *J*= 7.0, *J*= 0.5 Hz, 3 H), 1.16 (q, *J*= 12.1 Hz, 1 H), 1.01-0.94 (m, 1 H), 0.89 (d, *J* = 7.0 Hz, 6 H), 0.88-0.79 (m, 1 H), 0.78 ppm (d, *J*= 6.9 Hz, 3 H). ^{13}C-NMR δ 79.10 (d, *J*=7.6 Hz), 62.89 (d, *J*=6.1 Hz), 52.21 (d, *J*=136.2 Hz), 48.28 (d, *J*= 6.2 Hz), 43.10, 41.16 (d, *J*=3.0 Hz), 33.78, 31.48, 25.48, 22.68, 21.79, 20.81, 16.25 (d, *J*=6.7 Hz), 15.49 ppm. Anal. Calcd for $C_{14}H_{29}O_4PS$: C, 51.83; H, 9.01; S, 9.88. Found C, 51.64; H, 9.62; S, 10.16.

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