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Working with Hazardous Chemicals

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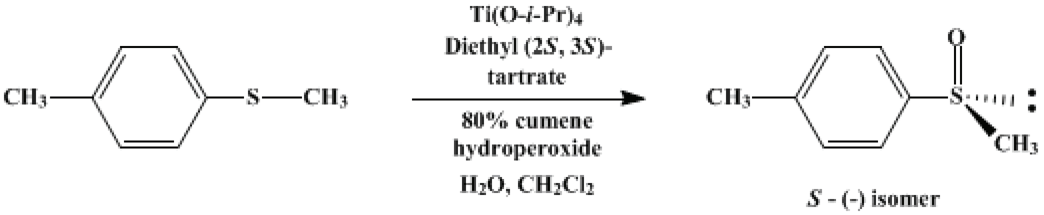
ENANTIOSELECTIVE OXIDATION OF A SULFIDE: (*S*)-(−)-METHYL *p*-TOLYL SULFOXIDE

[Benzene, 1-methyl-4-(methylsulfinyl)-, (*S*)-]



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1. Procedure

Into a 1-L flask containing 125 mL of methylene chloride (Note 1) and a magnetic stirring bar (4-cm length) is added at room temperature (20°C) 5.35 mL, 6.19 g (0.030 mol) of (*S,S*)-(−)-diethyl tartrate (DET) (Note 2) by means of a 10-mL syringe. The flask is stoppered with a septum cap and purged with argon. Titanium(IV) isopropoxide, Ti(OiPr)$_4$, (4.48 mL, 0.015 mol) (Note 3) is introduced through the septum via a 10-mL syringe. The stirred limpid solution immediately turns yellow. After a few minutes distilled water (0.27 mL, 0.015 mol) is added dropwise using a calibrated syringe. Strong stirring is maintained until there is total dissolution of water and formation of a pale-yellow solution (after 25 min). Methyl *p*-tolyl sulfide (4.09 mL, 4.20 g, 0.030 mol) (Note 4) dissolved in 5 mL of methylene chloride is introduced with a 10-mL syringe that is then rinsed with 5 mL of methylene chloride. The flask is cooled (−30°C) with an acetone–dry ice bath while it is stirred for 40 min. At this point 5.54 mL of 80% cumene hydroperoxide (Note 5) (0.030 mol, 5.70 g) is added dropwise from a 10-mL syringe, with stirring, during 5 min. The reaction flask is kept in a freezer (−23°C) overnight (15 hr) (Note 6). Hydrolysis is then effected by adding 5.05 mL of water followed by vigorous stirring for 90 min at room temperature (20°C).

A large sintered-glass funnel (9-cm diameter, porosity grade 2) is partially filled with Celite (Celite height: 2.5 cm) and then impregnated with methylene chloride. The suspension resulting from hydrolysis is poured in portions onto the Celite under suction by a water pump. The Celite is washed many times with 50-mL portions of technical-grade methylene chloride. In order to accelerate filtration and to improve washing, the surface of the Celite is disturbed from time to time with a spatula. The filtration time is approximately 50 min. The filtrate (300 mL) is then vigorously stirred for 1 hr in a mixture of 80 mL of 2 *N* sodium hydroxide and 40 mL of saturated aqueous sodium chloride. The organic phase [negative test for peroxides using a Merck kit (Merkoquant 1001 l)] is decanted, dried (magnesium sulfate or sodium sulfate), filtered and concentrated in a Büchi apparatus (bath temperature: 45°C) to leave 10 g of an oily material that is a mixture of methyl *p*-tolyl sulfoxide, 2-phenyl-2-propanol, and some starting sulfide.

Optically pure sulfoxide is then easily isolated as follows. The crude product (10 g) is diluted with 4 mL of a solvent mixture (ethyl acetate/cyclohexane = 9 : 1). This solution is poured onto a column (75-mm diameter) filled with 120 g of silica gel (Merck 230–400 mesh) for flash chromatography. Elution is performed under gravity and requires ca. 200 mL of the above solvent system, followed by ca. 200 mL of ethyl acetate. 2-Phenyl-2-propanol mixed with methyl *p*-tolyl sulfide is eluted in the first fraction (ca. 150 mL, monitored by TLC). The subsequent fractions are collected (ca. 300 mL) and evaporated, giving 4.0 g of methyl *p*-tolyl sulfoxide $[\alpha]_D$ −88° (acetone, *c* 1), 89% ee, 85% yield. This material is crystallized once from 60 mL of hot hexane, to afford, after 2 hr at 20°C, 3.14 g (68%) of enantiomerically pure (Note 7) (*S*)-(−)-methyl *p*-tolyl sulfoxide as needles, $[\alpha]_D$ −142° (acetone, *c* 1), mp 73–76°C (Reichert microscope with heating system).

The chemical purity of the compound is checked by ^{1}NMR (250 MHz) and thin-layer chromatography (silica gel, eluent: ethyl acetate), which show the complete absence of the corresponding sulfide and sulfone (Note 8).

2. Notes

1. Methylene chloride, technical grade (99.5%), was passed through a column of basic alumina (grade I) and then stored over molecular sieves (Linde 4A).
2. (−)-Diethyl (*S,S*)-tartrate was obtained from the Aldrich Chemical Company, Inc. and was distilled (bp 120°C at 2 mm).
3. Titanium(IV) isopropoxide, $Ti(OiPr)_4$ (Aldrich Chemical Company, Inc.) was distilled under an inert atmosphere (nitrogen or argon) and stored in a flask with a septum cap under argon (bp 85°C at 1.5 mm).
4. Methyl *p*-tolyl sulfide, available from Aldrich Chemical Company, Inc., was distilled (bp 95°C at 18 mm) before use.
5. Cumene hydroperoxide, obtained from Aldrich Chemical Company, Inc., technical grade (80%), was dried overnight over Linde 4A molecular sieves (pellets) prior to use.
6. A standard freezer without accurate temperature control was used; it is estimated that the temperature is −23 ± 1°C. One night is a convenient reaction time, but oxidation is in fact complete after a few hours.
7. Enantiomerically pure (*R*)-(+)-methyl *p*-tolyl sulfoxide, prepared from (−)-menthyl *p*-tolylsulfinate,[2,3,4] was described with the following specific rotations: $[\alpha]_D$ +145.5° (acetone),[3] $[\alpha]_D^{25}$ +168° (acetone, *c* 1.8),[4] $[\alpha]_D$ +189° ($CHCl_3$, *c* 1).[5] The submitters checked a sample prepared[3,4] and kindly provided by Professor G. Solladié (Strasbourg), which was recrystallized from hexane: $[\alpha]_D$ +146° ± 1 (acetone, *c* 1), mp 76–77°C. HPLC analysis carried out on a chiral stationary phase shows the absence of the enantiomer (Dr. Tambute, private communication). The same analysis shows that the product obtained by the procedure described above is of 99.5% ee.
8. The checkers attempted chromatography of the three-component mixture on a 150-mmol scale using 55- and 75-mm diameter columns. However, mixed fractions were obtained even with seemingly large R_f differences for the components.

3. Discussion

Both enantiomers of methyl *p*-tolyl sulfoxide are available from this procedure by selection of the appropriate diethyl tartrate. This procedure describes the preparation of (*S*)-(−)-methyl *p*-tolyl sulfoxide, which is not easy to prepare by the Andersen method[2,3,4] using (+)-menthol.

Cumene hydroperoxide was selected because it was recently observed[6] that it gives in many cases better ee values in asymmetric oxidation of sulfides than the original procedure with *t*-butyl hydroperoxide.[7,8,9]

The enantiomeric purity of the crude (*S*)-methyl *p*-tolyl sulfoxide produced from the oxidation is close to 90% (measurement made on a sample of 200 mg of material purified by flash chromatography on silica gel; eluant: ethyl acetate : ethanol = 96 : 4). However, when oxidation is performed on a 10-mmol scale, enantioselectivity is improved (96% ee, 87% isolated yield).[6] We have no explanation for this optimum scale effect. It could be because of easier temperature control on a small scale (there is a decrease of enantioselectivity above −20°C or below −25°C).[7]

tert-Butyl hydroperoxide (anhydrous toluene solution prepared as described in [9]) was also used as the oxidant on a 0.11-mol scale in the presence of 0.10 mol of methyl *p*-tolyl sulfide and 0.053 mol of chiral titanium complex ($Ti/DET/H_2O = 1 : 2 : 1$). The procedure is identical to the one described above using cumene hydroperoxide. The ee of the crude sulfoxide is 84%. Pure (*S*)-methyl *p*-tolyl sulfoxide $[\alpha]_D$ −146° (acetone, *c* 1) is obtained without flash chromatography by three recrystallizations of the crude material from hexane in 50% yield (with respect to sulfide).

Preparation of various enantiomerically pure sulfoxides by oxidation of sulfides seems feasible in the cases where asymmetric synthesis occurs with ee values in the range of 90% giving crystalline products that can usually be recrystallized up to 100% ee. Aryl methyl sulfides usually give excellent enantioselectivity during oxidation[6,7,8,9] and are good candidates for the present procedure. For example, we have shown on a 10-mmol scale that optically pure (*S*)-(−)-methyl phenyl sulfoxide $[\alpha]_D$ −146° (acetone, *c* 1)[6] could be obtained in 76% yield after oxidation with cumene hydroperoxide followed by flash-chromatographic purification on silica gel and recrystallizations at low temperature in a mixed solvent (ether-pentane). Similarly, (*S*)-(−)-methyl *o*-methoxyphenyl sulfoxide, $[\alpha]_D$ −339° (acetone, *c* 1.5; 100% ee measured by HPLC), was obtained in 80% yield by recrystallizations from hexane.

The method with cumene hydroperoxide has recently been used with success[10] to prepare both enantiomers of methyl *p*-methoxyphenyl sulfoxide, which were then taken as starting material for the total synthesis of biological compounds. It also applies to transformation of some 1,3-dithianes into 1,3-dithiane 1-monoxides, with ee values up to 80%.[11] This enantioselectivity was achieved by optimization of reaction temperature; ee was maximum at −40°C.

References and Notes

1. Laboratoire de Synthèse Asymétrique, UA CNRS 255, Université Paris-Sud, 91405 Orsay, France.
2. Andersen, K. K. *Tetrahedron Lett.* **1962**, 93.
3. Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958.
4. Solladié, G. *Synthesis* **1981**, 185.
5. Tsuchihashi, G.-i.; Iriuchijima, S.; Ishibashi, M. *Tetrahedron Lett.* **1972**, 4605.
6. Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135.
7. Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.
8. Duñach, E.; Kagan, H. B. *Nouv. J. Chim.* **1985**, *9*, 1.
9. Kagan, H. B.; Duñach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S. -H. *Pure Appl. Chem.* **1985**, *57*, 1911.
10. Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.
11. Samuel, O.; Ronan, B.; Kagan, H. B. *J. Organometal. Chem.* **1989**, *370*, 43.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(S)-(−)-METHYL p-TOLYL SULFOXIDE

(S,S)-(−)-diethyl tartrate

(−)-Diethyl (S,S)-tartrate

(−)-menthyl p-tolylsulfinate

titanium complex

(S)-(−)-methyl phenyl sulfoxide

(S)-(−)-methyl o-methoxyphenyl sulfoxide

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

acetone (67-64-1)

Pentane (109-66-0)

(+)-menthol (15356-60-2)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

argon (7440-37-1)

tert-butyl hydroperoxide,
t-butyl hydroperoxide (75-91-2)

diethyl tartrate

titanium(IV) isopropoxide (546-68-9)

cumene hydroperoxide

2-phenyl-2-propanol (617-94-7)

methyl p-tolyl sulfide (623-13-2)

Benzene, 1-methyl-4-(methylsulfinyl)-, (S)-,
(S)-methyl p-tolyl sulfoxide (5056-07-5)

methyl p-tolyl sulfoxide (1519-39-7)

(R)-(+)-methyl p-tolyl sulfoxide

methyl p-methoxyphenyl sulfoxide