Syntheses and Reactions of Optically Active Alkoxyaminosulfonium Salts

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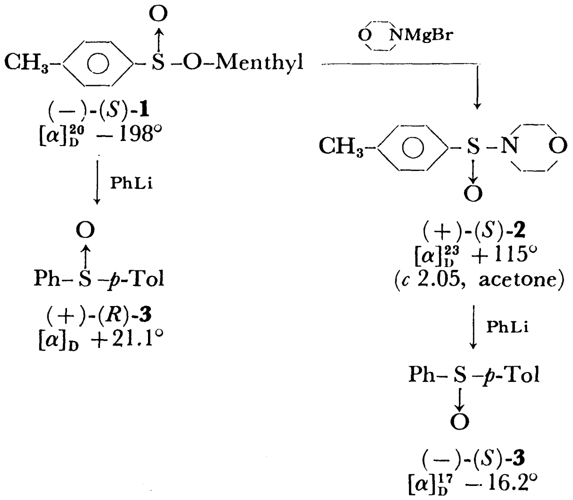
The optically active methoxymorpholino-*p*-tolylsulfonium salt has been synthesized by the reaction of optically active *N*-*p*-toluenesulfinylmorpholine with methyl trifluoromethanesulfonate. The sulfonium ion methylated benzylethylphenylamine and benzyl ethyl sulfide with asymmetric induction to give the optically active benzylethylmethylphenylammonium ion and benzylethylmethylsulfonium ion respectively. The optically active methoxymorpholino-*p*-tolylsulfonium salt and diaminosulfonium salts have been prepared in a one pot reaction between *N*-*p*-toluenesulfenylmorpholine and 1-chlorobenzotriazole with methanol in the presence of l-menthol at −80 °C.

Stereochemically, the sulfonium ions are of great interest. The absolute configuration of the ethylmethylphenylsulfonium ion has been reported,1) and the syntheses and absolute configuration of the oxosulfonium ions have been reported.2–4) Johnson and Schroeck have studied the syntheses of optically active sulfoximines and the reactions of aminooxosulfonium methylide with carbonyl compounds.5)

Several kinds of alkoxyaminosulfonium salts have been reported and it has been found that the sulfonium ions alkylate amines and sulfides to give the corresponding ammonium and sulfonium salts in high yields.6) It is expected that the optically active alkoxyaminosulfonium ions alkylate amines and sulfides with asymmetric induction. In this paper, the syntheses of optically active alkoxyamino- and diaminosulfonium salts and their optical resolution will be described.

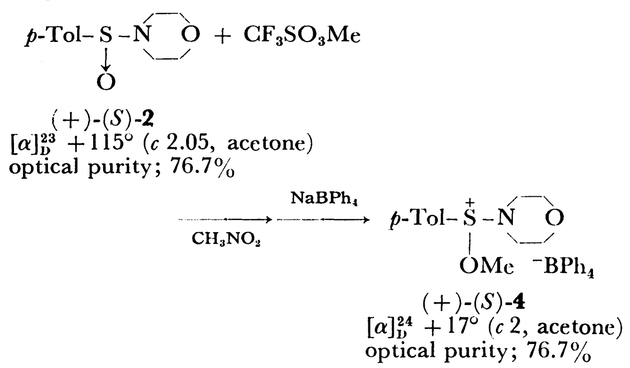
Results and Discussion

(−)-(*S*)-Menthyl *p*-toluenesulfinate ($[\alpha]_D^{20}$ −198°)(**1**) was treated with morpholinomagnesium bromide according to the literature7) to give the optically active *N*-*p*-toluenesulfinylmorpholine (**2**); $[\alpha]_D^{23}$ +115°. In the handling of **2**, it was necessary to work below room temperature in the absence of light and oxygen in order to prevent optical deterioration. The treatment of **2** with phenyllithium gave phenyl *p*-tolyl sulfoxide in good yields; $[\alpha]_D^{23}$ −16.2°. Mislow prepared phenyl *p*-tolyl sulfoxide ($[\alpha]_D$ +21.1°) by the reaction of **1** with phenyllithium, and determined its absolute configuration to be (+)-(*R*).8) Therefore, the absolute configuration of phenyl *p*-tolyl sulfoxide ($[\alpha]_D^{23}$ −16.2°) obtained in this reaction should be (−)-(*S*), and the optical purity was calculated as 76%. The reaction of sulfinamide with organolithium compounds is known to proceed with 100% inversion of configuration around the sulfur atom,9) and consequently the absolute configuration of **2** obtained in the reaction of **1** with morpholinomagnesium bromide should be (+)-(*S*), with an assumed optical purity of 76%. The configurational relationships between the sulfinic ester, the sulfinamide and the sulfoxide are illustrated in the following scheme.

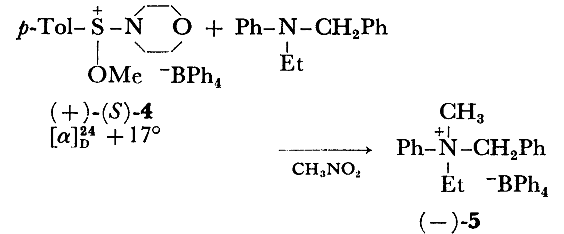


It has been reported that alkoxyaminosulfonium ions alkylate amines and sulfides quantitatively.6) With optically active sulfonium ions, asymmetric induction is to be expected and this has been investigated by the reactions of optically active methoxymorpholino-*p*-tolylsulfonium tetraphenylborate (**4**) with benzylethylphenylamine and benzyl ethyl sulfide.

Optically active **4** ($[\alpha]_D^{24}$ +17°) was prepared by the methylation of optically active (+)-(*S*)-**2** with methyl trifluoromethanesulfonate in nitromethane at 0 °C for 5 h followed by the anion exchange reaction with sodium tetraphenylborate. Assuming the optical purity of the sample is the same as the starting sulfinamide, the optical activity of pure (+)-(*S*)-**4** is estimated to be $[\alpha]_D^{24}$ +22.2°.



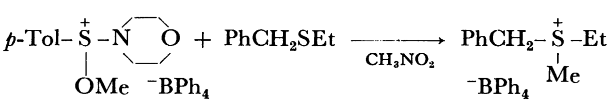
Optically active **4** ($[\alpha]_D^{24}$ +17°) was treated with benzylethylphenylamine in nitromethane at room temperature for 7 d and a salt-like product was obtained. This was shown to be benzylethylmethylphenylammonium tetraphenylborate (**5**), the optical activity of which was found to be $[\alpha]_D^{23}$ −4.0°. Optically pure (+)-**5** was prepared separately by the anion exchange reaction of optically pure benzylethylmethylphenylammonium *d*-camphorsulfonate with sodium tetraphenylborate,[9] $[\alpha]_D^{20}$ +6.5°. Assuming $[\alpha]_D^{20}$ −6.5° for the optically pure (−)-**5**, the optical purity of the methylated amine by the reaction of **4** with benzylethylphenylamine was estimated as 62%.



(+)-(*S*)-**4** $[\alpha]_D^{24}$ +17°

(−)-**5** $[\alpha]_D^{25}$ −4.0° optical purity; 62%

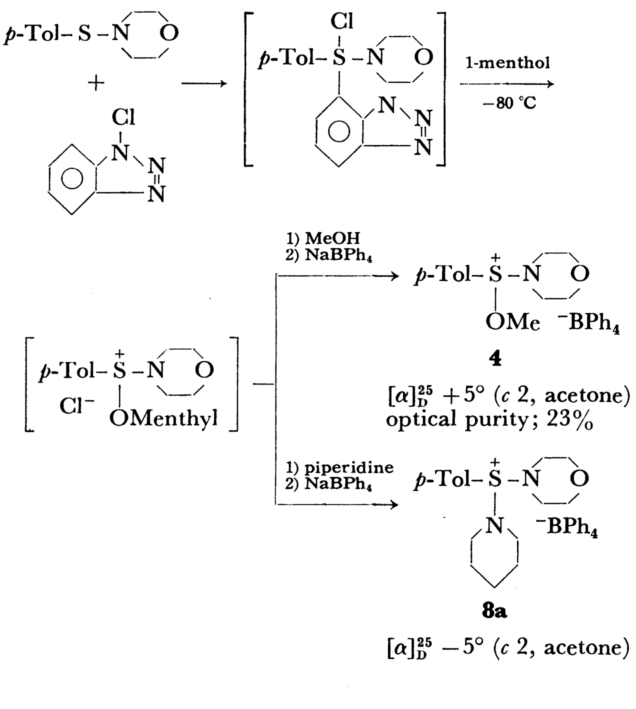
Opically active **4** ($[\alpha]_D^{24}$ +17°) was allowed to react with benzyl ethyl sulfide in nitromethane at room temperature for 5 h and asymmetric benzylethylsulfonium tetraphenylborate (**6**) was formed. The optical activity of the salt (**6**) was determined; $[\alpha]_D^{23}$ −4°.



(+)-(*S*)-**4** $[\alpha]_D^{24}$ +17°

(−)-**6** $[\alpha]_D^{24}$ −4°

Oae and coworkers reported the syntheses of optically active diarylsulfilimines by the reaction of diarylsulfides and *t*-butyl hypochlorite in the presence of l-menthol, followed by treatment with sodium *N*-tosylamide.[10] The asymmetric syntheses of **4** were investigated by applying the method of Oae. *N*-*p*-toluenesulfenylmorpholine was treated with 1-chlorobenzotriazole in dichloromethane at −80 °C for 10 min and l-menthol was added to this solution. The subsequent addition of methanol and sodium tetraphenylborate gave **4**, exhibited optical activity; $[\alpha]_D^{25}$ +5° (*c* 2, acetone).



4 $[\alpha]_D^{25}$ +5° (*c* 2, acetone) optical purity; 23%

8a $[\alpha]_D^{25}$ −5° (*c* 2, acetone)

The optical purity of **4** thus obtained was only 23%. This synthetic method for optically active sulfonium salts has an advantage however in that the reaction can be conducted in one pot. **8a** was prepared in a similar method by the addition of piperidine replacing methanol; $[\alpha]_D^{25}$ −5° (*c* 2, acetone). This is the first example of the optically active diaminosulfonium ion (**8**).

On the basis of these findings, the optically active alkoxyaminosulfonium ion appears to be more useful for asymmetric inducing alkylation for amines and sulfides than the optically active alkoxysulfonium ion.[11]

Experimental

General. Optical rotation was measured on a Applied Electric Lab. MP-1T polarimeter using a 0.5-dm cell. Infrared spectra were obtained on a Hitachi EPI-G_2 spectrometer. NMR spectra were recorded on a Hitachi R-20B spectrometer. Melting points are uncorrected.

Materials. (−)-(*S*)-Menthyl *p*-toluenesulfinate was prepared according to the usual manner; $[\alpha]_D^{20}$ −198° (*c* 2, acetone); lit,[8] $[\alpha]_D^{25}$ −202° (*c* 2, acetone). 1-Chlorobenzotriazole was prepared from benzotriazole and 10% aq NaOCl solution according to the method in the literature.[12] *N*-*p*-toluenesulfenylmorpholine was prepared by the method reported previously; bp 80 °C/4.5 mmHg, mp 39—42 °C.[13]

Preparation of Optically Active N-p-*Toluenesulfinylmorpholine (2).* An anhydrous THF solution (30 ml) of morpholinomagnesium bromide (20 mmol), which was prepared by the reaction of phenylmagnesium bromide (3.73 g; 20 mmol) with morpholine (1.74 g; 20 mmol) was added dropwise to a stirred ether solution (80 ml) of **1** (5.88 g; 20 mmol) for 1 h at 0 °C. The reaction mixture was stirred at 0 °C for an additional 3 h. A saturated ammonium chloride solution (100 ml) was added to the above solution and the ether–THF layer separated. The aqueous layer was extracted three times, with dichloromethane (20 ml), and the combined extracts were concentrated under reduced pressure below 30 °C to give a pale yellow oil. The residue subjected to elution chromatography on silica gel (hexane–ether eluent) afforded 1.24 g of (+)-**2** (5.54 mmol; 28%); $[\alpha]_D^{23}$ +115° (*c* 2.05, acetone).

To ascertain the optical purity, the reaction of **2** with phenyllithium was conducted. An anhydrous ether solution (30 ml) of phenyllithium (10 mmol) was added dropwise to a stirred ether solution (20 ml) of **2** (500 mg; 2.4 mmol) for 30 min at 0 °C. The mixture was stirred at 0 °C for an additional 1 h. A saturated sodium chloride solution (40 ml) was added to the reaction mixture, and the ether layer separated. The aqueous layer was extracted three times with ether. The combined extracts were dried over anhydrous magnesium sulfate, and the solvent evaporated to give oil. The residual oil was separated by column chromatography on silica gel (hexane–ether eluent) to afford (−)-(*S*)-**3**; 150 mg (29%), $[\alpha]_D^{17}$ +21.1° (*c* 1.64, acetone).[8] These rsults indicate that (−)-**2**, which was obtained by the reaction of (−)-(*S*)-**1** with morpholinomagnesium bromide, has 76% optical purity.

*Preparation of Optically Active Methoxymorpholino-*p*-tolylsulfonium Tetraphenylborate (4).* A nitromethane solution (10 ml) of (+)-(*S*)-**2** (620 mg; 2.76 mmol) and methyl trifiuoromethanesulfonate was stirred for 5 h at 0 °C. To this orange solution a nitromethane solution (10 ml) of sodium tetraphenylborate (950 mg; 2.8 mmol) was added. The addition of ether (30 ml) to the reaction mixture formed a precipiatate of sodium trifluoromethanesulfonate, which was removed by filtration. The further addition of ether (60 ml) to the filtrate resulted in the precipitation of **4**; 650 mg, 1.16 mmol (42%). Found: C, 77.37; H, 7.06; N, 2.74%. Calcd for $C_{36}H_{38}NO_2SB$: C, 77.27; H, 6.84; N, 2.56%. $[\alpha]_D^{24}$ +17° (*c* 2, acetone).

Preparation of Optically Active 4. A dichloromethane solution (10 ml) of *N*-*p*-toluenesulfenylmorpholine (3 mmol) and a dichloromethane solution (10 ml) of 1-chlorobenzotriazole (3 mmol) were mixed at −80 °C to give yellow solution. A dichloromethane solution (10 ml) of l-menthol (3 mmol) and methanol (10 ml) was added to this solution at −80 °C. A cooled acetonitrile solution (10 ml) of sodium tetraphenylborate (3 mmol) was added to this solution at −80 °C, and the addition of ether caused the precipitation of a mixture of **4** and sodium chloride which was removed by filtration. Ether was added to the acetone solution to give **4** as colorless needles; 1.05 mmol, yield, 35%, $[\alpha]_D^{25}$ −5° (*c* 2, acetone), mp 149—150 °C.

Preparation of Optically Active 8. A dichloromethane solution (10 ml) of *N*-*p*-toluenesulfenylmorpholine (3 mmol) and a dichloromethane solution (10 ml) of 1-chlorobenzotriazole (3 mmol) were mixed at −80 °C. The addition of a dichloromethane solution (5 ml) of l-menthol (3 mmol) to this yellow solution at −80 °C caused the solution to lose color. A dichloromethane solution (10 ml) of piperidine (3 mmol) was added immediately to this solution, and the solution warmed to room temperature. A nitromethane solution (15 ml) of sodium tetraphenylborate (3 mmol) was added to this pale yellow solution. After 3 h, the addition of ether precipitated a mixture of sodium chloride and morpholinopiperidino-*p*-tolylsulfonium tetraphenylborate (**8a**), which dissolved in acetone–ether to give colorless crystals of **8a**; 200 mg (0.32 mmol; 11.1%), mp 220.5—222 °C, $[\alpha]_D^{25}$ −5° (*c* 2, acetone). Found: C, 78.88; H, 7.04; N, 4.07%. Calcd for $C_{40}H_{45}N_2OSB$: C, 78.41; H, 7.40: N, 4.57%. Optically active *N*-methylphenylaminomorpholino-*p*-tolylsulfonium tetraphenylborate (**8b**), (0.79 mmol, 26%) was prepared in a similar manner from *N*-*p*-toluenesulfenylmorpholine (3 mmol) and *N*-methylaniline (3 mmol), mp 155—156 °C, $[\alpha]_D^{25}$ −4.8° (*c* 2.4, acetone). Found: C, 79.26; H, 6.70, N, 4.41%. Calcd for $C_{42}H_{43}N_2OSB$: C, 79.48; H, 6.83; N, 4.42%.

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