# Reaction of α-Halosulfoxides with Amines[1]

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When optically active bromomethyl *p*-tolyl sulfoxide was treated with sodium methylmercaptide or sodium ethoxide, optically active α-substituted methyl *p*-tolyl sulfoxides were obtained in good yields. By contrast, reaction with secondary amines produced achiral *p*-toluenesulfenamides, methylenediamines, and amine hydrobromides in nearly quantitative yields. The reaction with an amine is presumed to proceed through the initial nucleophilic substitution at α-carbon of the sulfoxide to form aminomethyl *p*-tolyl sulfoxide, followed by rearrangement to the corresponding sulfenate, and subsequent attack of the amine at the sulfur atom of the sulfenate to form the final product. Meanwhile, a facile interconversion of alkoxymethyl *p*-tolyl sulfoxide and corresponding sulfenate was also observed.

α-Halosulfoxides have become useful in the synthesis of various derivatives of sulfoxides. As a typical example,[2] α-epoxysulfoxide can be readily synthesized by the reaction of α-chlorosulfoxide with ketone in the presence of base. However, the nucleophilic substitution reactions of α-chloroalkyl sulfoxides are known to take place slowly.[3]

Recently, Ogura and Tsuchihashi[4] reported that this reaction proceeds through an $S_N2$ process with inversion of configuration at the α-carbon atom of an α-chloroalkyl sulfoxide.

For convenient synthesis of optically active α-substituted methyl aryl sulfoxides, however, this reaction is the shortest route, and hence we examined in detail the reaction of a more reactive and optically active bromomethyl *p*-tolyl sulfoxide with various nucleophiles.

## Results and Discussion

When bromomethyl *p*-tolyl sulfoxide (**1**) was treated with $CH_3S^-$, $C_6H_5S^-$, $CH_3O^-$, and $C_2H_5O^-$, the corresponding α-substituted methyl *p*-tolyl sulfoxides were obtained in good yields (Eq. (1)).

$$\underset{\underset{\text{O}}{\downarrow}}{\text{Tol-S-CH}_2\text{Br}} + \text{X}^- \longrightarrow \underset{\underset{\text{O}}{\downarrow}}{\text{Tol-S-CH}_2\text{-X}} \qquad (1)$$

**1**

$X^- = CH_3S^-,\ C_6H_5S^-,\ CH_3O^-,\ C_2H_5O^-$

$Tol = p\text{-}CH_3C_6H_4$

Further, in the reaction of optically active bromomethyl *p*-tolyl sulfoxide with $CH_3S^-$ and $C_2H_5O^-$, the corresponding optically active α-substituted methyl sulfoxides were obtained in good yields, and the starting optically active α-bromosulfoxide was also readily synthesized by bromination of optically active methyl *p*-tolyl sulfoxide with *N*-bromosuccinimide (NBS), bromine and pyridine in dichloromethane. The optical rotations of these sulfoxides are summarized in Table.

Table Optical rotation[a] of $Tol\text{-}\overset{*}{S}(O)\text{-}CH_2\text{-}X$

| X | H | Br | $SCH_3$ | $OC_2H_5$ |
|---|---|---|---|---|
| $[\alpha]_D$ | +201.0 | +176.7 | +193.3 | +229.5 |
| (*c*,*l*) | (1.00,1) | (1.05,1) | (1.04,1) | (0.83,1) |

a) measured in benzene at 20°C

The data in this Table indicate that the configuration of the sulfoxide is little affected by α-bromination of the sulfoxide or by displacement reaction at the α-carbon atom of the sulfoxide.

However, in the reaction of optically active bromomethyl *p*-tolyl sulfoxide (**1**) with secondary amines (**2**), achiral *p*-toluenesulfenamides (**3**) were produced quantitatively, instead of forming optically active aminomethyl *p*-tolyl sulfoxides.

These reactions occurred when bromomethyl sulfoxide (**1**) was heated at 70°C for 1—2 hr with excess amine (**2a**—**c**) in benzene under nitrogen atmosphere, and *p*-toluenesulfenamide (**3a**—**c**), methylenediamine (**4a**—**c**) and amine hydrobromide (**5a**—**c**) were obtained in nearly quantitative yields (Eq. (2)).

$$\underset{\underset{\text{O}}{\downarrow}}{\text{Tol-S-CH}_2\text{-Br}} + 4\text{RR'NH} \xrightarrow{70^\circ} \text{Tol-S-N-RR'} + \text{RR'NCH}_2\text{NRR'} + \text{RR'NH}\cdot\text{HBr} + \text{H}_2\text{O} \qquad (2)$$

**1** **2a—c** **3a—c** **4a—c** **5a—c**

**a**) R, R′=morpholino
**b**) R, R′=piperidino
**c**) R=R′=$C_2H_5$

This reaction was little affected by the solvent used, since the reaction in acetonitrile or ethanol proceeded smoothly in a similar fashion under the same condition in benzene to form the same products (**3**, **4**, **5**).

The physical and spectroscopic properties of sulfenamides (**3a**—**c**) are identical with those of authentic samples synthesized by the reaction of *p*-toluenesulfenyl chloride with the corresponding amines.

When chloromethyl *p*-tolyl sulfoxide (**6**) was allowed to react with morpholine (**2a**) in chlorobenzene, sulfenamide (**3a**), methylenediamine (**4a**), and amine hydrochloride were formed in nearly quantitative yields, as in the case of bromomethyl sulfoxide (**1**), though a somewhat more drastic condition was necessary. Similarly, chloromethyl methyl sulfoxide (**7**) was

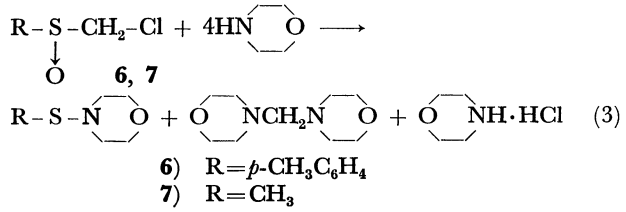
1) Paper XLV on Sulfoxides. A preliminary accounts of this work was given in *Int. J. Sulfur Chem.*, *A*, **1**, 215 (1971).

2) a) D. F. Tavares, R. E. Estep, and M. Blezard, *Tetrahedron Lett.*, **1970**, 2373. b) T. Durst, *J. Amer. Chem. Soc.*, **91**, 1034 (1969). c) T. Durst and K.-C. Tin, *Tetrahedron Lett.*, **1970**, 2369.

3) a) F. G. Bordwell and W. T. Brannen, Jr., *J. Amer. Chem. Soc.*, **86**, 4645 (1964). b) M. Hojo and Z. Yoshida, *ibid.*, **90**. 4496 (1968).

4) K. Ogura and G. Tsuchihashi, *Chem. Commun.*, **1970**, 1689,

found to react with morpholine (**2a**) a little more readily, and methanesulfenomorpholide (*N*-methylthiomorpholine) was also obtained quantitatively (Eq. (3)).



(3)

**6**) R=*p*-$CH_3C_6H_4$
**7**) R=$CH_3$

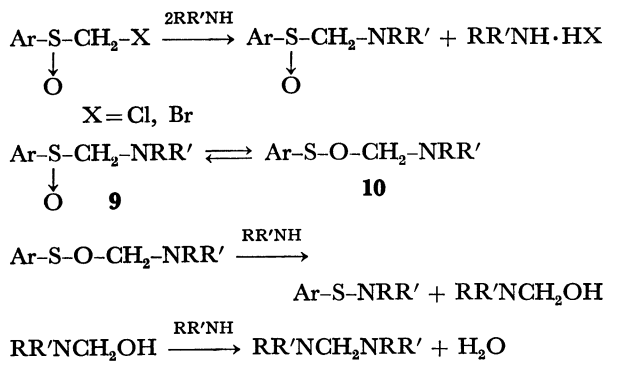
This reaction is influenced markedly by the steric requirement around the α-carbon atom of the sulfoxide, since when α-bromoethyl phenyl sulfoxide (**8**) with excess morpholine was heated in refluxing benzene for 50 hr, benzenesulfenomorpholide was produced in only 40% yield, accompanying with the formation of diphenyl disulfide (15%), while the starting sulfoxide was recovered in 40%. The formation of diphenyl disulfide is presumed to be due to the thermal decomposition of the sulfenamide produced *via* a homolytic pathway.

In the reaction of **1** or **7** with primary amine (*i.e.*, *n*-butylamine, cyclohexylamine, and aniline), *p,p'*-ditolyl disulfide or dimethyl disulfide was formed as main products in 50—80% yields. This appears to be related to the thermal instability of the sulfenamides formed.[5]

As for the stoichiometry, four molar equivalents of amine per one equimolar amount of the α-bromosulfoxide were necessary to complete the reaction according to Eq. (2).

When a solution of an equimolar mixture of the sulfoxide (**1**) and morpholine (**2a**) was heated at 70°C for 5 hr, **3a**, **4a**, and **5a** were formed in 21, 20, and 24% yields, respectively, and the starting sulfoxide (**1**) was recovered in 73%. This means that an intermediate of this reaction would be very reactive and cannot be isolated.

Based on the stoichiometry of the reaction, the following reaction scheme may be suggested:



From the order of the reactivities of α-halosulfoxides (**1**, **6**, **7**, **8**) with morpholine, the reaction is presumed to proceed through the initial nucleophilic substitution at the α-carbon atom of the sulfoxide to form incipiently α-aminomethyl *p*-tolyl sulfoxide (**9**), followed by rearrangement to the sulfenate (**10**). Subsequent attack of an amine at the sulfur atom of the sulfenate (**10**) to afford the sulfenamide and aminomethanol would probably be very rapid. Aminomethanol thus formed would undergo condensation with the amine to afford methylenediamine and water.

Although the sulfenyl ester was not detected in this work, it may be reasonable to postulate that the conversion of the sulfoxide (**9**) to the sulfenyl ester (**10**) is facilitated because of the electron-releasing amino group at the α-carbon.

The reaction between the sulfenate (**10**) and an amine to form the sulfenamide would be very facile, though the reactions of the sulfenate with nucleophiles have little been studied.[6] While aminomethyl *p*-toluenesulfenate (**10**) is not available to test this pathway because of the difficulty in synthesis of this compound, a slightly more stable ethoxymethyl *p*-toluenesulfenate than aminomethyl sulfenate has been prepared and this was found to react readily with morpholine at room temperature to give *p*-toluenesulfenomorpholide quantitatively.

This interpretation for the α-halosulfoxides-amine reaction may also be supported by the observation that substituted ethoxymethyl (or methoxymethyl) *p*-toluenesulfenate is formed in the equilibrium when the corresponding ethoxymethyl (or methoxymethyl) *p*-tolyl-sulfoxide (which has another effective electron-releasing group at α-carbon) was heated under high vacuum. Meanwhile, the reverse conversion of this sulfenate to the sulfoxide is also found to occur readily by dissolving of the sulfenate in nonpolar aprotic solvents such as chloroform.[7]

Such a rearrangement is known in allyl aryl sulfoxides and aryl benzyl sulfoxides.[8]

A somewhat analogous formation of sulfenamides in the reaction of allyl or α-naphthylmethyl aryl sulfoxides with piperidine, apparently *via* the prior rearrangements of the sulfoxides to the sulfenates, was reported recently by Abbott and Stirling.[9]

## Experimental

*Materials.* *Optically Active Methyl* p-*Tolyl Sulfoxide* was prepared by the method of Mislow[10] in which (−)menthyl (−)*p*-toluenesulfinate was reacted with methylmagnesium iodide in ether. mp 75°C, $[\alpha]_D$ +201.0° (*c*=1.00, benzene) Lit,[10] mp 73—74°C, $[\alpha]_D$ +145.5° (*c*=2, acetone).

*Optically Active Bromomethyl* p-*Tolyl Sulfoxide* (*1*) was prepared by bromination of optically active methyl *p*-tolyl sulfoxide with bromine, *N*-bromosuccinimide (NBS), and pyridine in dichloromethane in 80% yield, according to the procedure

5) N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970).

6) C. Brown and D. R. Hogg, *Chem. Commun.*, **1967**, 38.

7) Without solvent, the sulfenate is completely decomposed upon standing overnight at room temperature to form *p*-tolyl *p*-toluenethiolsulfinate quantitatively.

8) a) E. G. Miller, D. R. Rayner, H. T. Thomas, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4861 (1968). b) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *ibid.*, **90**, 4869 (1968). c) R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970). d) S. Bravermann and Y. Stabinsky, *Chem. Commun.*, **1967**, 270.

9) D. J. Abbott and C. J. M. Stirling, *J. Chem. Soc., C*, **1969**, 818.

10) K. Mislow, M. Green, P. Laur, J. T. Mellio, T. Simmons, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **87**, 1958 (1965).

developed by Tsuchihashi.[11] The sulfoxide obtained was recrystallized from cyclohexane. mp 88—89°C, $[\alpha]_D$ +176.7° ($c$=1.05, benzene), $\nu_{SO}$ (KBr) 1044 $cm^{-1}$, NMR ($CDCl_3$) $\delta$=2.53 (3H, s), 4.50 (2H, AB quartet, $J$=11 Hz, $\Delta_{AB}$= 8.3 Hz), 7.74 (4H, m).

*Optically Active Methylthiomethyl* p-*Tolyl Sulfoxide* was prepared by the reaction of optically active bromomethyl *p*-tolyl sulfoxide with sodium mercaptide in 50% $CH_3CN$-$H_2O$ at room temp. for 2 hr in 90% yield. The sulfoxide obtained was recrystallized from cyclohexane. mp 42—44°C, $[\alpha]_D$ +193.3° ($c$=1.04, benzene), $\nu_{SO}$ (KBr) 1038 $cm^{-1}$, NMR ($CDCl_3$) $\delta$=2.35 (3H, s), 2.59 (3H, s), 3.96 (2H, s), 7.82 (4H, m) Found: C, 53.92; H, 5.72%. Calcd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04%.

*Optically Active Ethoxymethyl* p-*Tolyl Sulfoxide* was prepared by the reaction of optically active bromomethyl *p*-tolyl sulfoxide with sodium ethoxide in ethanol at 70° for 5 hr in 85% yield. The sulfoxide obtained was purified by preparative TLC (silica gel) with chloroform as eluent. $[\alpha]_D$ +229.5° ($c$=0.83, benzene), $\nu_{SO}$ (neat) 1050 $cm^{-1}$, NMR ($CDCl_3$) $\delta$=1.33 (3H, t, $J$=7 Hz), 2.56 (3H, s), 4.07 (2H, quartet $J$=7 Hz), 4.64 (2H, s), 7.80 (4H, m) Found: C, 60.72; H, 7.06%. Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12%.

*Chloromethyl* p-*Tolyl Sulfoxide* (**6**) was prepared by the chlorination of methyl *p*-tolyl sulfoxide, which was synthesized by bromine-oxidation of methyl *p*-tolyl sulfide in usual manner,[12] with *N*-chlorosuccinimide (NCS) and pyridine, according to the procedure developed by Tsuchihashi.[13] The sulfoxide obtained was recrystallized from ether-hexane. mp 60.0—61.0°C (lit:[14] mp 61.5—62°C).

*Bromomethyl* p-*Tolyl*, *Methylthiomethyl* p-*Tolyl*, *Methoxymethyl* p-*Tolyl*, *and Ethoxymethyl* p-*Tolyl Sulfoxides* were prepared by the same way used for synthesis of the corresponding optically active compounds as mentioned above.

Bromomethyl isomer, mp 63.0—64.0°C (lit,[11] mp 63°C); methylthiomethyl isomer, mp 61.0—61.5°C; methoxymethyl isomer, $\nu_{SO}$ (neat) 1049 $cm^{-1}$, NMR ($CDCl_3$) $\delta$=2.40 (3H, s), 3.65 (3H, s), 4.38 (2H, s), 7.45 (4H, m).

*Phenylthiomethyl* p-*Tolyl Sulfoxide* was prepared by the reaction of bromomethyl *p*-tolyl sulfoxide with sodium thiophenoxide in ethanol at 70°C for 4 hr in 84% yield. The sulfoxide obtained was recrystallized from benzene-hexane. mp 51—52°C, $\nu_{SO}$ (KBr) 1042 $cm^{-1}$, NMR ($CCl_4$) $\delta$=2.35 (3H, s), 4.12 (2H, s), 7.52 (9H, m) Found: C, 63.79; H, 5.08%. Calcd. for $C_{14}H_{14}OS_2$: C, 64.09; H, 5.38%.

*α-Bromoethyl Phenyl Sulfoxide* (**8**) was prepared by the bromination of ethyl phenyl sulfoxide with bromine, NBS and pyridine in 69% yield. bp 129—130°C/0.5 mmHg, $\nu_{SO}$ (neat) 1056 $cm^{-1}$, NMR ($CDCl_3$) $\delta$=1.90 (3H, d, $J$=7 Hz), 4.87 (1H, quartet $J$=7 Hz), 7.69 (5H, m). Found: C, 41.35; H, 3.68%. Calcd for $C_8H_9OSBr$: C, 41.22; H, 3.89%.

*Chloromethyl Methyl Sulfoxide* (**7**) was prepared by the chlorination of dimethyl sulfoxide with NCS in the presence of $K_2CO_3$ according to the procedure of Tsuchihashi.[13] bp 66—68°C/1 mmHg, (lit,[13] 90°C/4 mmHg).

p-*Toluenesulfenamides* (**3**) were synthesized by the reaction of *p*-toluenesulfenyl chloride, which was synthesized by the method described in the text book,[15] with corresponding excess amines in dichloromethane.

*p*-Toluenesulfenodiethylamide, bp 67°C/1 mmHg; *p*-toluenesulfenomorpholide, bp 100°C/0.5 mmHg; *p*-toluenesulfenopiperidide bp 98°C/0.8 mmHg (Lit[9] 90°C/0.3 mmHg).

*Methanesulfenomorpholide* was prepared by the reaction of methanesulfenyl chloride, which was synthesized from the reaction of dimethyl disulfide with dry chlorine gas according to the procedure of Mislow,[8a] with excess morpholine in dichloromethane. bp 79°C/24 mmHg. (lit,[16] 48—49°C/ 5 mmHg).

*Dimorpholino Methane* (**4a**) was synthesized by condensation of morpholine and formaline according to the procedure of Harradence.[17] bp 120°C/23 mmHg (lit,[17] 139—140°C/29 mmHg).

*Amines* used were purified by twice distillation under nitrogen atmosphere.

*Reaction of α-Haloalkyl Aryl Sulfoxides with Amines.* *i*) *α-Bromosulfoxide with Secondary Amine*: α-Bromosulfoxide (0.5—1 g) was heated at 70°C for 1—2 hr with an excess amine (1—3 g) in dry benzene (5—10 cc) under nitrogen atmosphere until the spot of sulfoxide in thin layer chromatography (tlc) analysis disappeared and amine hydrobromide salt precipitated. After collecting the precipitated amine hydrobromide salt and evaporation of solvent and excess amine *in vacuo*, the oily residue was separated by preparative tlc (silica gel) to afford the sulfenamide and methylenediamine in 90—96% yields.

*ii*) *α-Chlorosulfoxide with Morpholine*: α-chlorosulfoxide (0.5 g) was heated at 120°C for 2.5 hr to complete the reaction with morpholine (1 g) in dry chlorobenzene (5 cc). Method of work up and product analysis are described above.

*Reaction of Chloromethyl Methyl Sulfoxide with Morpholine.* The sulfoxide (1 g) was heated at 70°C for 8 hr with morpholine (5 g) in benzene (20 cc). After collecting amine hydrochloride precipitated, fractional distillation of the reaction mixture under reduced pressure gave first benzene and unchanged morpholine, and subsequently the fraction of methanesulfenomorpholide (79°C/24 mmHg), and the final fraction of dimorpholino methane (120°C/23 mmHg).

*Conversion of Ethoxymethyl* p-*Tolyl Sulfoxide to Sulfenate* The sulfenate was produced as a distillate by rapid vacuum distillation of the sulfoxide using a micro-distillation apparatus in 70—80% yield. bp 100—110°C/1.5 mmHg, IR (neat) 1150, 1120, 920, 800 $cm^{-1}$.

11) S. Iriuchijima and G. Tsuchihashi, *Synthesis*, **1970**, 588.
12) S. Oae, Y. Ohnishi, S. Kozuka, and W. Tagaki, This Bulletin, **39**, 364 (1966).
13) G. Tsuchihashi and S. Iriuchijima, *ibid.*, **44**, 1726 (1971).
14) G. Tsuchihashi and S. Iriuchijima, *ibid.*, **43**, 2271 (1970).
15) F. Kurzer and J. Roy Powell, "Organic Synthesis," Coll. Vol. IV (1963), p. 934.
16) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).
17) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 22 (1939).