Preparation of Optically Active Sulfoxides Bearing Heterocycles and Stereoselective Methylation Using Their α-Sulfinyl Carbanions

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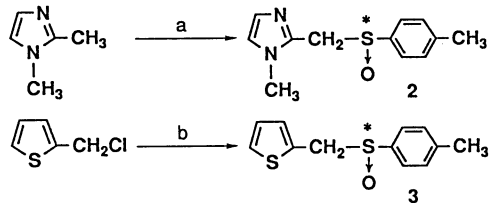
Synopsis. Optically active sulfoxides bearing heterocycles i.e., (1-methyl-2-imidazolyl)methyl and 2-thienylmethyl groups were prepared and their stereoselective methylations were conducted.

Optically active sulfoxides have been widely utilized for asymmetric synthesis,[1] while only a few investigations on the preparation and utilization of optically active heteroaryl sulfoxides have been reported.[2] Recently, we reported the preparation of optically active 2-pyridylmethyl *p*-tolyl sulfoxide (**1**) and highly stereoselective methylation reaction using α-sulfinyl carbanion of **1**.[3] This carbanion also gave highly stereoselective aldol condensation products by treatment with aldehydes.[4] High stereoselectivity of the α-sulfinyl carbanion of **1** observed in the methylation below −70 °C suggests that the structure of carbanion of **1** is highly oriented by chelating Li cation by both the pyridyl nitrogen and the sulfinyl oxygen atoms.[5] This note describes the synthesis of optically active (1-methyl-2-imidazolyl)methyl and 2-thienylmethyl *p*-tolyl sulfoxides (**2** and **3** respectively) together with corresponding racemic sulfoxides and 2-furylmethyl, (1-methyl-2-benzimidazolyl)methyl, and *o*-methoxyphenylmethyl *p*-tolyl sulfoxides (**4**, **5**, and **6** respectively) and a comparison of the stereoselectivity on the methylation reaction of their α-sulfinyl carbanions with iodomethane.

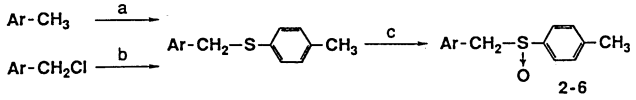
Optically active sulfoxides **2** and **3** were prepared according to the Andersen's procedure[6] as shown in Scheme 1. The reaction of (1-methyl-2-imidazolyl)-



a: *n*-BuLi, THF, *l*-menthyl *p*-toluenesulfinate,
b: Mg, THF, *l*-menthyl *p*-toluenesulfinate.

Scheme 1.

methyllithium and *l*-menthyl *p*-toluenesulfinate was carried out in tetrahydrofuran (THF) to give optically active sulfoxide **2** in 41% yield. However, similar treatment of 2-thienylmethyllithium with *l*-menthyl *p*-toluenesulfinate afforded not the desired sulfoxide **3** but 2-[tris(*p*-tolylsulfinyl)methyl]thiophene in quantitative yield and hence the preparation of optically active sulfoxide **3** was performed using the corresponding Grignard reagent generated from 2-(chloromethyl)thiophene. Racemic sulfoxides **2**—**6** were prepared by oxi-



a: *n*-BuLi, THF, (*p*-Tol-S-)$_2$, b: EtOH–H_2O, *p*-Tol-SH, KOH, c: *m*CPBA, CH_2Cl_2.

Scheme 2.

dation of corresponding sulfides with *m*-chloroperbenzoic acid (*m*CPBA) in moderate yields as shown in Scheme 2.

In order to determine the absolute configurations of these sulfoxides **2** and **3**, their CD spectra were taken and compared with those of the sulfoxides (*R*)-(+)-[2-pyridylmethyl *p*-tolyl sulfoxide] (**1**) and (*R*)-(+)-[benzyl *p*-tolyl sulfoxide] (**7**).[7] Mislow has demonstrated that the absolute configurations of optically active compounds having similar structures can be determined by

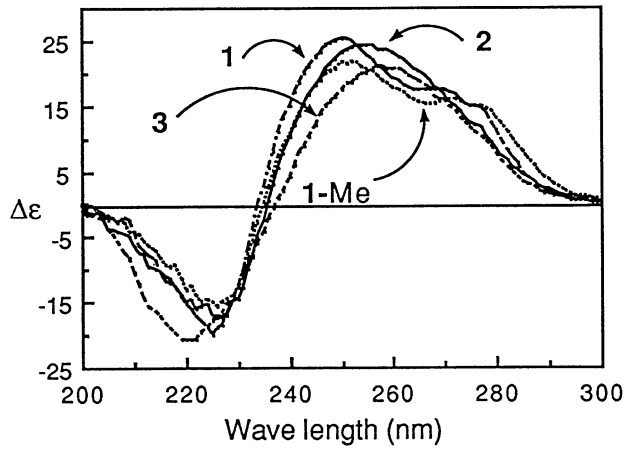


Fig. 1.

Table 1. Spectral Data of Optically Active Sulfoxides

Sulfoxide	UV		CD		
	λ_{max}(nm)	ε	λ_{ext}(nm)	Δε	$[\theta]_{max}\times10^{-4}$
1	266.0	8500	250.0	25.3	+8.4
			225.0	−20.1	−6.6
2	241.5	11500	258.0	21.1	+7.0
			220.0	−20.6	−6.8
3	254.0	8300	254.0	24.3	+8.0
			227.9	−17.4	−5.7
1-Me[a]	264.0	7800	253.0	21.8	+7.2
			223.0	−14.8	−4.9
7[b]			258.0		+7.7
			223.0		−11.7

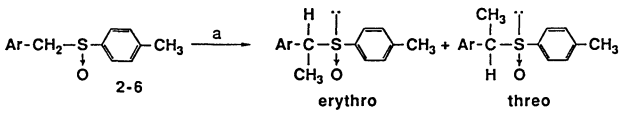
a) (*R*,*R*)-1-(2-Pyridyl)-1-(*p*-tolylsulfinyl)ethane. b) See Ref. 7.

Table 2. Stereoselective Methylation of α-Lithio Sulfoxides Bearing Heteroaromatics with Iodomethane

Sulfoxide	Ar	Temp °C	Yield %	Diastereomeric ratio erythro : threo
2	1-Methyl-2-imidazolyl	−80	87	12.3 : 1
		−20	100	9.7 : 1
		7	100	9.5 : 1
3	2-Thienyl	−90	100	4.5 : 1
		−77	87	4.1 : 1
		−55	91	2.6 : 1
		4	97	1.4 : 1
4	2-Furyl	−90	93	5.2 : 1
		−75	73	4.3 : 1
		−55	93	2.4 : 1
		4	65	1.4 : 1
5	1-Methyl-2-benzimidazolyl	−80	24	1.3 : 1
6	*o*-Methoxyphenyl	−80	97	6.0 : 1

measurement of their CD spectra and presented the empirical rule that the sulfoxides having positive Cotton curves have *R* configuration and vice versa.[8] The CD spectra are shown in Fig. 1 and the data are summarized in Table 1. The CD spectra of **1**—**3** indicate clearly that all the sulfoxides employed in the present investigation have the same sign of Cotton curves and nearly identical magnitudes of the absorptions $[\theta]_{max}$ even by comparing their spectra with (*R*,*R*)-1-(2-pyridyl)-1-(*p*-tolylsulfinyl)ethane.[3] Therefore, the absolute configurations of sulfoxides **2** and **3** were determined to be *R*.

The methylation reaction was carried out using LDA as a base and then iodomethane in THF as shown in Scheme 3 and Table 2. In the reaction of sulfoxide **2** at −80 °C, *erythro*-1-(1-methyl-2-imidazolyl)]-1-(*p*-tolylsulfinyl)ethane was obtained more preferentially than the *threo* derivative with a ratio of 12.3 : 1. This result reveals that the reaction of the carbanion with iodomethane proceeds via a nearly identical manner with the methylation of sulfoxide **1**, namely via an initial formation of a rigid chelation complex which prevents the approach of iodomethane from its *threo* site as shown in Fig. 2. Interestingly, stereoselectivity for the methylation of the carbanion generated from **2** is rather insensitive to the reaction temperature. This result is markedly contrasted to methylations of other sulfoxides. In the case of sulfoxides **3**—**6** the ratios of isomers were found not to be as high as those obtained from **1** and **2** suggesting that their α-sulfinyl carbanions are unable to form a rigid chelation complexes. These results also support that the chelation of Li cation by the heteroatoms plays an important role in the stereoselectivity. The values of log(*erythro*/*threo*) of the methylation products shown in Table 2 were plotted against the temperatures giving straight lines and the $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values were calculated by conventional Arrhenius equation; $\Delta\Delta G^{\neq}=\Delta\Delta H^{\neq}-T\Delta\Delta S^{\neq}=-RT \ln[erythro]/[threo]$. The results are summarized in Table 3.



a: LDA, THF, CH_3I.

Scheme 3.

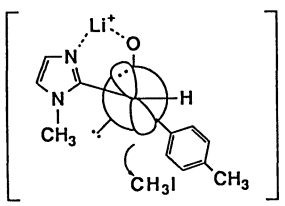


Fig. 2.

Table 3. Activation Parameter for Methylation of Sulfoxides **2**, **3**, and **4**

Sulfoxide	$\Delta\Delta H^{\neq}$/kJ mol^{-1}	$\Delta\Delta S^{\neq}$/kJ mol^{-1} deg^{-1}
2	1.40	−13.55
3	5.48	16.93
4	6.12	19.62

The results are consistent roughly with our previous result obtained from the methylation reaction of the α-sulfinyl carbanion of **1** with iodomethane. The present results demonstrate that the carbanion generated from sulfoxide **2** is somewhat different from that of other sulfoxides bearing heterocycles. Among these heterocycles, 1-methylimidazolyl group should have highest capability for chelation with Li cation to provide a conformer which is attacked preferentially by iodomethane from the *erythro* site, thus enhancing the *erythro* stereoselectivity of its carbanion. The present investigation demonstrates the synthetic utility of the sulfoxides bearing azaheterocycles.

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO A-3 spectrometer. ^{1}H NMR spectra were obtained with a Hitachi R-600 or a Bruker AM-500, or a JEOL EX-270. Preparative liquid chromatography was performed on a Japan Analytical Co., Ltd., LC-09. Elemental analyses were carried out by Chemical Analysis Center at this university. The CD spectra were measured on a JASCO J-600 spectrometer. All reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co., Ltd., or Aldrich Chemical Co. The solvents were purified by general methods.

Preparation of Optically Active Sulfoxides. (*R*)-(+)-[(1-Methyl-2-imidazolyl)methyl *p*-Tolyl Sulfoxide] (2). To a stirred solution of 1,2-dimethylimidazole (9.6 g, 0.1 mol) in THF (300 mL) at −78 °C was added 1.66 M *n*-BuLi (1 M=1 mol dm^{-3}) in hexane solution (65 mL, 0.11 mol). The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. The mixture was added dropwise to (*S*)-(−)-*l*-menthyl *p*-toluenesulfinate (29.5 g, 0.1 mol) in THF (300 mL) with stirring at −78 °C for 0.5 h and then −20 °C for 4 h. After hydrolysis and neutralization with aqueous ammonium chloride, the mixture was extracted with chloroform (3×500 mL). The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent, ethyl acetate–methanol=10 : 1) to give sulfoxide **2** in 41% yield. Recrystallization from benzene–hexane gave colorless crystals; mp 86—87 °C; ^{1}H NMR ($CDCl_3$) δ=7.36 (d, J=8 Hz, 2H, 2,6-ArH), 7.29 (d, J=8 Hz, 2H, 3,5-ArH), 6.99 (d, J=1 Hz, 1H, 5-ImdH), 6.82 (d, J=1 Hz, 1H, 4-ImdH), 4.26, 4.10 (ABq, J=15 Hz, 2H, CH_2), 3.45 (s, 3H, Imd-CH_3), 2.41 (s, 3H, Ar-CH_3); IR (KBr) 1050 cm^{-1} (SO); $[\alpha]_D$ +177.9° (c=0.5, acetone). Optical purity was estimated ca. 100% by ^{1}H NMR using Eu(tfc)$_3$ as a chiral shift reagent. Found: C, 61.47 H, 6.02; N, 11.92%. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96%.

(*R*)-(+)-[2-Thienylmethyl *p*-Tolyl Sulfoxide] (3). This sulfoxide was prepared similarly as sulfoxide **2** using 2-thienylmethylmagnesium chloride. Yield 18%; mp 123—124 °C; ^{1}H NMR ($CDCl_3$) δ=7.33 (d, J=8 Hz, 2H, 2,6-ArH), 7.25 (d, J=8 Hz, 2H, 3,5-ArH), 7.23—7.22 (m, 1H, 5-ThH), 6.94—6.92 (m, 1H, 4-ThH), 6.74 (m, 1H, 3-ThH), 4.24, 4.19 (ABq, J=14 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3); IR (KBr) 1040 cm^{-1} (SO); MS (m/z) 139 (M^+−97); $[\alpha]_D$ +139.7° (c=0.5, chloroform). Found: C, 60.94; H, 5.14%. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12%.

Preparation of Racemic Sulfoxides Bearing Heterocycles. (1-Methyl-2-imidazolyl)methyl *p*-Tolyl Sulfoxide (2). Yield 52%; mp 128—130 °C; ^{1}H NMR ($CDCl_3$) δ=7.36 (d, J=8 Hz, 2H, 2,6-ArH), 7.29 (d, J=8 Hz, 2H, 3,5-ArH), 6.99 (d, J=1 Hz, 1H, 5-ImdH), 6.82 (d, J=1 Hz, 1H, 4-ImdH), 4.26, 4.10 (ABq, J=15 Hz, 2H, CH_2), 3.45 (s, 3H, Imd-CH_3), 2.41 (s, 3H, Ar-CH_3); IR (KBr) 1050 cm^{-1} (SO). Found: C, 61.44; H, 6.03; N, 11.92%. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96%.

2-Thienylmethyl *p*-Tolyl Sulfoxide (3). Yield 93%; mp 95—96 °C; ^{1}H NMR ($CDCl_3$) δ=7.33 (d, J=8 Hz, 2H, 2,6-ArH), 7.25 (d, J=8 Hz, 2H, 3,5-ArH), 7.23—7.22 (m, 1H, 5-ThH), 6.94—6.92 (m, 1H, 3-ThH), 6.74 (m, 1H, 4-ThH), 4.24, 4.19 (ABq, J=14 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3); IR (KBr) 1040 cm^{-1} (SO). Found: C, 61.02; H, 5.23%. Calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12%.

2-Furylmethyl *p*-Tolyl Sulfoxide (4). Yield 74%; colorless liquid; ^{1}H NMR ($CDCl_3$) δ=7.37 (d, J=8 Hz, 2H, 2,6-ArH), 7.33 (m, 1H, 5-FurH), 7.28 (d, J=8 Hz, 2H, 3,5-ArH), 6.31 (m, 1H, 3-FurH), 6.15 (m, 1H, 4-FurH), 4.15, 4.02 (ABq, J=14 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3); IR (neat) 1040 cm^{-1} (SO). Found: C, 65.30; H, 5.52%. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49%.

(1-Methyl-2-benzimidazolyl)methyl *p*-Tolyl Sulfoxide (5). Yield 12%; mp 157—160 °C; ^{1}H NMR ($CDCl_3$) δ=7.72—7.24 (m, 8H, ArH), 4.43, 4.29 (ABq, J=15 Hz, 2H, CH_2), 3.67 (s, 3H, BzImd-CH_3), 2.40 (s, 3H, Ar-CH_3); IR (KBr) 1010 cm^{-1} (SO). Found: C, 67.75; H, 5.51; N, 9.87%. Calcd for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85%.

***o*-Methoxyphenylmethyl *p*-Tolyl Sulfoxide (6).** Yield 90%; colorless liquid; ^{1}H NMR ($CDCl_3$) δ=7.49—6.69 (m, 8H, ArH), 4.18, 4.00 (ABq, J=14 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 2.38 (s, 3H, Ar-CH_3); IR (neat) 1030 cm^{-1} (SO). Found : C, 68.97; H, 6.17%. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19%.

Methylation of Lithiated Sulfoxides 2—6 with Iodomethane. Typical experimental procedure is as follows: Sulfoxide **2** (200 mg, 0.854 mmol) was dissolved into THF (10 mL) under argon atmosphere. The solution was cooled to −80 °C, and solution of LDA (0.928 mmol) in THF (2.7 mL) was added with stirring for 30 min. To this solution was added iodomethane (0.27 mL, 4.34 mmol) and the mixture was stirred for 8 h. The reaction was stopped by adding water (5 mL) and the mixture was warmed to room temperature. After hydrolysis and neutralization with aqueous ammonium chloride, the mixture was extracted with chloroform (3×30 mL) and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, ethyl acetate) to give 1-(1-methyl-2-imidazolyl)-1-(*p*-tolylsulfinyl)ethane in 87% yield. The products contained in 12.3 : 1 ratio of *erythro* and *threo* isomers. The *erythro* isomer was separated by preparative liquid chromatography. Mp 128—130 °C; ^{1}H NMR ($CDCl_3$) δ=7.28 (s, 4H, ArH), 7.02 (m, 1H, 5-ImdH), 6.92 (m, 1H, 4-ImdH), 4.14 (q, J=7 Hz, 1H, CH), 3.68 (s, 3H, Imd-CH_3), 2.42 (s, 3H, Ar-CH_3), 1.53 (d, J=7 Hz, 3H, CH-CH_3); IR (KBr) 1030 cm^{-1} (SO); MS (m/z) 246 (M^+). Found: C, 62.59 ; H, 6.60; N, 11.29%. Calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28%. The *threo* isomer could not be isolated and was determined the structure by ^{1}H NMR chemical shifts of the mixture. Other sulfoxides were treated similarly and the ratios of isomers were determined by ^{1}H NMR spectra.

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