ortho-Sulfenylation of *N,N*-Dimethyl-1-phenylethylamine and Oxidation of the Resultant Sulfides

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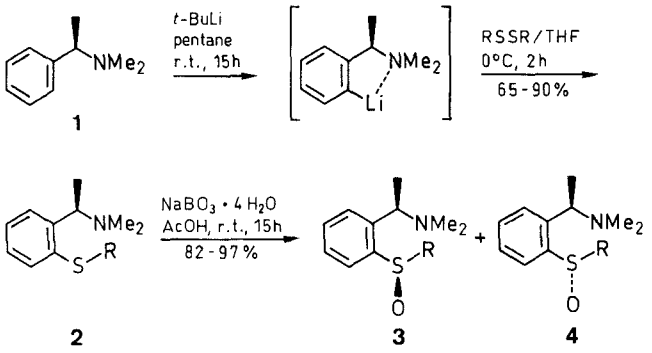
The ortho-lithiation of chiral *N,N*-dimethyl-1-phenylethylamine (**1**) followed by sulfenylation and oxidation of the resulting sulfides afforded chiral sulfoxides **3** and **4**. Use of sodium perborate as the oxidant gave the highest de.

Recently, chiral sulfoxides have established themselves a significant position in asymmetric syntheses[1] and many methods for their synthesis are known.[2] However, an attempt to obtain chiral sulfoxides by the oxidation of aryl sulfides substituted by a chiral group at the ortho position has never been reported. In 1978 van Koten et al. published a paper[3] on the ortho-lithiation of *N,N*-dimethyl-1-phenylethylamine (**1**). This chiral amine is prepared from a very cheap chiral reagent, 1-phenylethylamine and therefore easily accessible. We have now carried out the sulfenylation of the 2-lithio compound prepared from (+)-(*R*)-**1** with dialkyl disulfides to obtain the corresponding aryl sulfides **2a–d** carrying a chiral group (Scheme 1). The oxidation of **2a–d** with various agents and the stereochemistry of the product mixture of sulfoxides **3a–d** and **4a–d** were studied.



Scheme 1

The lithiation of (*R*)-**1** was carried out with *tert*-butyllithium in pentane and the solvent was removed under reduced pressure at room temperature. After dissolving the residual solid in tetrahydrofuran, dialkyl disulfides were added to the solution and the mixture was stirred at room temperature for 2 hours give the desired products (R)-**2a–d** (Table 1). When the addition of dialkyl disulfide was carried out without changing the solvent from pentane to tetrahydrofuran, the yield of the target compounds obviously went down.

The ability of various reagents to oxidize (*R*)-**2b** with diastereoselectivity was examined. As shown in Table 2, sodium perborate reported by McKillop and Tarbin[4] gave good results, while organic peracids were ineffective for this diastereoselective oxidation.

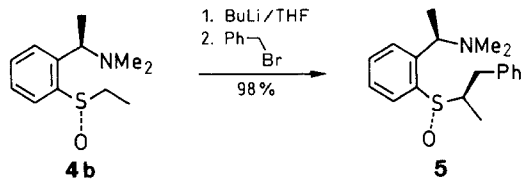
Oxidation of (*R*)-**2a–d** was then carried out with sodium perborate and the results are shown in Table 3. The resulting two sulfoxides could be separated from each other by column chromatography on silica gel using a mixture of hexane, ethyl acetate and 2-propanol as eluent. The first eluted sulfoxides **3a–d** have the same signs (+) for the optical rotations as their starting materials and more polar sulfoxides **4a–d** have the reverse sign (−). The yield of (+)-**3a–d** was lower than (−)-**4a–d**. With regard to their ^{1}H NMR spectra, the signal based on an α-methine proton neighboring to an amino group in **3a–d** appeared at a lower field than **4a–d** with a difference of about 0.7 ppm (Table 4).

The absolute structure of these sulfoxides was established as (*Rc, Rs*)-**3a–d** and (*Rc, Ss*)-**4a–d** by X-ray diffraction (Figure) pattern of the *N,N*-dimethyl-1-[2-(1-benzylethylsulfinylphenyl]ethylamine (**5**) prepared from **4b**[5] (Scheme 2).

Table 1. Compounds **2a–d** Prepared

Product	R	Yield[a] (%)	bp (°C)/ Torr	$[\alpha]_D$[b]	Molecular Formula[c]	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (M^+) (*m/z*)
2a	Me	74	100–105/5	+48.2°	$C_{11}H_{17}NS$ (195.1)	1.30 (d, 3H, *J* = 6.0), 2.21 (s, 6H), 2.42 (s, 3H), 3.74 (q, 1H, *J* = 6.0), 7.16–7.26 (m, 3H), 7.45 (dd, 1H, *J* = 1.4, 7.6)	195
2b	Et	90	110–113/3	+83.4°	$C_{12}H_{19}NS$ (209.1)	1.22 (d, 3H, *J* = 7.0), 1.26 (t, 3H, *J* = 7.0), 2.19 (s, 6H), 2.82 (q, 2H, *J* = 7.0), 3.76 (q, 1H, *J* = 7.0), 7.03–7.21 (m, 3H), 7.39 (dd, 1H, *J* = 1.4, 7.6)	209
2c	*c*-C_6H_{11}	65	125–130/3	+28.4°	$C_{16}H_{25}NS$ (263.2)	1.28 (d, 3H, *J* = 6.6), 1.30–1.40 (m, 10H), 2.22 (s, 6H), 3.05–3.15 (m, 1H), 3.97 (q, 1H, *J* = 6.6), 7.13–7.39 (m, 2H), 7.40 (dd, 1H, *J* = 1.5, 7.7)	263
2d	$PhCH_2$	70	colorless syrup	+42.4°	$C_{17}H_{21}NS$ (271.1)	1.26 (d, 3H, *J* = 6.8), 2.22 (s, 6H), 3.12 (q, 1H, *J* = 6.8), 3.95 (s, 2H), 7.13–7.42 (m, 9H)	271

[a] Yield of isolated products.
[b] Optical rotations measured in $CHCl_3$ (*c* = 1.0).
[c] Satisfactory HRMS values obtained: ±0.0024 amu.



Scheme 2

Table 2. Oxidation of **2b** with Various Oxidants

Oxidant[a]	Solvent	Yield (%)[b] 3b	4b	Ratio[c] 3b/4b	de (%)
PMA	$CHCl_3$	19	20	49/51	1
30% H_2O_2	AcOH	31	36	46/54	7
MCPBA	AcOH	29	41	41/59	18
$K_2S_2O_8$	AcOH	15	83	17/83	66
$NaBO_3$	AcOH	14	84	17/83	66
$NaBO_3$	5% AcOH	28	38	40/60	20

[a] PMA = permaleic acid, MCPBA = *m*-chloroperbenzoic acid.
[b] Yield of isolated products.
[c] Ratio measured from ^1H NMR of the reaction mixture.

Table 3. Oxidation of **2a–d** with Sodium Perborate

Substrate	R	Products (Yield; %)[a]	Ratio[b] 3/4	de (%)
2a	Me	**3a** (10), **4a** (72)	11/89	78
2b	Et	**3b** (14), **4b** (84)	17/83	66
2c	*c*-C_6H_{11}	**3c** (17), **4c** (80)	18/82	64
2d	$PhCH_2$	**3d** + **4d** (92)	40/60	20

[a] Yield of isolated products. The mixture of **3d** and **4d** could not be separated.
[b] Ratio measured from ^1H NMR of the reaction mixture.

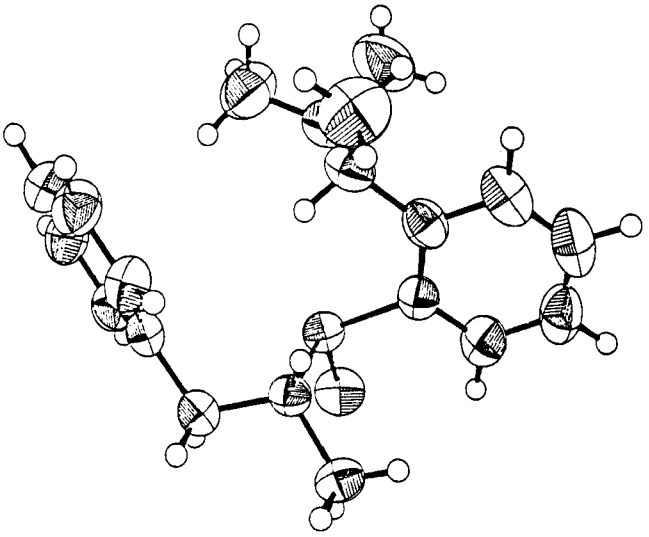


Figure. Ortep diagram of **5**

All reagents were of commercial quality. 1.7 M solution of *t*-BuLi in pentane was purchased from Aldrich Chemical Co. Dialkyl disulfides were purchased from Tokyo Kasei Kogyo Co., Ltd. $NaBO_3 \cdot 4H_2O$, $K_2S_2O_8$ and *m*-chloroperbenzoic acid were purchased from Wako Pure Chemical Industries, Ltd. (+)-(*R*)-*N*,*N*-Dimethyl-1-phenylethylamine (**1**) was prepared from (+)-(*R*)-1-phenylethylamine (Tokyo Kasei Kogyo Co.) according to the reported procedure.[3] Permaleic acid was prepared from maleic anhydride with 60% H_2O_2 according to the reported procedure.[6] THF and pentane were dried over molecular sieves and sodium metal. The other reagent quality solvents were used without further purification. Melting points were taken using Yanagimoto micro melting points apparatus and are uncorrected. Mass spectra were obtained using Hitachi M-80B spectrometer. ^1H NMR spectra were recorded on Bruker AM-400 spectrometer using TMS as an internal standard. Optical rotations were measured at the Na-D line with Japan Spectroscopic Co. DIP-360 polarimeter.

(+)-(*R*)-*N*,*N*-Dimethyl-1-(2-ethylthiophenyl)ethylamine (2b); Typical Procedure:

Under an argon atmosphere, *t*-BuLi (1.7 M solution in pentane, 12 mL, 20 mmol) was added to a solution of (+)-(*R*)-*N*,*N*-dimeth-

Table 4. Compounds **3a–c** and **4a–c** Prepared

Product	Yield (%)	$[\alpha]_D$[b]	Molecular Formula[c]	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (DCI) m/z ($M^+ + 1$)
3a	10	+147°	$C_{11}H_{17}NOS$ (211.1)	1.36 (d, 3H, J = 6.5), 2.24 (s, 6H), 2.76 (s, 3H), 4.44 (q, 1H, J = 6.5), 7.30 (dd, 1H, J = 1.3, 7.9), 7.43 (dt, 1H, J = 1.4, 8.0), 8.07 (dd, 1H, J = 1.4, 7.9)	212
3b	14	+176°	$C_{12}H_{19}NOS$ (225.1)	1.31 (d, 3H, J = 6.8), 1.39 (t, 3H, J = 7.6), 2.11 (s, 6H), 2.71 (dq, 1H, J = 7.4, 13), 2.99 (dq, 1H, J = 7.6, 13), 4.03 (q, 1H, J = 6.6), 7.31 (dd, 1H, J = 1.3, 7.5), 7.41 (dt, 1H, J = 1.4, 7.6), 7.47 (dt, 1H, J = 1.4, 7.5), 8.04 (dd, 1H, J = 1.4, 7.6)	226
3c	18	+215°	$C_{16}H_{25}NOS$ (279.2)	1.29 (d, 3H, J = 6.8), 1.18–1.92 (m, 10H), 2.18 (s, 6H), 2.75–2.88 (m, 1H), 3.87 (q, 1H, J = 6.8), 7.39–7.45 (m, 3H), 7.92 (dd, 1H, J = 1.3, 7.6)	280
4a	72	−106°	$C_{11}H_{17}NOS$ (211.1)	1.44 (d, 3H, J = 6.8), 2.18 (s, 6H), 2.69 (s, 3H), 3.37, 7.34 (dd, 1H, J = 1.4, 7.6), 7.41 (dt, 1H, J = 1.3, 7.5), 7.49 (dt, 1H, J = 1.4, 7.4), 8.14 (dd, 1H, J = 1.3, 7.6)	212
4b	84	−132°	$C_{12}H_{19}NOS$ (225.1)	1.29 (t, 3H, J = 7.6), 1.41 (d, 3H, J = 6.8), 2.19 (s, 6H), 2.63 (dq, 1H, J = 7.4, 13), 2.93 (dq, 1H, J = 7.5, 13), 3.40 (q, 1H, J = 6.8), 7.39 (dd, 1H, J = 1.3, 7.5), 7.42 (dt, 1H J = 1.3, 7.6), 7.46 (dt, 1H, J = 1.3, 7.6), 8.03 (dd, 1H, J = 1.4, 7.5)	226
4c	80	−160°	$C_{16}H_{25}NOS$ (279.2)	1.38 (d, 3H, J = 6.8), 1.18–1.93 (m, 10H), 2.20 (s, 6H), 2.56–2.66 (m, 1H), 3.49 (q, 1H, J = 6.8), 7.41–7.46 (m, 3H), 7.91 (dd, 1H, J = 1.3, 7.5)	280

[a] Yield of isolated products. All the products were obtained as colorless syrups, except **4c**; mp 72–73°C (heptane). For R, see Table 2.
[b] Optical rotations were measured in $CHCl_3$.
[c] Satisfactory HRMS values obtained for **3a–c** (±0.0037 amu) and **4a, b** (±0.0013 amu). Satisfactory microanalyses obtained for **4c**: C −0.17, H ±0.0, N −0.06.

yl-1-phenylethylamine (**1**; 3.0 g, 20 mmol) in pentane (20 mL) cooled in an ice-water bath. The mixture was stirred for 15 h at r.t. to give a colorless turbid suspension. This was concentrated in vacuo at r.t. and dry THF (20 mL) was added. To the resulting pale yellow clear solution was added diethyl disulfide (2.5 g, 21 mmol) under cooling in an ice-water bath. The mixture was stirred for 2 h and poured into 10% HCl (100 mL). After washing with Et_2O (3 × 30 mL), the aqueous solution was neutralized with solid K_2CO_3 and extracted with Et_2O (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed to give a pale yellow oil, which was purified by distillation under reduced pressure; yield: 3.76 g (90%).

Oxidation of 2b with Sodium Perborate; Typical Procedure:
To a solution of **2b** (2.1 g, 10 mmol) in glacial AcOH (50 mL) was added powdered $NaBO_3 \cdot 4H_2O$ (1.6 g, 10.4 mmol). The mixture was stirred for 15 h at r.t. and poured into 10% HCl (100 mL). The resulting aqueous solution was extracted with Et_2O (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed to give a pale yellow viscous oil, which was applied to a column packed with silica gel (Wakogel C-200, 150 g). Elution with a mixture of hexane/EtOAc (80:20) afforded first (+)-(*Rc*, *Rs*)-*N,N*-dimethyl-1-(2-ethylsulfinylphenyl)ethylamine (**3b**); yield: 315 mg (14%). Further elution with a mixture of hexane/EtOAc/*i*-PrOH (60:30:10) gave (−)-(*Rc*, *Ss*)-*N,N*-dimethyl-1-(2-ethylsulfinylphenyl)ethylamine (**4b**); yield: 1.88 g (84%).

(−)-(*Rc*,*Ss*)-*N,N*-Dimethyl-1-[2-(1-(*R*)-benzylethylsulfinylphenyl]-ethylamine 5:
To a solution of **4b** (1.13 g, 5 mmol) in dry THF (20 mL) was added BuLi (1.6 M solution in hexane, 3.7 mL, 6 mmol) at −78 °C under an argon atmosphere. After stirring for 30 min at −78 °C, benzyl bromide (1.00 g, 6 mmol) was added and the mixture stirred for 2 h and poured into 10% HCl (100 mL). The aqueous solution was first washed with Et_2O (3 × 30 mL) to remove impurities and then neutralized with solid K_2CO_3 and extracted again with Et_2O (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed to give a colorless solid; yield: 1.55 g (98%). Recrystallization from heptane gave **5** as colorless prisms; mp 100–101 °C; $[\alpha]_D^{25}$ −109° (*c* = 1.0, $CHCl_3$).

$C_{19}H_{25}NOS$	calc.	C 72.34	H 7.99	N 4.44
(315.4)	found	72.28	8.04	4.41

MS (DCI): $m/z = 316\ (M + 1)^+$.

^1H NMR ($CDCl_3$/TMS): δ = 1.01 (d, 3 H, *J* = 6.5 Hz), 1.29 (d, 3 H, *J* = 6.7 Hz), 2.04 (s, 6 H), 2.89 (dd, 1 H, *J* = 7.7, 13 Hz), 2.90–3.00 (m, 1 H), 3.04 (dd, 1 H, *J* = 6.7, 13 Hz), 3.23 (q, 1 H, *J* = 6.7 Hz), 7.26–7.46 (m, 8 H), 7.93 (dd, 1 H, *J* = 2.2 and 6.8 Hz).

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(5) X-ray crystallographic data for **5** were measured on Rigaku AFC5R diffractometer (CuK_α radiation). Atomic coordinates, bond lengths and angles, structure factors, thermal parameters, final fractional coordinates, torsion angles, and least-squares planes results have been deposited with us. (*Rc*, *Rs*) means (*R*) on the asymmetric carbon and (*R*) on the asymmetric sulfur. (*Rc*, *Ss*) menas (*R*) on the asymmetric carbon and (*S*) on the asymmetric sulfur.
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