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Resolution of racemic aryl dichloromethyl sulfoxides with (−)-menthone

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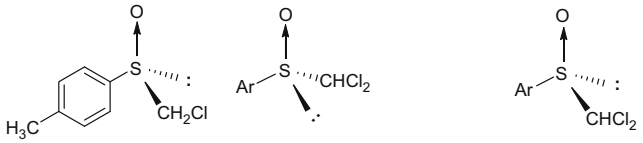
ABSTRACT

The addition reaction of the sodium α-sulfinyl carbanion of a racemic aryl dichloromethyl sulfoxide to (−)-menthone in the presence of boron trifluoride diethyl etherate gave an adduct as a mixture of two easily separable diastereomers. After separation of the diastereomers, they were each treated with sodium hydride to afford enantiomerically pure aryl dichloromethyl sulfoxides and (−)-menthone both in high yields. This procedure provides a simple and efficient method for the resolution of racemic aryl dichloromethyl sulfoxides.

1. Introduction

Chiral sulfoxides are one of the most widely used chiral auxiliaries in asymmetric synthesis. In view of their importance in organic synthesis, their synthesis, chemistry, and synthetic uses have long been investigated and reviewed.[1] Previously, we studied the preparation of chiral chloromethyl *p*-tolyl sulfoxide **1** and 1-chloroalkyl *p*-tolyl sulfoxides,[2] and their uses in new asymmetric syntheses.[3] In continuation of our interest in aryl 1-halogenated-alkyl sulfoxides in organic synthesis, we recently started to investigate the use of aryl dichloromethyl sulfoxide and some new synthetic methods have appeared (Fig. 1).[4]



1 (*S*)-**2a** Ar = 4-Methylphenyl; **b** Ar = Phenyl; **c** Ar = 2-Naphthyl; **d** Ar = 4-Methoxyphenyl; **e** Ar = 4-Chlorophenyl; **f** Ar = 4-Nitrophenyl (*R*)-**2**

Figure 1.

In our aforementioned new synthetic methods using aryl dichloromethyl sulfoxide, in some cases, it was anticipated that when optically active aryl dichloromethyl sulfoxide was used, a new asymmetric synthesis could be performed.[4b,c] However, to the best of our knowledge, only one report has been published for the preparation of chiral aryl dichloromethyl sulfoxides **2**.[5] Herein, we report a new method for the preparation of chiral aryl dichloromethyl sulfoxides (*S*)-**2** and (*R*)-**2** by the resolution of their racemates with (−)-menthone.

2. Results and discussion

A representative example is reported for the resolution of racemic dichloromethyl *p*-tolyl sulfoxide **2a** as shown in Scheme 1. At first, racemic dichloromethyl *p*-tolyl sulfoxide **2a** was synthesized from methyl *p*-tolyl sulfoxide with NCS in THF in high yield.[4a] A solution of sodium hexamethyldisilazide (NaHMDS; 1.9 mol/L solution in THF; 1.26 mL, 2.4 mmol) was added dropwise to a solution of racemic **2a** (446 mg; 2.0 mmol), (−)-menthone (0.52 mL; 3.0 mmol), and BF_3–OEt_2 (0.39 mL; 3.0 mmol) in 20 mL of dry THF at −78 °C. The reaction mixture was stirred at −78 °C for 10 min and the reaction was quenched by adding satd aq NH_4Cl. The addition reaction proceeded from the equatorial side of the ketone group in menthone[6], and adduct **3a** was obtained as a mixture of two diastereomers with respect to the sulfur stereogenic center. Starting material **2a** was recovered in 9% yield from this reaction. It is also noteworthy that when this reaction was conducted without the Lewis acid, only a complex mixture was obtained. Fortunately, the diastereomers were found to be easily separable on silica gel column chromatography to give the more polar adduct **3a-P** (R_f value 0.25; Merck Silica Gel TLC plate $60F_{254}$ (hexane–AcOEt = 5:1); 335 mg; 44%) and the less polar adduct **3a-L** (R_f value 0.48; 305 mg; 40%) both as amorphous solids. The structure of adducts **3a** was not clear at this stage; however, later, the whole structures of **3a-P** and **3a-L** were determined as shown in Scheme 1.

Next, NaH (1.8 mmol) was added to a solution of the main product **3a-P** (335 mg; 0.89 mmol) in 10 mL of THF at 0 °C and the reaction mixture was stirred for 10 min. By this treatment, a retro-aldol-type reaction took place to give enantiomerically pure dichloromethyl *p*-tolyl sulfoxide (+)-**2a** ($[\alpha]_D$ = +172.3, acetone;

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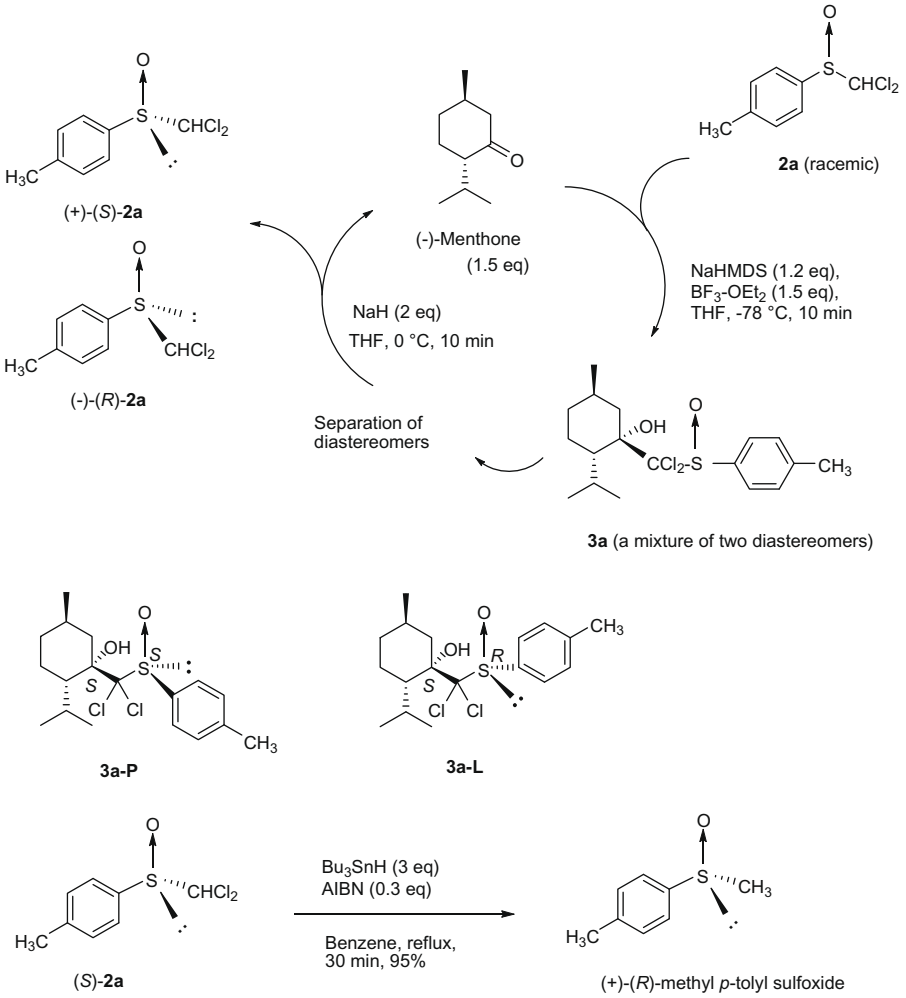
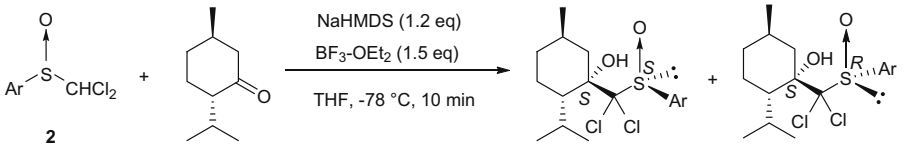
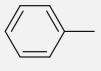
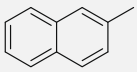
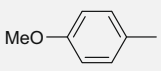
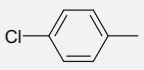
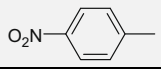


Scheme 1. Resolution of racemic dichloromethyl *p*-tolyl sulfoxide **2a** with (−)-menthone.

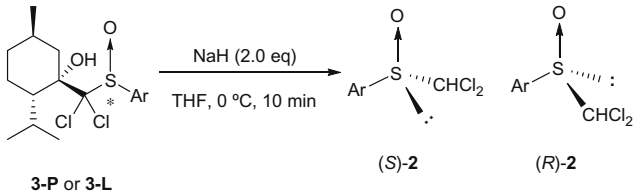
Table 1
Addition reaction of sodium α-sulfinyl carbanion of aryl dichloromethyl sulfoxide **2** to (−)-menthone



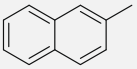
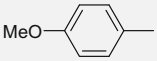
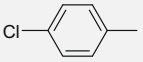
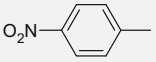
Entry	2		Yield (%)		
		Ar	3-P	3-L	2[a]
1	**2b**		38	41	13
2	**2c**		39	43	9
3	**2d**		30	34	19
4	**2e**		36	35	11
5	**2f**		31	34	17

[a] The yield for the recovered starting aryl dichloromethyl sulfoxide **2**.

Table 2
The retro-aldol-type reaction of adducts **3-P** and **3-L** with NaH to afford (*S*)-**2** and (*R*)-**2**, respectively



3-P or **3-L** (*S*)-**2** (*R*)-**2**

Entry	Ar	(*S*)-**2**			(*R*)-**2**		
		Yield (%)	ee[a] (%)	$[\alpha]_D$[b]	Yield (%)	ee[a] (%)	$[\alpha]_D$[b]
1		88	98	+152.3	90	97	−150.7
2		91	99	+182.8	94	99	−179.7
3		88	98	+152.8	91	99	−145.3
4		90	99	+160.6	90	99	−158.0
5		93	99	+153.6	85	99	−159.6

[a] The enantiomeric purity was determined by HPLC with chiral stationary column, CHIRALCEL OD.
[b] All specific rotations were measured in acetone at room temperature.

183 mg; 92%) as colorless crystals. The enantiomerical purity of the product was easily determined to be over 99% by HPLC with chiral stationary column, CHIRALCEL OD. In this reaction, at the same time, (−)-menthone was obtained in 93% yield. The chlorine atoms in the dichloromethyl *p*-tolyl sulfoxide (+)-**2a** produced were reduced with Bu_3SnH under radical conditions[7] to give (+)-(*R*)-methyl *p*-tolyl sulfoxide[8] in 95% yield. The absolute configuration of the dichloromethyl *p*-tolyl sulfoxide (+)-**2a** produced was determined to be (*S*) from the results of this reduction. The same treatment of adduct **3a-L** gave (−)-(*R*)-dichloromethyl *p*-tolyl sulfoxide (*R*)-**2a** ($[\alpha]_D$ = −174.4, acetone) in 90% yield with (−)-menthone (90%).

The whole procedure can be expressed as a cycle shown in Scheme 1. Thus, the reaction of (−)-menthone with racemic **2a** gives an adduct as an about 1:1 mixture of two diastereomers **3a**. These diastereomers are easily separated by a silica gel column chromatography to give **3a-P** and **3a-L**. A retro-aldol-type reaction takes place when adducts **3a-P** and **3a-L** are treated separately with NaH to give enantiomerically pure (+)-(*S*)-**2a** and (−)-(*R*)-**2a**, respectively, with (−)-menthone, both in high yields. Needless to say, the recovered (−)-menthone can be used in the next experiment without further purification.

The generality of this procedure was investigated with racemic dichloromethyl phenyl sulfoxide **2b**, dichloromethyl 2-naphthyl sulfoxide **2c**, dichloromethyl 4-methoxyphenyl sulfoxide **2d**, dichloromethyl 4-chlorophenyl sulfoxide **2e**, and dichloromethyl 4-nitrophenyl sulfoxide **2f**. The results for the addition reaction of the sodium α-sulfinyl carbanion of racemic aryl dichloromethyl sulfoxides **2** with (−)-menthone are summarized in Table 1. As shown in Table 1, all the reactions gave an almost 1:1 mixture of adducts **3-P** and **3-L** in up to 82% yields with 9–19% yields of recovered starting material **2**. The separation of the two diastereomers by silica gel column chromatography proved to be a straightforward task.

The removal of the chiral auxiliary, (−)-menthone, from adducts **3-P** and **3-L** proceeded smoothly with NaH in THF at 0 °C and the results are summarized in Table 2. All the reactions gave optically active aryl dichloromethyl sulfoxides in between 85% and 94% yields and in about 99% enantiomeric purity. Data for the produced enantiomerically pure aryl dichloromethyl sulfoxides are reported in the Ref. 9.

3. Conclusion

In conclusion, a simple, efficient, and reliable procedure for the resolution of racemic aryl dichloromethyl sulfoxides was achieved by using (−)-menthone as the chiral auxiliary in two steps. Moreover, the (−)-menthone used is recovered in almost quantitative yield and can be reused without special purification. The procedure presented herein should contribute greatly to the synthesis of enantiomerically pure aryl dichloromethyl sulfoxides and to asymmetric synthesis using chiral sulfoxides.

Acknowledgments

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Motohashi, S.; Kimura, S.; Tokutake, N.; Yamakawa, K. *Tetrahedron Lett.* **1993**, *34*, 4823; (b) Satoh, T.; Kobayashi, S.; Nakanishi, S.; Horiguchi, K.; Irisa, S. *Tetrahedron* **1999**, *55*, 2515; (c) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891; (d) Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281; (e) Satoh, T.; Fukuda, Y. *Tetrahedron* **2003**, *59*, 9803; (f) Wakasugi, D.; Satoh, T. *Tetrahedron* **2005**, *61*, 1245; (g) Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **2005**, *16*, 665; (h) Satoh, T.; Hirano, M.; Kuroiwa, A.; Kaneko, Y. *Tetrahedron* **2006**, *62*, 9268; (i) Kido, M.; Sugiyama, S.; Satoh, T. *Tetrahedron: Asymmetry* **1934**, *2007*, 18; (j) Sugiyama, S.; Nakaya, N.; Satoh, T. *Tetrahedron: Asymmetry* **2008**, *19*, 401; (k) Nakaya, N.; Sugiyama, S.; Satoh, T. *Tetrahedron Lett.* **2009**, *50*, 4212.

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9. Data for enantiomerically pure aryl dichloromethyl sulfoxides **2a**–**2f** are as follows.

(+)-(*S*)-Dichloromethyl *p*-tolyl sulfoxide (*S*)-**2a**: Colorless crystals; mp 49.5–50 °C (AcOEt–hexane); IR (KBr) 2965, 1593, 1490, 1165, 1086, 1063, 1014, 809, 787, 648, 511 cm^{-1}; ^1H NMR δ 2.45 (3H, s), 6.15 (1H, s), 7.35–7.40 (2H, m), 7.66–7.70 (2H, m). MS *m*/*z* (%) 222 (8), 139 (100), 91 (12), 77 (6), 55 (7). Calcd for $C_8H_8Cl_2OS$: *M*, 221.9673. Found: *m*/*z* 221.9675. $[\alpha]_D^{28} = +172.3$ (*c* 0.36, acetone).

(−)-(*R*)-Dichloromethyl *p*-tolyl sulfoxide (*R*)-**2a**: Colorless crystals; mp 49.5–50 °C (AcOEt–hexane); $[\alpha]_D^{28} = -174.4$ (*c* 1.0, acetone).

(+)-(*S*)-Dichloromethyl phenyl sulfoxide (*S*)-**2b**: Colorless oil; IR (neat) 3060, 2960, 1445, 1060, 782, 688, 515 cm^{-1}; ^1H NMR δ 6.17 (1H, s), 7.54–7.67 (3H, m), 7.78–7.82 (2H, m). MS *m*/*z* (%) 208 (7), 125 (100), 97 (20), 77 (22), 51 (12), 28 (16). Calcd for $C_7H_6Cl_2OS$: *M*, 207.9516. Found: *m*/*z* 207.9513. $[\alpha]_D^{29} = +152.3$ (*c* 0.50, acetone).

(−)-(*R*)-Dichloromethyl phenyl sulfoxide (*R*)-**2b**: Colorless oil. $[\alpha]_D^{29} = -150.7$ (*c* 0.50, acetone).

(+)-(*S*)-Dichloromethyl 2-naphthyl sulfoxide (*S*)-**2c**: Colorless crystals; mp 95.5–96 °C (AcOEt–hexane); IR (KBr) 2954, 1585, 1348, 1183, 1073, 1053, 817, 784, 739, 477 cm^{-1}; ^1H NMR δ 6.25 (1H, s), 7.59–7.69 (2H, m), 7.79 (1H, dd, *J* = 1.74, 8.62 Hz), 8.00 (1H, s), 7.93–8.03 (2H, m), 8.33 (1H, s). MS *m*/*z* (%) 258 (10), 175 (100), 147 (18), 127 (23), 115 (8). Calcd for $C_{11}H_8Cl_2OS$: *M*, 257.9673. Found: *m*/*z* 257.9675. $[\alpha]_D^{28} = +182.8$ (*c* 0.30, acetone).

(−)-(*R*)-Dichloromethyl 2-naphthyl sulfoxide (*R*)-**2c**: Colorless crystals; mp 95.5–96 °C (AcOEt–hexane); $[\alpha]_D^{28} = -179.7$ (*c* 0.31, acetone).

(+)-(*S*)-Dichloromethyl 4-methoxyphenyl sulfoxide (*S*)-**2d**: Colorless oil; IR (neat) 2963, 1593, 1497, 1259, 1066, 832, 786, 529 cm^{-1}; ^1H NMR δ 3.89 (3H, s), 6.14 (1H, s), 7.04–7.09 (2H, m), 7.70–7.75 (2H, m). MS *m*/*z* (%) 238 (4), 155 (100), 139 (5), 123 (4), 92 (5), 77 (5), 64 (3), 28 (10). Calcd for $C_8H_8Cl_2O_2S$: *M*, 237.9622. Found: *m*/*z* 237.9620. $[\alpha]_D^{28} = +152.8$ (*c* 0.30, acetone).

(−)-(*R*)-Dichloromethyl 4-methoxyphenyl sulfoxide (*R*)-**2d**: Colorless oil. $[\alpha]_D^{28} = -145.3$ (*c* 0.50, acetone).

(+)-(*S*)-Dichloromethyl 4-chlorophenyl sulfoxide (*S*)-**2e**: Colorless crystals; mp 57.5–58 °C (AcOEt–hexane); IR (KBr) 2963, 1568, 1471, 1387, 1088, 1061, 785, 741, 505 cm^{-1}; ^1H NMR δ 6.18 (1H, s), 7.54–7.59 (2H, m), 7.72–7.77 (2H, m). MS *m*/*z* (%) 242 (9), 161 (45), 159 (100), 131 (13), 111 (12), 75 (12), 28 (16). Calcd for $C_7H_5Cl_3OS$: *M*, 241.9127. Found: *m*/*z* 241.9123. $[\alpha]_D^{28} = +160.6$ (*c* 0.25, acetone).

(−)-(*R*)-Dichloromethyl 4-chlorophenyl sulfoxide (*R*)-**2e**: Colorless crystals; mp 57.5–58 °C (AcOEt–hexane); $[\alpha]_D^{28} = -158.0$ (*c* 0.18, acetone).

(+)-(*S*)-Dichloromethyl 4-nitrophenyl sulfoxide (*S*)-**2f**: Colorless crystals; mp 83.5–84 °C (AcOEt–hexane); IR (KBr) 2986, 1606, 1533, 1343, 1087, 1063, 852, 791, 752, 680, 535 cm^{-1}; ^1H NMR δ 6.29 (1H, s), 8.00–8.03 (2H, m), 8.42–8.45 (2H, m). MS *m*/*z* (%) 253 (22), 170 (52), 154 (11), 124 (17), 96 (12), 83 (100), 76 (20), 70 (10), 50 (18), 28 (20). Calcd for $C_7H_5Cl_2NO_3S$: *M*, 252.9367. Found: *m*/*z* 252.9365. $[\alpha]_D^{28} = +153.6$ (*c* 0.30, acetone).

(−)-(*R*)-Dichloromethyl 4-nitrophenyl sulfoxide (*R*)-**2f**: Colorless crystals; mp 83.5–84 °C (AcOEt–hexane); $[\alpha]_D^{28} = -159.6$ (*c* 0.19, acetone).