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Reductive α-Substitution of Sulfoxides with Grignard Reagents Promoted by a Magnesium Amide

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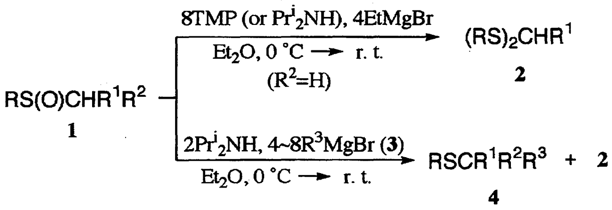
The reactions of sulfoxides bearing α-hydrogen(s) ($RSOCHR^1R^2$: R-alkyl or aryl; R^1, R^2 = H, alkyl, or aryl) with Grignard reagents (R^3MgBr: R^3 = Et, Ph, or vinyl) in the presence of the diisopropylaminomagnesium reagent, generated in situ by the treatment of diisopropylamine with the appropriate Grignard reagents in diethyl ether, have resulted in the formation of the corresponding sulfides ($RSCR^1R^2R^3$) in moderate to good isolated yields.

We have recently reported that the reaction of sulfoxides bearing α-hydrogens **1** (R^2=H) with magnesium amides generated in situ by the treatment of ethylmagnesium bromide (EtMgBr) with a secondary amine (1 : 2) affords the corresponding dithioacetals **2** (Eq. 1; **1**→**2**) through the sulfur-stabilized carbonium ion **5** (Eq. 2).$^{1)}$ As a part of our study on the reactivities of magnesium amides toward sulfoxides, the reaction of sulfoxides with Grignard reagents in the presence of a magnesium amide has been undertaken. There have been a number of reports on reactions of sulfoxides with Grignard reagents.$^{2—5)}$ In 1961, Oda and Yamamoto reported that the reaction of dimethyl sulfoxide with Grignard reagents without using any catalysts under refluxing conditions in diethyl ether gave the corresponding α-substituted dimethyl sulfides up to 36% yield.$^{3)}$ Later, for a specific example, Hojo et al. reported on the reductive α-substitution of methyl (methylthio)methyl sulfoxide with Grignard reagents in satisfactory yields.$^{4)}$ We have found that the reaction of various sulfoxides bearing α-hydrogen(s) **1** with the reagents generated in situ by the treatment of Grignard reagents **3**, such as ethyl-, vinyl-, or phenyl-magnesium bromide, with diisopropylamine (2—4 : 1) gives the corresponding sulfides **4** including a tertiary alkyl sulfide (Eq. 1; **1**→**4**+**2**) in moderate to good yields.



(1)

$$R\overset{+}{S}=CR^1R^2 \longleftrightarrow RS\overset{+}{C}R^1R^2 \qquad (2)$$

5

A solution of a Grignard reagent (4 mmol) in diethyl ether was allowed to react with diisopropylamine (DIPA) (2 mmol) for 1 h at 0 °C, and the resulting mixture was treated with each sulfoxide **1** (1 mmol) for an additional 1 h at room temperature. The use of less than 2 molar amounts of DIPA resulted in a lowering of the yield of sulfides **4**. The results obtained are summarized in Table 1. We first examined the reaction of methyl phenyl sulfoxide (**1a**) with EtMgBr (**3a**) in the presence of a magnesium amide generated from **3a** and DIPA and found that phenyl propyl sulfide (**4a**) was produced in 65% yield, along with the formation of bis(phenylthio)methane (**2a**)$^{1)}$ in 15% yield (Entry 1). The use of methyl 4-methylphenyl sulfoxide (**1b**) gave a similar result (Entry 2). When sulfoxides bearing an α-substituent **1c**, **d**, and **e** were allowed to react under the same conditions, the addition products **4c**, **d**, and **e**, respectively, were obtained in moderate to good yields (59—78%) without any formation of the corresponding dithioacetals (Entries 3, 4, and 5). This reaction has been extended to the preparation of tertiary alkyl sulfides. First, isopropyl phenyl sulfoxide (**1f**) was treated with the reagent generated from DIPA (2 molar amounts) and **3a** (4 molar amounts) to give 1,1-dimethylpropyl phenyl sulfide (**4f**) in 36% yield along with 1-methylethenyl phenyl sulfide (**6**) (48%).$^{1)}$ However, the use of 8 molar amounts of **3a** provided a better result: Simultaneous increase in the yield of **4f** (72%) and decrease in the yield of **6** (23%) (Entry 6). Phenylmagnesium bromide (**3b**) and vinylmagnesium bromide (**3c**) were also usable for this reaction and gave the corresponding sulfides **4g** and **h**, respectively (entries 7 and 8).

The results described above have shown that the magnesium amide improves the yields of the reductive α-substitution of sulfoxides by promoting the generation of the sulfur-stabilizing carbonium ion **5**, which may be possible with only a Grignard reagent,$^{5)}$ and that the present reaction offers an efficient method for the α-alkylative reduction of sulfoxides to sulfides.

Experimental

General. The mps were recorded with a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were determined with a Perkin–Elmer 1600 Series FT IR

Table 1. Reactions of Sulfoxides **1** with Grignard Reagents **3** in the Presence of the Diisopropylaminomagnesium Reagent

Entry	**1**	**3**[a)]	Yield/%[b)]	
			4	**2**
1	**1a** (R=Ph, R^1=R^2=H)	**3a** (R^3=Et)	65 (**4a**)	15 (**2a**)
2	**1b** (R=*p*-Tol, R^1=R^2=H)	**3a**	62 (**4b**)	12 (**2b**)
3	**1c** (R=*p*-Tol, R^1=Me, R^2=H)	**3a**	66 (**4c**)	—
4	**1d** (R=Bn, R^1=Ph, R^2=H)	**3a**	59 (**4d**)	—
5	**1e** (R=*n*-Bu, R^1=*n*-Pr, R^2=H)	**3a**	78 (**4e**)	—
6	**1f** (R=Ph, R^1=R^2=Me)	**3a** [c)]	72 (**4f**)	—[d)]
7	**1g** (R=Me, R^1=R^2=H)	**3b** (R^3=Ph)	61 (**4g**)	—
8	**1a**	**3c** (R^3=Vinyl)	58 (**4h**)	—

a) Four molar amounts unless otherwise stated. b) Isolated yields determined by preparative TLC on SiO_2 or Kugelrohr distillation. c) Eight molar amounts. d) 1-Methylethenyl phenyl sulfide (**6**) was produced in 23% yield.

spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference in $CDCl_3$ with a Hitachi R-90 FT NMR spectrometer operating at 90 MHz. High- and low-resolution mass spectra were recorded with a JEOL JMS-DX 303 spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All of the reactions were carried out under argon.

Starting Materials. Sulfoxides **1a**, **d**, and **g** were commercially available. Methyl 4-methylphenyl sulfoxide (**1b**)[6)] was prepared by the $NaIO_4$ oxidation of the corresponding sulfide obtained commercially. Ethyl 4-methylphenyl sulfoxide (**1c**)[7)] and isopropyl phenyl sulfoxide (**1f**)[8)] were prepared by the standard method (alkylation of the corresponding sodium thiolates followed by the $NaIO_4$ oxidation of the resulting sulfides).

Phenyl Propyl Sulfide (4a). General Procedure. To a stirred solution of EtMgBr (4 mmol) in Et_2O (7 ml) was added DIPA (0.20 g, 2 mmol) at 0 °C. After this was stirred for 1 h, phenyl methyl sulfoxide (**1a**) (0.14 g, 1 mmol) was added and the resulting mixture was stirred for an additional 1 h at room temperature. The reaction mixture was quenched with aq NH_4Cl and the product was extracted with Et_2O. The extract was washed with brine, dried over anhyd $MgSO_4$, and evaporated. The residue was subjected to PLC on SiO_2 (1 : 10 EtOAc–hexane) to give **4a**[9)] (99 mg, 65%) and **2a** (17 mg, 15%).

The spectral and physical data of the products **4b**, **c**, **d**, **e**, **g**, **h**, and **2b** are as follows.

4-Methylphenyl Propyl Sulfide (4b):[9)] R_f 0.68 (1 : 10 EtOAc–hexane); IR (neat) 1492 and 804 cm^{-1}; ^{1}H NMR δ=1.00 (3H, t, J=7.5 Hz), 1.45—1.85 (2H, m), 2.31 (3H, s), 2.77 (2H, t, J=7.5 Hz), 7.07 (2H, d, J=8.4 Hz), and 7.26 (2H, d, J=8.4 Hz).

Bis(4-methylphenylthio)methane (2b):[10)] Identified by a comparison of its ^{1}H NMR spectrum with that reported by Kakimoto et al.[11)]

4-Methylphenyl 1-Methylpropyl Sulfide (4c):[12)] R_f 0.70 (1 : 10 EtOAc–hexane); IR (neat) 1492 and 804 cm^{-1}; ^{1}H NMR δ=0.99 (3H, t, J=7.5 Hz), 1.24 (3H, d, J=6.8 Hz), 1.45—1.8 (2H, m), 2.32 (3H, s), 2.8—3.2 (1H, m), 7.08 (2H, d, J=7.9 Hz), and 7.31 (2H, d, J=7.9 Hz).

Benzyl 1-Phenylpropyl Sulfide (4d): R_f 0.45 (1 : 10 EtOAc–hexane); IR (neat) 1493, 1453, 758, and 698 cm^{-1}; ^{1}H NMR δ=0.83 (3H, t, J=7.3 Hz), 1.85 (2H, m), 3.36 (1H, d, J=14.1 Hz), 3.54 (1H, t, J=6.4 Hz), 3.55 (1H, d, J=14.1 Hz), 7.22 (5H, s), and 7.29 (5H, s); MS *m*/*z* (%) 242 (M^+; 22), 119 (59), and 91 (100). Found: *m*/*z* 242.1107. Calcd for $C_{16}H_{18}S$: M, 242.1130.

1-Ethylbutyl Butyl Sulfide (4e): Bp 75 °C (bath temp)/16 Torr[#]; IR (neat) 1464 and 1378 cm^{-1}; ^{1}H NMR δ=0.8—1.1 (9H, m), 1.2—1.8 (10H, m), and 2.4—2.8 (3H, m); MS *m*/*z* (%) 174 (M^+; 96) and 145 (100). Found: *m*/*z* 174.1439. Calcd for $C_{10}H_{22}S$: M, 174.1443.

Benzyl Methyl Sulfide (4g): This compound was identified by a direct comparison with a sample obtained commercially.

Phenyl 2-Propenyl Sulfide (4h):[13)] Bp 110 °C (bath temp)/22 Torr (lit,[7)] 104—106 °C/25 Torr); IR (neat) 1630, 1581, 1477, 1438, 998, 913, 740, and 690 cm^{-1}; ^{1}H NMR δ=3.46 (2H, d, J=6.4 Hz), 4.8—5.2 (2H, m), 5.5—6.2 (1H, m), and 7.0—7.4 (5H, m).

1,1-Dimethylpropyl Phenyl Sulfide (4f). Isopropyl phenyl sulfoxide (**1f**) (0.15 g, 1.0 mmol) was treated with the reagent generated from DIPA (2.0 mmol) and EtMgBr (8.0 mmol) under the reaction conditions described in General Procedure to give, after isolation by PLC (hexane), **4f** (1.3 g, 72%; R_f 0.33), which was characterized by comparing its spectral data (IR and ^{1}H NMR) with those reported by Babin et al.,[14)] and **6**[1,15)] (35 mg, 23%; R_f 0.48).

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