An Efficient Synthesis of Unsymmetrical Dithioacetals from Sulfoxides and Thiols by the Magnesium Amide-Induced Pummerer-Type Reaction

Kazuhiro Kobayashi,* Masataka Kawakita, Hideki Akamatsu, Osamu Morikawa, and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680

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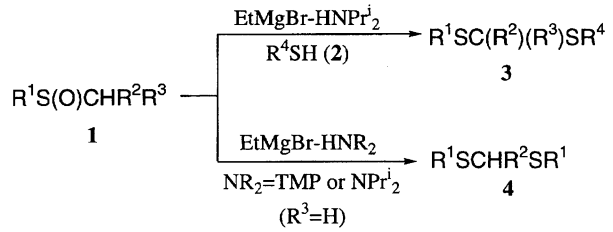
It has been found that the reactions of sulfoxides bearing hydrogen(s) at the α-position ($R^1SOCHR^2R^3$: R^1 = alkyl or Ph; R^2 = H, alkyl, or Ph; R^3 = H or Me) with thiols (R^4SH: R^4 = alkyl or aryl) in the presence of the (diisopropylamino)magnesium reagent, generated in situ from the reaction of ethylmagnesium bromide and diisopropylamine, in diethyl ether gave unsymmetrical dithioacetals ($R^1SCR^2R^3SR^4$) in isolated yields ranging from 44 to 91%.

We have recently reported that the reaction of sulfoxides bearing α-hydrogens **1** (R^3 = H) with magnesium amides, generated in situ by a treatment of ethylmagnesium bromide (EtMgBr) with a secondary amine, such as diisopropylamine or 2,2,6,6-tetramethylpiperidine (TMP), affords the corresponding symmetrical dithioacetals **4** (Scheme 1; **1**→**4**).[1] As a part of our study on the reactivities of magnesium amides toward sulfoxides[1,2] we examined the reaction of sulfoxides bearing hydrogen(s) at the α-position **1** with various thiols **2** in the presence of a magnesium amide, aiming at the development of a more efficient method for preparing unsymmetrical dithioacetals. A selective synthesis of unsymmetrical dithioacetals has been achieved by the reaction of α-halo sulfides with thiolates,[3] the action of Grignard reagents upon dithioesters,[4] and by the Pummerer-type reaction of sulfoxides with thiols induced by trifluoroacetic anhydride[5] or *O*-*t*-butyldimethylsilyl *O*-methyl ketene acetal in the presence of zinc iodide.[6] Among these methods, the Pummerer-type reaction seems to be the most efficient because of its advantages over the other methods: It has not only milder reaction conditions, but also exhibits a ready availability of the starting materials. However, no application to the preparation of ketone dithioacetals has yet been achieved by this method. We found that the reaction of **1** with **2** in the presence of the (diisopropylamino)magnesium reagent affords the corresponding unsymmetrical dithioacetals **3**, including ketone dithioacetals **3e** and **f**, in moderate-to-good yields, and that it provides a new efficient method for a general preparation of this class of compounds (Scheme 1; **1**→**3**),[7] which are of interest because of their potential biogenetic activities.[3,8] The magnesium amide is illustrated to be a more useful reagent for the synthesis of unsymmetrical dithioacetals from sulfoxides and thiols.



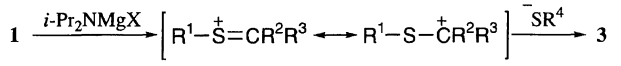
Scheme 1.

The reaction depicted in Scheme 1 (**1**→**3**) was carried out as follows. Ethylmagnesium bromide (4 mmol) was treated with diisopropylamine (4 mmol) in diethyl ether at 0 °C for 1 h. To the resulting turbid solution of the (diisopropylamino)magnesium reagent was successively added one of the thiols **2** (2 mmol); after 20 min one of the sulfoxides **1** (1 mmol) was added at the same temperature. The reaction mixture was then allowed to warm up to room temperature and was stirred overnight. After the usual work-up of the resulting reaction mixture, the crude product was purified by preparative thin-layer chromatography on silica gel. Table 1 summarizes the yields of unsymmetrical dithioacetals **3** obtained by experiments using various sulfoxides **1** and thiols **2** under the reaction conditions described above, which are indicative of the scope and usefulness of this reaction. Both of the aliphatic and aromatic thiols worked well to give the corresponding dithioacetals **3** in moderate-to-good yields. Green and Jenkins have reported that 4-chlorophenylthio(phenylthio)methane (**3a**) (Entry 1) displays mite ovicidal activity.[3] Benzylthio(phenylthio)methane (**3b**) (Entry 2) has been reported to display strong activity as a miticide.[8] When the sulfoxide bearing two α-substituents was used, the yield of product **3e** was somewhat diminished, most probably due to a steric hindrance of the starting sulfoxide (Entry 5); a simultaneous production of 2-phenylthiopropene in 24% yield, which resulted from the eliminative deoxygenation of **2e**,[1b] was observed. This is the first time that the preparation of a ketone dithioacetal has been achieved by a Pummerer-type process.[5,6] A cyclic sulfoxide, such as tetrahydrothiophene 1-oxide (**1f**), was successfully employed in the present transformation to give the cyclic dithioacetal **3i** (Entry 9). It is

Table 1. Formation of Dithioacetals **3** from Sulfoxides **1** and Thiols **2**

Entry	Sulfoxide	Thiol	3 (Yield/%)[a]
1	**1a** (R^1 = Ph, R^2 = R^3 = H)	**2a** (R^4 = *p*-ClC_6H_4)	**3a** (91)
2	**1a**	**2b** (R^4 = Bn)	**3b** (68)
3	**1a**	**2c** (R^4 = Et)	**3c**[b] (62)
4	**1b** (R^1 = Ph, R^2 = Me, R^3 = H)	**2a**	**3d**[b] (63)
5	**1c** (R^1 = Ph, R^2 = R^3 = Me)	**2a**	**3e** (52)
6	**1c**	**2d** (R^4 = Ph)	**3f** (53)
7	**1d** (R^1 = Me, R^2 = R^3 = H)	**2d**	**3g** (87)
8	**1e** (R^1 = Bn, R^2 = Ph, R^3 = H)	**2d**	**3h** (75)
9	**1f** [R^1, R^2 = $(CH_2)_3$, R^3 = H]	**2d**	**3i** (44)

a) Yields reported here are for the products isolated by preparative TLC on SiO_2. b) Not previously described.



Scheme 2.

natural that the present reaction has been applied to the preparation of a symmetrical dithioacetal, such as 2,2-bis(phenylthio)propane (**3f**), from 1-methylethyl phenyl sulfoxide (**1c**) and benzenethiol (**2d**) (Entry 6). Compound **3f** could not be produced from only **1c** through treatment with a magnesium amide.[1] Only a trace amount of the corresponding symmetrical dithioacetal **4**, which was produced from two molecules of the starting sulfoxide,[1] was obtained in each experiment.

Based on the mechanism for the formation of dithioacetals **4** from **1** (reported previously by us[1b]), a probable pathway for the transformation of **1** into **3**, which involves a nucleophilic attack of a thiolate anion to Pummerer-type intermediate **5**, resulting from the action of the magnesium amide upon **1**, is proposed (Scheme 2).

In the present work it was demonstrated that the reaction between sulfoxides bearing α-hydrogens with thiols in the presence of a magnesium amide provides a general and convenient preparation of unsymmetrical dithioacetals. The simple operation and wide applicability of the starting materials make the present method attractive.

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 spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with either a JEOL JNX-PMX 60 NMR spectrometer operating at 60 MHz in CCl_4 or a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Low-resolution mass spectra were recorded with a JEOL AUTOMASS 20 spectrometer (Center for Cooperative Research and Development, this University). High-resolution mass spectra were recorded with a JEOL JMS-DX 303 spectrometer. Thin-layer chromatography was carried out on a 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**, **e**, and **f** and thiols **2a**, **b**, **c**, and **d** were commercially available. Sulfoxides **1b**[9] and **c**[10] were prepared by the standard method (alkylation of the corresponding sodium thiolates followed by the $NaIO_4$ oxidation of the resulting sulfides).

(4-Chlorophenylthio)(phenylthio)methane (3a).[3] **Typical Procedure for the Preparation of Unsymmetrical Dithioacetals 3.** Diisopropylamine (0.40 g, 4 mmol) was added dropwise to a stirred solution of ethylmagnesium bromide (4 mmol) in diethyl ether (5 ml) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. To the resulting turbid solution was added dropwise a solution of 4-chlorobenzenethiol (**2a**) (0.28 g, 2 mmol) in diethyl ether (3 ml). After 20 min, methyl phenyl sulfoxide (**1a**) (0.14 g, 1 mmol) was added dropwise. The resulting mixture was allowed to stand overnight at the same temperature with stirring, and was then quenched by adding aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with diethyl ether twice. The combined extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was subjected to purification by preparative thin-layer chromatography on silica gel to give the dithioacetal **3a** (0.24 g, 91%): R_f 0.21 (hexane); IR (neat) 1582, 1570, 1476, 1438, 1388, 1199, 1094, 1011, 811, 739, and 690 cm^{-1}; ^{1}H NMR (270 MHz) δ = 4.29 (2H, s) and 7.25—7.5 (9H, m).

Following the procedure described above, products **3b**, **c**, **d**, **e**, **f**, **g**, **h**, and **i** were obtained. The spectral data of these compounds are as follows.

Benzylthio(phenylthio)methane (3b):[8] R_f 0.31 (1 : 5 EtOAc–hexane); IR (neat) 1601, 1583, 1493, 1480, 1453, 1438, 1388, 1194, 1025, 739, and 698 cm^{-1}; ^{1}H NMR (60 MHz) δ = 3.74 (s, 2H), 3.83 (2H, s), and 7.0—7.5 (10H, m).

Ethylthio(phenylthio)methane (3c):[11] R_f 0.33 (hexane); IR (neat) 1583, 1480, 1440, 1266, 1199, 1088, 1025, 738, and 690 cm^{-1}; ^{1}H NMR (60 MHz) δ = 1.27 (3H, t, J = 7.2 Hz), 2.70 (2H, q, J = 7.2 Hz), 3.96 (2H, s), and 7.1—7.45 (5H, m).

1-(4-Chlorophenylthio)-1-(phenylthio)ethane (3d): R_f 0.12 (1 : 10 EtOAc–hexane); IR (neat) 1582, 1572, 1474, 1438, 1388, 1172, 1094, 1049, 1012, 821, 747, and 691 cm^{-1}; ^{1}H NMR (60 MHz) δ=1.56 (3H, d, J = 6.4 Hz), 4.40 (1H, q, J = 6.4 Hz), and 7.05—7.55 (9H, m); MS *m/z* (%) 280 (M^+; 4.8), 171 (32), and 137 (100). Found: *m/z* 280.0149. Calcd for $C_{14}H_{13}ClS_2$: 280.0148.

2-(4-Chlorophenylthio)-2-(phenylthio)propane (3e): Along with 2-phenylthiopropene[1b] (24%); R_f 0.25 (hexane); IR (neat) 1582, 1572, 1473, 1438, 1360, 1107, 1091, 1025, 1014, 823, 749, and 692 cm^{-1}; ^{1}H NMR (60 MHz) δ = 1.47 (6H, s) and 7.1—7.65 (9H, m); MS *m/z* (%) 294 (M^+; 0.6), 185 (37), and 151 (100). Found: *m/z* 294.0305. Calcd for $C_{15}H_{15}ClS_2$: M, 294.0305.

2,2-Bis(phenylthio)propane (3f):[12] Along with 2-phenylthiopropene[1b] (20%); R_f 0.43 (hexane); identified by a comparison

of its ^{1}H NMR spectrum with that reported by Schoenberg and Praefcke.[13]

Methylthio(phenylthio)methane (3g):[14] R_f 0.35 (1 : 10 EtOAc–hexane); IR (neat) 1583, 1480, 1438, 1201, 740, and 690 cm^{-1}; ^{1}H NMR (60 MHz) δ = 2.23 (3H, s), 3.87 (2H, s), and 7.1—7.65 (5H, m).

Benzylthio(phenyl)(phenylthio)methane (3h): R_f 0.15 (hexane); identified by a comparison of its ^{1}H NMR spectrum with that reported by Arai and Oki.[15]

2-(Phenylthio)tetrahydrothiophene (3i):[16] R_f 0.18 (1 : 10 EtOAc–hexane); IR (neat) 1582, 1479, 1438, 1024, 739, and 691 cm^{-1}; ^{1}H NMR (270 MHz) δ = 2.0—2.3 (4H, m), 2.8—2.95 (1H, m), 3.0—3.15 (1H, m), 4.86 (1H, dd, J = 4.7 and 4.0 Hz), 7.2—7.35 (3H, m), and 7.4—7.45 (2H, m).

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