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A Convenient Synthesis of Methyl Methylthiomethyl Sulfoxide

Katsuyuki Ogura and Gen-ichi Tsuchihashi
Sagami Chemical Research Center, Ohnuma, Sagamihara, Kanagawa 229

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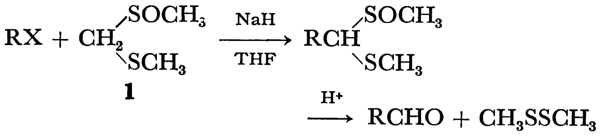
Recently we have developed a new method for synthesizing labile aldehydes by using methyl methylthiomethyl sulfoxide (**1**); the method is shown by the following scheme:[1]



$$\mathrm{RX} + \mathrm{CH_2}\genfrac{}{}{0pt}{}{\diagup \mathrm{SOCH_3}}{\diagdown \mathrm{SCH_3}} \xrightarrow[\text{THF}]{\text{NaH}} \mathrm{RCH}\genfrac{}{}{0pt}{}{\diagup \mathrm{SOCH_3}}{\diagdown \mathrm{SCH_3}} \xrightarrow{\mathrm{H^+}} \mathrm{RCHO} + \mathrm{CH_3SSCH_3}$$

1

The synthetic utility of this method seems to be widely recognized, and we have received many inquiries about the details of the method for the preparation of this new reagent (**1**). In this note we will describe a convenient way to synthesize **1** and the related compounds.

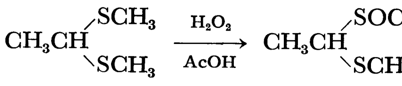
Although **1** can be obtained by the substitution reaction of chloromethyl methyl sulfoxide[2] with the methyl mercaptide anion, as has previously been reported by us,[3] this method does not appear to be suitable for the large-scale preparation of **1**, because chloromethyl methyl sulfoxide is relatively unstable. Therefore, we searched for a way to obtain **1** on a large scale and developed the improved method for the synthesis of **1** which will be described below.

Formaldehyde dimethyl mercaptal, which had easily been obtained by the acid-catalyzed condensation of formaldehyde with methyl mercaptan, was oxidized by one mole-equivalent of hydrogen peroxide in acetic acid to afford **1** in a 78% yield. In a similar manner, ethyl ethylthiomethyl sulfoxide (**2**), isopropyl isopropylthiomethyl sulfoxide (**3**), and phenyl phenylthiomethyl sulfoxide (**4**) were formed in yields of 83, 76, and 96% respectively. The oxidation with other oxidizing reagents did not give satisfactory results. For example, *m*-chloroperbenzoic acid and sodium metaperiodate converted formaldehyde diethyl mercaptal into **2** in yields of 56% and 9% respectively.

$$\mathrm{RSCH_2SR} \xrightarrow[\text{AcOH}]{\mathrm{H_2O_2}} \mathrm{RSOCH_2SR}$$

1, R=Me
2, R=Et
3, R=*i*-Pr
4, R=Ph

It should be noted that the oxidation of acetaldehyde dimethyl mercaptal with hydrogen peroxide in acetic acid gave a mixture of two diastereoisomeric methyl 1-methylthioethyl sulfoxides (**5**, 66% yield, in a ratio of 66: 34).[4]



$$\mathrm{CH_3CH}\genfrac{}{}{0pt}{}{\diagup \mathrm{SCH_3}}{\diagdown \mathrm{SCH_3}} \xrightarrow[\text{AcOH}]{\mathrm{H_2O_2}} \mathrm{CH_3CH}\genfrac{}{}{0pt}{}{\diagup \mathrm{SOCH_3}}{\diagdown \mathrm{SCH_3}}$$

5

Experimental

Oxidation of Formaldehyde Dimethyl Mercaptal. To a solution containing 25.09 g of formaldehyde dimethyl mercaptal in 50 m*l* of acetic acid, 26.5 m*l* of an aqueous solution of hydrogen peroxide (concentration: 30%) was added under cooling with ice, and then the resulting mixture was stirred for 30 min at room temperature. After 300 m*l* of methylene chloride had been added, the acetic acid was neutralized with 60 g of potassium carbonate. The mixture was filtered, and the filtrate was dried with anhydrous sodium sulfate. Upon the removal of the solvent, the residue was subjected to fractional distillation to yield 22.41 g of methyl methylthiomethyl sulfoxide (**1**) as a colorless liquid; bp 92—93°C/2.5 mmHg, IR (neat): 1040 cm^{-1}, NMR (in $\mathrm{CDCl_3}$): δ 3.63 (s, 2H), 2.59 (s, 3H), and 2.32 (s, 3H).

Found: C, 28.97; H, 6.78%. Calcd for $\mathrm{C_3H_8OS_2}$: C, 29.00; H, 6.49%.

The oxidation of this sulfoxide (**1**) with excess hydrogen peroxide in acetic acid yielded bis(methylsulfonyl)methane; mp 148—149°C (lit,[5] mp 145°C).

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[1] K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1971**, 3151.

[2] G. Tsuchihashi and K. Ogura, This Bulletin, **44**, 1726 (1971).

[3] K. Ogura and G. Tsuchihashi, *Chem. Commun.*, **1970**, 1689.

[4] There are a number of examples of the asymmetric oxidation of a sulfide to a sulfoxide in which one of a pair of diastereoisomers is produced predominantly. For example, J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J. (1971), p. 351.

[5] H. Böhme, R. Frand, and W. Kause, *Chem. Ber.*, **82**, 433 (1949).

Oxidation of Formaldehyde Diethyl Mercaptal. (a) To a solution containing 2.486 g of formaldehyde diethyl mercaptal in 15 m*l* of acetic acid, 2.07 m*l* of an aqueous solution of hydrogen peroxide (concentration: 30%) was added while cooling with ice, and then the resulting mixture was stirred for 2 hr at room temperature. The same work-up as above and the fractional distillation of the leavings afforded 2.305 g of ethyl ethylthiomethyl sulfoxide (**2**) as a colorless liquid; bp 95—97°C/2.5 mmHg, IR: 1042 cm^{-1}, NMR (in $CDCl_3$): δ 1.32 (t, 3H, J=7.4 Hz), 1.36 (t, 3H, J=7.4 Hz), 2.5—3.3 (m, 4H), and 3.72 (s, 2H).

Found: C, 39.22; H, 8.00; S, 42.04%. Calcd for $C_5H_{12}OS_2$: C, 39.43; H, 7.94; S, 42.12%.

(b) To a solution containing 871 mg of formaldehyde diethyl mercaptal in 10 m*l* of methylene chloride, a 1.382-g portion of *m*-chloroperbenzoic acid (80% active) was added while the mixture was being cooled with ice. After continuous stirring for 1.5 hr, the mixture was neutralized with 500 mg of potassium carbonate and then subjected to filtration. The subsequent concentration of the filtrate under reduced pressure and the purification of the residue by column chromatography (Florisil, methylene chloride) gave 543 mg of ethyl ethylthiomethyl sulfoxide (**2**). (c) To a solution containing 2.652 g of formaldehyde diethyl mercaptal in 14 m*l* of water and 7 m*l* of methanol, a 4.11-g portion of sodium metaperiodate was added under cooling with ice. After 1 hr of stirring, the mixture was subjected to filtration, and then the filtrate was extracted with methylene chloride. The extract was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was separated by column chromatography (silica gel, methylene chloride, and ethyl acetate) to afford 260 mg of ethyl ethylthiomethyl sulfoxide (**2**).

Oxidation of Formaldehyde Diisopropyl Mercaptal. To a solution containing 4.324 g of formaldehyde diisoproply mercaptal in 15 m*l* of acetic acid, a 3.00-m*l* portion of an aqueous solution of hydrogen peroxide (concentration: 30%) was added while cooling with ice, and then the resulting mixture was stirred for 4.5 hr at room temperature. The same work-up as above, followed by the distillation of the residue under reduced pressure, gave 3.606 g of isopropyl isopropylthiomethyl sulfoxide (**3**) as colorless crystals; mp 39—40°C (bp 87—88°C/1 mmHg), IR: 1048 cm^{-1}, NMR (in $CDCl_3$): δ 1.28 (d, 3H, J=6.8 Hz), 1.32 (d, 3H, J=6.8 Hz), 1.34 (d, 6H, J=6.8 Hz), 2.7—3.6 (m, 2H), and 3.68 (s, 2H).

Found: C, 46.51; H, 9.00; S, 35.76%. Calcd for $C_7H_{16}OS_2$: C, 46.62; H, 8.92; S, 35.56%.

Oxidation of Formaldehyde Diphenyl Mercaptal. To a solution containing 1.538 g of formaldehyde diphenyl mercaptal in 5 m*l* of acetic acid, 0.75 m*l* of an aqueous solution of hydrogen peroxide (concentration: 30%) was added, and then the mixture was stirred for 1 hr at room temperature. After 100 m*l* of methylene chloride, 6 g of potassium carbonate, and a small amount of water had then been added, the resulting mixture was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was separated by column chromatography (silica gel, methylene chloride) to afford 1.585 g of phenyl phenylthiomethyl sulfoxide (**4**) as a colorless liquid; IR: 1049 cm^{-1}, NMR (in CCl_4): δ 3.98 (d, 1H, J=13.5 Hz), 4.03 (d, 1H, J=13.5 Hz), and 7.1—7.8 (m, 10H).

Found: C, 62.78; H, 4.85; S, 25.87%. Calcd for $C_{13}H_{12}OS_2$: C, 62.87; H, 4.87; S, 25.82%.

Oxidation of Acetaldehyde Dimethyl Mercaptal. To a solution containing 4.72 g of acetaldehyde dimethyl mercaptal in 10 m*l* of acetic acid, 4.05 m*l* of an aqueous solution of hydrogen peroxide (concentration: 30%) was added, drop by drop, while the mixture was being cooled with ice. After the addition of methylene chloride, the mixture was neutralized with potassium carbonate and filtered. The filtrate was dried with anhydrous sodium sulfate, and, on distilling under reduced pressure, a 3.62-g portion of methyl 1-methylthioethyl sulfoxide (**5**, bp 84°C/2 mmHg) was obtained as a colorless liquid. This liquid was shown by its NMR analysis to consist of two diastereoisomers in a ratio of 66: 34. NMR (in $CDCl_3$): the major component; δ 1.62 (d, 3H, J=7.2 Hz), 2.23 (s, 3H), 2.69 (s, 3H), and 3.64 (q, 1H, J=7.2 Hz), the minor component; δ 1.57 (d, 3H, J=7.2 Hz), 2.31 (s, 3H), 2.55 (s, 3H), and 3.73 (q, 1H, J=7.2 Hz).

Found: C, 34.36; H, 7.44%. Calcd for $C_4H_{10}OS_2$: C, 34.75; H, 7.29%.