

Oxidation of Methyl (Methylthio)methyl Sulfoxide

Katsuyuki OGURA,*† Michiyo SUZUKI, and Gen-ichi TSUCHIHASHI*

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagami-hara Kanagawa 229

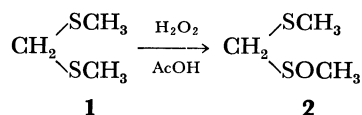
† Department of Synthetic Chemistry, Faculty of Engineering, Chiba University,

Yayoi-cho 1-33, Chiba 260

(Received November 9, 1979)

Oxidation of methyl (methylthio)methyl sulfoxide (**2**) with hydrogen peroxide in acetic acid or methanol produced bis(methylsulfinyl)methane in high yield. Similar results were obtained in oxidation of **2** with ozone, sodium metaperiodate, and *m*-chloroperbenzoic acid. In contrast, methyl (methylthio)methyl sulfone (**4**) was exclusively formed when oxidation of **2** with hydrogen peroxide was carried out in methanol in the presence of sodium hydroxide. Furthermore, we established a convenient and efficient method of preparing **4** by oxidation of **2** with potassium permanganate.

Methyl (methylthio)methyl sulfoxide (**2**) can be easily obtained by oxidation of bis(methylthio)methane (**1**) with hydrogen peroxide in acetic acid¹⁾ and this compound has been revealed to be a versatile reagent for synthesizing many kinds of organic compounds.²⁾

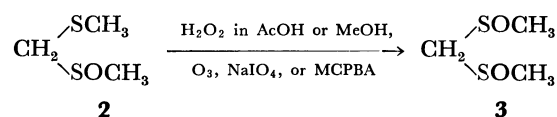


In order to search further uses for **2**, we examined oxidation of **2** with various oxidants and found an effective method leading to either bis(methylsulfinyl)methane (**3**) or methyl (methylthio)methyl sulfone (**4**), both of which are expected to be useful synthetic reagents. Details of these oxidation reactions are described in the present paper.

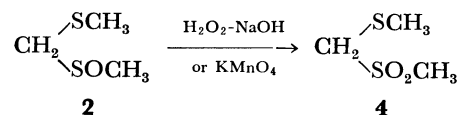
Results and Discussion

Methyl (methylthio)methyl sulfoxide (**2**) was oxidized with one equiv-mol of hydrogen peroxide. In acetic acid, a smooth reaction took place and bis(methylsulfinyl)methane (**3**) was given in 71% yield (86% yield based on the consumed **2**) as a mixture of its *meso* and *dl* diastereomers in the ratio of 61:39.³⁾ This ratio remained unchanged under moderate heating (150 °C) which is in sharp contrast with reported easy epimerization of bis(benzylsulfinyl)diphenylmethane.⁴⁾ In methanol, oxidation of **2** with hydrogen peroxide also afforded **3**, although the reaction proceeded rather slowly, and analogous results were obtained in oxidation of **2** with ozone, sodium meta-

periodate, or *m*-chloroperbenzoic acid (MCPBA). The results are summarized in Table 1.



When oxidation of **2** with hydrogen peroxide was performed under alkaline conditions, methyl (methylthio)methyl sulfone (**4**) was exclusively produced instead of **3**. Thus, large excess of hydrogen peroxide (utilized as a 35% aqueous solution) was dropwise added to a solution containing **2** and sodium hydroxide (one equiv to **2**) in methanol under keeping the reaction temperature below 50 °C and **4** was isolated in 78% yield. It is worth noting that **3** was not detected in the reaction mixture by NMR and TLC analyses. The structure of **4** was confirmed by the comparison of its IR and NMR spectra with an authentic specimen prepared by substitution of chloromethyl methyl sulfone with methanethiolate anion.⁵⁾



This exclusive formation of **4** from **2** can be explained in terms of nucleophilic oxidation with a peroxide anion formed by the reaction of hydrogen peroxide with sodium hydroxide, since perbenzoate anion in water-dioxane⁶⁾ and 1-phenylethylperoxide anion in a nonpolar solvent⁷⁾ were known to attack preferentially the positively-charged sulfur atom of a sulfoxide and convert it into the corresponding sulfone. Similar phenomena were also reported in the reactions with permanganate ion and osmium tetroxide which could oxidize a sulfoxide without affecting a coexistent sulfide.^{8,9)} Hence, we tried to oxidize **2** with potassium permanganate and established an efficient transformation of **2** into **4**. To a solution of **2** in acetone containing a small amount of water, was added an equiv-mol of potassium permanganate and the mixture was stirred at room temperature for 18 h. Usual work-up followed by column chromatography afforded **4** in 97% yield.

During the course of our investigation, Poje and Balenović reported that **4** was selectively obtained by oxidation of bis(methylthio)methane (**1**) with potassium permanganate.¹⁰⁾ However, the present method seems advantageous to the Poje-Balenović's method

TABLE 1. PRODUCT DISTRIBUTION IN OXIDATION OF **2**

Oxidant	Solvent	Yield/(% ^{a)})	
		3	4
H ₂ O ₂	AcOH	71 (61 : 39)	—
H ₂ O ₂	MeOH	84 (61 : 39)	—
H ₂ O ₂ -NaOH	MeOH	—	78
O ₃	CH ₂ Cl ₂	90 (66 : 34)	—
NaIO ₄	H ₂ O	85 (69 : 31)	—
MCPBA ^{b)}	CH ₂ Cl ₂	73 (64 : 36)	—
KMnO ₄	CH ₃ COCH ₃	—	97

a) The value in the parenthesis shows the ratio of the *meso* and *dl* forms. b) *m*-Chloroperbenzoic acid.

from the synthetic viewpoint,¹¹) since the latter method requires controlling the reaction temperature at 0 °C for a longer period of time (8–10 d) and gives **4** in only moderate yield (70%).

Experimental

Oxidation of Methyl (Methylthio)methyl Sulfoxide (2) with Hydrogen Peroxide. a) *In Acetic Acid:* To a solution containing **2** (4.058 g: 32.7 mmol) in acetic acid (40 ml), was dropwise added a 30% aqueous solution (3.70 ml: 32.7 mmol) of hydrogen peroxide under cooling with ice-water and the resulting mixture was stirred for 7 h at room temperature. After addition of dichloromethane (500 ml), the acetic acid was neutralized with potassium carbonate (46.4 g) and the deposited solid was filtered off. The filtrate was dried (Na₂SO₄), evaporated *in vacuo*, and column-chromatographed on silica gel (using ethyl acetate-methanol as an eluent) to give the unconsumed **2** (729 ml: 5.88 mmol) and **3** (3.238 g: 23.1 mmol; 71%) as a colorless oil which crystallized on cooling. An NMR analysis showed that **3** consisted of two diastereomers in the ratio of 61:39: NMR (CDCl₃) of the major component: δ 2.94 (6H, s), 3.89 (1H, d, J =13.5 Hz), and 4.15 (1H, d, J =13.5 Hz);³) NMR (CDCl₃) of the minor component: δ 2.85 (6H, s) and 4.09 (2H, s).

An analytical sample (*meso:dl*=57:43) was obtained by recrystallization from chloroform-diethyl ether: mp 44–84 °C¹²) (lit,³) mp of the *meso* form and the *dl* form 46–49 °C¹³) and 92–94 °C, respectively); IR (neat) 1037 cm⁻¹. Found: C, 25.55; H, 5.80; S, 45.44%. Calcd for C₃H₈O₂S₂: C, 25.70; H, 5.75; S, 45.73%.

(b) *In Methanol:* To a solution of **2** (2.357 g: 19.0 mmol) in methanol (10 ml), was added a 35% aqueous solution (2.0 ml: 20.6 mmol) of hydrogen peroxide and the resulting solution was stirred at room temperature for 81.5 h. After addition of dichloromethane (100 ml), the resulting mixture was dried (Na₂SO₄), and evaporated *in vacuo* to give a colorless oil (2.422 g), which was shown by an NMR analysis to consist of **2** (199 mg: 1.60 mmol) and two diastereomers (*meso:dl*=61:39) of **3** (2.223 g: 15.9 mmol; 84%).

c) *In the Presence of NaOH:* To a solution containing **2** (7.020 g: 56.6 mmol) and sodium hydroxide (2.25 g: 56.2 mmol) in methanol (20 ml), was dropwise added a 35% aqueous solution (8.0 ml: 82.3 mmol) of hydrogen peroxide over 40 min under keeping the reaction temperature below 50 °C. Further, a 35% aqueous solution (1.0 ml: 10.3 mmol) of hydrogen peroxide was added in one portion to cause gentle reflux for a time and then the reaction mixture was stirred at room temperature for 30 min. After addition of water (30 ml) and extraction with dichloromethane (70 ml $\times$ 3), the organic layer was dried (Na₂SO₄), evaporated *in vacuo*, and subjected to column chromatography on silica gel, affording **4** (6.185 g: 44.2 mmol; 78%) as colorless crystals: mp 50–51.2 °C (from diethyl ether) (lit,⁵) mp 50–51 °C); IR (KBr) 1293 and 1122 cm⁻¹; NMR (CDCl₃) δ 2.40 (3H, s), 3.01 (3H, s), and 3.82 (2H, s). Found: C, 25.78; H, 5.78; S, 45.83%. Calcd for C₃H₈O₂S₂: C, 25.70; H, 5.75; S, 45.73%.

These physical data were in complete agreement with those of an authentic sample prepared by substitution reaction of chloromethyl methyl sulfone with sodium methanethiolate as described below.

To a mixture containing dimethyl sulfoxide (19.7 g: 253 mmol) and potassium carbonate (10.0 g) in dichloromethane (150 ml), was portionwise added *N*-chlorosuccinimide (35.0 g: 262 mmol) over 30 min at room temperature under stirring. Then, the insoluble solid was filtered off and the filtrate

was evaporated *in vacuo* to give an oil including crystals. After addition of carbon tetrachloride, the insoluble succinimide was removed by filtration and the filtrate was evaporated *in vacuo* to give a colorless oil which consisted mainly of chloromethyl methyl sulfoxide.¹⁴) Without further purification, this oil was dissolved in acetic acid (45 ml) and, after addition of a 35% aqueous solution (45 ml) of hydrogen peroxide, the resulting solution was stirred at room temperature for 2 d. The reaction mixture was neutralized with an aqueous solution of potassium carbonate and extracted with dichloromethane. The extract was dried (Na₂SO₄), evaporated *in vacuo* and crystallized from ethanol to give chloromethyl methyl sulfone (27.43 g: 213 mmol; 79%) as colorless crystals: mp 55–56.5 °C (lit, mp 57.2–58.2 °C¹⁵) and 55–56 °C¹⁶).

To a solution of chloromethyl methyl sulfone (2.57 g: 20.0 mmol) in *N,N*-dimethylformamide (45 ml), was added a 15% aqueous solution (15 ml: purchased from Tokyo Kasei Kogyo Co. Ltd.) of sodium methanethiolate and the resulting mixture was stirred at 50 °C for 3 h. After addition of water followed by extraction with dichloromethane, the organic layer was dried (Na₂SO₄) and evaporated *in vacuo*. The residue was recrystallized from ethanol to afford **4** (1.608 g: 11.5 mmol; 57%) as colorless crystals: mp 48.5–50 °C.

Oxidation of 2 with m-Chloroperbenzoic Acid. *m*-Chloroperbenzoic acid (85% active; 1.08 g: 5.32 mmol) was added to a solution of **2** (620 mg; 5.0 mmol) in dichloromethane (10 ml), and then the resulting mixture was stirred for 1.5 h under cooling with ice-water. After addition of water (*ca.* 1 ml) and neutralization with potassium carbonate, the insoluble matter was filtered off and washed with ethyl acetate. The filtrate and the washings were combined and dried (Na₂SO₄). Evaporation *in vacuo* gave a colorless oil which was separated by column-chromatography on silica gel to give **3** (510 mg: 3.64 mmol; 73%). An NMR analysis showed that this product consisted of two diastereomers (*meso:dl*=64:36).

Oxidation of 2 with Ozone. Ozone, produced by silent discharge of oxygen, was passed through a solution of **2** (1.040 g: 8.39 mmol) in dichloromethane (10 ml) until the solution became blue. Evaporation *in vacuo* followed by column chromatography on silica gel gave **3** (1.051 g: 7.50 mmol; 90%) as a colorless oil which was shown by an NMR analysis to consist of two diastereomers (*meso:dl*=66:34).

Oxidation of 2 with Sodium Metaperiodate. A small amount (*ca.* 1 ml) of water and sodium metaperiodate (863 mg: 4.03 mmol) were added to **2** (498 mg: 4.02 mmol) and the resulting mixture was stirred for 4.5 h under cooling with ice-water. The insoluble solid was filtered off and washed with dichloromethane and ethyl acetate. The filtrate and the washings were combined, dried (Na₂SO₄), and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel to afford **3** (476 mg: 3.40 mmol; 85%) as a colorless oil which was shown by an NMR analysis to consist of two diastereomers (*meso:dl*=69:31).

Oxidation of 2 with Potassium Permanganate. To a solution containing **2** (1.327 g: 10.7 mmol) in acetone (50 ml) and water (2 ml), was added potassium permanganate (1.694 g: 10.7 mmol) in several portions and the resulting mixture was stirred at room temperature for 19 h. The insoluble matter was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in dichloromethane and dried (Na₂SO₄). After evaporation *in vacuo*, the residue was subjected to column chromatography on silica gel (dichloromethane) to afford **4** (1.455 g: 1.03 mmol; 97%) as colorless crystals.

The authors would like to express their thanks to Professor Hirotada Iida of Chiba University for his encouragement and helpful discussion. We also wish to thank Mr. Shigeo Tomisawa and Mr. Hiroshi Kitazawa for their technical assistance.

References

- 1) K. Ogura and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **45**, 2203 (1972).
 - 2) K. Ogura, Y. Ito, and G. Tsuchihashi, *Bull. Chem. Soc. Jpn.*, **52**, 2013 (1979) and the references cited therein.
 - 3) **3** was obtained by periodate oxidation of **1** and the meso isomer of **3** showed nonequivalent diastereotopic methylene protons in the NMR spectrum: R. Louw and H. Nieuwenhuyse, *Chem. Commun.*, **1968**, 1561.
 - 4) C. Y. Meyers and L. L. Ho, *Tetrahedron Lett.*, **1974**, 729.
 - 5) P. Robson, P. R. H. Speakman, and D. G. Stewart, *J. Chem. Soc., C*, **1968**, 2180. We found that this substitution reaction proceeded more smoothly in *N,N*-dimethylformamide, compared with the reaction in ethanol previously reported (see Experimental Section).
 - 6) R. Curci and G. Modena, *Tetrahedron Lett.*, **1963**, 1749 and **1965**, 863.
 - 7) Y. Ogata and S. Suyama, *Chem. Ind. (London)*, **1971**, 707 and *J. Chem. Soc., Perkin Trans. 2*, **1973**, 755.
 - 8) F. D. Chattaway and E. G. Kellett, *J. Chem. Soc.*, **1930**, 1352.
 - 9) H. B. Henbest and S. A. Khan, *Chem. Commun.*, **1968**, 1036.
 - 10) M. Poje and K. Balenović, *Tetrahedron Lett.*, **1978**, 1231.
 - 11) **2** is commercially available and can be purchased from Nippon Soda Co. Ltd.
 - 12) Since this mixture was very hygroscopic, the melting point was measured by using a sealed capillary tube in a H_2SO_4 bath and uncorrected. Other melting points reported herein were obtained with a Yanagimoto micro melting point apparatus and uncorrected.
 - 13) This value was given for the melting point of the meso isomer containing a small amount of the *dl* isomer.³⁾
 - 14) G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Jpn.*, **44**, 1726 (1971).
 - 15) W. E. Truce, B. H. Birum, and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952).
 - 16) H. Richtzenhain and B. Alfredssohn, *Chem. Ber.*, **86**, 142 (1953).
-