Oxidation of Methyl (Methylthio)methyl Sulfoxide

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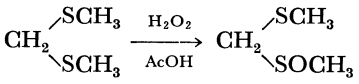
Oxidation of methyl (methylthio)methyl sulfoxide (**2**) with hydrogen peroxide in acetic acid or methanol produced bis(methylsulfinyl)methane in high yield. Similar results were obtained in oxidation of **2** with ozone, sodium metaperiodate, and *m*-chloroperbenzoic acid. In contrast, methyl (methylthio)methyl 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 acid[1] and this compound has been revealed to be a versatile reagent for synthesizing many kinds of organic compounds.[2]



1 **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.

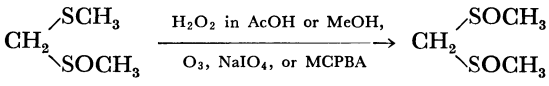
Results and Discussion

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

Table 1. Product distribution in oxidation of **2**

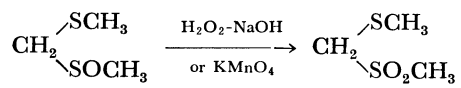
Oxidant	Solvent	Yield/%[a]	
		3	**4**
H_2O_2	AcOH	71 (61 : 39)	—
H_2O_2	MeOH	84 (61 : 39)	—
H_2O_2-NaOH	MeOH	—	78
O_3	CH_2Cl_2	90 (66 : 34)	—
$NaIO_4$	H_2O	85 (69 : 31)	—
MCPBA[b]	CH_2Cl_2	73 (64 : 36)	—
$KMnO_4$	CH_3COCH_3	—	97

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



2 **3**

When oxidation of **2** with hydrogen peroxide was performed under alkaline conditions, methyl (methylthio)methyl sulfone (**4**) was exclusively produced in stead 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]



2 **4**

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–dioxane[6] and 1-phenylethylperoxide anion in a nonpolar solvent[7] 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 tetraoxide which could oxidize a sulfoxide without affecting a coexistent sulfide.[8,9] Hence, we tried to oxidize **2** with potassium permangante 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

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 (Na_2SO_4), 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 ($CDCl_3$) 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 ($CDCl_3$) 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 °C[12] (lit,[3] mp of the *meso* form and the *dl* form 46—49 °C[13] and 92—94 °C, respectively); IR (neat) 1037 cm^{-1}. Found: C, 25.55; H, 5.80; S, 45.44%. Calcd for $C_3H_8O_2S_2$: 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 (Na_2SO_4), 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×3), the organic layer was dried (Na_2SO_4), 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 ($CDCl_3$) 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 $C_3H_8O_2S_2$: 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 additon 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 additon 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 (Na_2SO_4), 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 °C[15] and 55—56 °C[16]).

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 (Na_2SO_4) 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 (Na_2SO_4). 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 (Na_2SO_4), 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 (Na_2SO_4). 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.

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