Selective Synthesis of Sulfoxides and Sulfones by Methyltrioxorhenium-Catalyzed Oxidation of Sulfides with Hydrogen Peroxide

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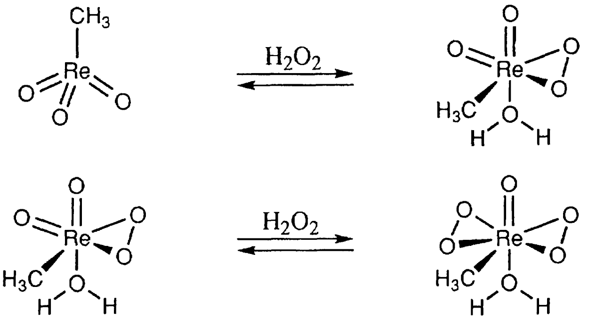
Methyltrioxorhenium-catalyzed oxidation of sulfides with hydrogen peroxide in ethanol has been found to be an efficient catalytic system for the selective formation of sulfoxides and sulfones. The oxidation using an equimolar amount of hydrogen peroxide afforded sulfoxides in excellent yield, and the use of two molar amounts of hydrogen peroxide gave sulfones quantitatively. Strongly deactivated sulfide, bis(4-nitrophenyl) sulfide, was converted smoothly to the corresponding sulfoxide and sulfone in excellent yields. The functional group in the side chain of sulfide such as a carbon–carbon double bond was not affected under the reaction conditions, and the sulfur atom was selectively oxidized.

The use of sulfoxides and sulfones as intermediate in organic synthesis has continually expanded.[1] Therefore, new and improved methods for the preparation of sulfoxides and sulfones have been explored extensively.[2,3] The oxidation of sulfide can yield either the corresponding sulfoxide or sulfone or both, depending on the method used. The selective oxidation of sulfides to sulfoxides without formation of sulfones requires highly selective methods,[4] whereas complete oxidation to the sulfone could be achieved much more easily. One of the reasons is the relative ease of overoxidation of sulfoxide to sulfone. The chemoselective oxidation of sulfide to sulfoxide or sulfone without affecting the functional group in the side chain of the sulfide is another point of interest.[4a,5]

Hydrogen peroxide alone or in the presence of various catalysts is an extensively studied reagents for the oxidation of sulfides.[2] Hydrogen peroxide is an environmentally advantageous oxidizing agent, since its only waste by-product is water.

In 1991, Herrmann and co-workers first reported the use of methyltrioxorhenium (MTO) as an effective catalyst for epoxidation of olefins with hydrogen peroxide.[6] Since then, the MTO/H_2O_2 oxidation catalyst system has been proved as an efficient system for various oxidations. These comprise sulfide oxidation,[7] Baeyer–Villiger type oxidation,[8] phenol oxidation,[9] arene oxidation,[10] alkyne oxidation,[11] oxidation of amines,[12] and others.[13—16] MTO is a homogeneous catalytic activator of hydrogen peroxide. MTO reacts with hydrogen peroxide to form η^2-peroxo complexes having 1 : 1 and 1 : 2 ratios of rhenium and peroxide (Scheme 1).[17,18] Either of the two or both complexes transfer one of the peroxo oxygen to the substrate. The important features of MTO as catalyst are its ease of synthesis (now it is commercially available), its stability in air (dioxygen and humidity), and its solubility in various solvents including water.

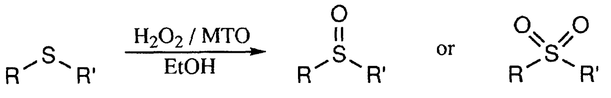


Scheme 1.

Though the MTO-catalyzed sulfoxidation has been reported recently,[7c] the results were not satisfactory for synthesis because of its long reaction time and low selectivity. The reported results did not reflect the real ability of the catalyst for the sulfide oxidation. This must be because the reaction was examined in $CDCl_3$, which was immiscible with aqueous H_2O_2. In this paper, we describe a successful application of MTO/H_2O_2 system for the selective oxidation of sulfides to sulfoxides and sulfides to sulfones by using ethanol as the solvent. By using this system, dialkyl, alkyl aryl, and diaryl sulfides were transformed to sulfoxides or sulfones in excellent selectivity according to the appropriate adjustment of the reaction conditions within a short reaction period (Scheme 2). Sulfides which have oxidatively sensitive functional groups in the side chain were converted to the corresponding sulfoxides or sulfones without affecting the functional groups such as the C–C double bond.

Results and Discussion

Effect of Solvent on Oxidation of Diphenyl Sulfide. At first, the oxidation of diphenyl sulfide in various solvents



Scheme 2.

was examined. The results are summarized in Table 1. The solvents examined were alcohols, tetrahydrofuran and acetonitrile; these were all miscible with H_2O_2. The reactions were carried out by stirring the sulfide with 1 mol% MTO and 1.1 molar amount of H_2O_2 (1.0 M, M = mol dm^{-3}) at room temperature for 60 min. The smooth oxidation proceeded exothermically. As shown in Table 1, diphenyl sulfoxide was obtained selectively in every solvent examined. Only 1—2% of diphenyl sulfone was produced as a by-product. Among the solvents examined, ethanol gave the best result on the conversion of the sulfide. The oxidation in methanol gave comparable results with ethanol. Isopropyl alcohol, *t*-butyl alcohol, tetrahydrofuran, and acetonitrile were inferior solvents to ethanol and methanol, because the reaction stopped at lower conversions in these solvents than those in ethanol and methanol. It was reported that the oxidation of diphenyl sulfide in $CDCl_3$ required 24 h for 91% conversion.[7c)] The reaction time was drastically shortened by simply changing the solvent to ethanol.

Effects of Amount of Oxidant and Catalyst. Next, the effects of the amount of oxidant and catalyst were examined with diphenyl sulfide as the substrate. The results are summarized in Table 2. The use of 0.5 molar amount of H_2O_2 and 0.5 mol% MTO converted exactly 50% of diphenyl sulfide to diphenyl sulfoxide (Entry 1). Though the use of 1.1 molar amount of H_2O_2 with 0.5 mol% MTO also produced diphenyl sulfoxide exclusively, 24% of diphenyl sulfide remained unreacted even after a long reaction period (Entry 3). This indicated that catalytic activity was lost during the reaction. The use of 1 mol% MTO converted 98% diphenyl sulfide, and 99% of diphenyl sulfoxide and 1% diphenyl sulfone were formed (Entry 4). On the other hand, the use of 2 mol% MTO caused overoxidation of the diphenyl sulfoxide, and 10% diphenyl sulfone was formed along with 89% diphenyl sulfoxide (Entry 5). The use of 2.2 molar amount of H_2O_2 and more than 2 mol% MTO resulted in quantitative formation of sulfone. Use of more catalyst shortened the reaction time in the case of sulfone formation (Entries 7,8). These results indicated that the oxidation of sulfide with an equimolar amount of H_2O_2 produces sulfoxide in excellent yield and the oxidation of sulfide with two molar amount of H_2O_2 produces sulfone quantitatively by using H_2O_2/MTO/EtOH system.

Oxidation of Various Sulfides. The oxidation catalyst system H_2O_2/MTO/EtOH was applied to a wide variety of simple dialkyl, alkyl aryl, and diaryl sulfides. The results are presented in Table 3. The oxidation of dibutyl sulfide, pentamethylene sulfide, dibenzyl sulfide, and methyl phenyl sulfide afforded corresponding sulfoxides or sulfones selectively in excellent yields in short reaction times (Entries 1, 2, 5—10). Di-*t*-butyl sulfide that bears a bulky group is smoothly oxidized to the corresponding sulfoxide or sulfone selectively in excellent yields (Entries 3, 4).[19)] Bis(4-nitrophenyl) sulfide which is deactivated by strong electron-withdrawing substituents was oxidized to the corresponding sulfoxide and sulfone when the oxidations were performed at higher reaction temperature (50 °C) and larger amount of catalyst (5 mol%) than those in the oxidation of other sulfides

Table 1. MTO-Catalyzed Hydrogen Peroxide Oxidation of Diphenyl Sulfide in Various Solvents[a)]

		Conversion	Yield/ % [b)]	
Entry	Solvent	%	Sulfoxide	Sulfone
1	MeOH	93	91	2
2	EtOH	98	97	1
3	*i*-PrOH	64	63	1
4	*t*-BuOH	40	40	0
5	THF	62	61	1
6	CH_3CN	78	77	1

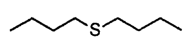
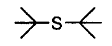
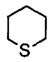
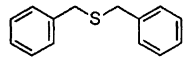
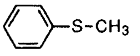
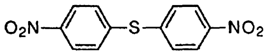
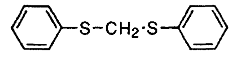
a) 1 mol% MTO, 1.1 molar amount H_2O_2 (1.0 M solution), at room temperature for 60 min. b) Isolated yield based on sulfide used.

Table 2. MTO-Catalyzed Hydrogen Peroxide Oxidation of Diphenyl Sulfide in Ethanol[a)]

	H_2O_2 [b)]	MTO	Time	Conv	Yield/ % [c)]	
Entry	Mol amt.	mol%	min	%	Sulfoxide	Sulfone
1	0.5[d)]	0.5	30	50	100	0
2	0.5[d)]	2	30	50	99	Trace
3	1.1	0.5	30	76	100	0
4	1.1	1	60	98	99	1
5	1.1	2	60	100	89	10
6	2.2	1	60	100	30	70
7	2.2	2	120	100	0	100
8	2.2	3	30	100	0	99

a) At room temperature. b) Solution in EtOH (1.0 M). c) Isolated yield based on sulfide consumed. d) Solution in EtOH (0.50 M).

Table 3. MTO-Catalyzed Hydrogen Peroxide Oxidation of Various Sulfides[a]

Entry	Sulfide	H_2O_2[b]	MTO	Time	Conv	Yield/ %[c]	
		Mol amt.	mol%	min	%	Sulfoxide	Sulfone
1		1.1	1	60	99	98	1
2		2.2	2	120	100	0	98
3		1.1	1	60	>99	86	2
4		2.2	2	180	100	0	100
5		1.1	1	60	100	98	0
6		2.2	2	180	100	0	89
7		1.1[d]	1	60	91	91	0
8		2.2[e]	2	180	100	0	99
9		1.1	1	60	>99	97	2
10		2.2	2	180	100	0	100
11		1.1[f]	5	300[g]	98	88	10
12		5.0[h]	5	480[g]	100	0	100
13		1.1[i]	1	180	64	60[j]	0
14		1.2[i]	1.5	90	99	85[j,k]	0

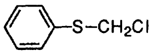
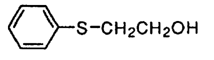
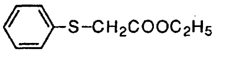
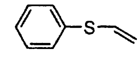
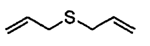
a) At room temperature. b) 1.0 M H_2O_2/EtOH solution unless otherwise mentioned. c) Isolated yield based on sulfide used. d) 0.25 M H_2O_2/EtOH solution. e) 0.50 M H_2O_2/EtOH solution. f) 0.025 M H_2O_2/CH_3CN solution. g) At 50 °C. h) 0.10 M H_2O_2/CH_3CN solution. i) 0.20 M H_2O_2/EtOH solution. j) Mono-sulfoxide. k) Di-sulfoxide (14%) was also isolated.

(Entries 11, 12). The oxidation of bis(4-nitrophenyl) sulfide at room temperature resulted in a large amount of the unreacted sulfide remaining even after 24 h, while the reaction at 50 °C completed within 8 h. Acetonitrile was used as the solvent to dissolve bis(4-nitrophenyl) sulfide completely. In the case of bis(phenylthio)methane, mono-sulfoxide was obtained selectively at relatively low conversion (Entry 13), while di-sulfoxide was produced as an only by-product at complete conversion (Entry 14).

Oxidation of Sulfides Having a Functional Group in the Side Chain. The oxidation of sulfides which have some other functional group in the side chain of the sulfide was examined using the H_2O_2/MTO/EtOH system. The results are summarized in Table 4. In the reaction of chloromethyl phenyl sulfide, the labile chloro substituent was not affected and the corresponding sulfoxide or sulfone was obtained in excellent yield (Entries 1, 2).[5a] Oxygen functional groups such as alcohol and ester did not interfere under the reaction conditions (Entries 3—6). The oxidation took place at the sulfur atom even in the presence of carbon–carbon double bonds such as allyl and vinyl groups (Entries 7—10).[5] Although H_2O_2/MTO is an efficient epoxidation catalyst system, sulfide sulfur is more reactive than carbon–carbon double bonds. The sulfoxides and sulfones obtained in Table 4 are useful intermediates for organic transformations.[5a]

In conclusion, MTO has been found to be an excellent oxidation catalyst for the transformation of sulfides to sulfoxides and sulfides to sulfones by hydrogen peroxide. The oxidation proceeds at room temperature within a short reaction period. Though the reactivity of this catalytic system is very high, selective sulfoxidation is easily achieved by appropriate adjustment of the reaction conditions. It is noteworthy that the reaction can tolerate oxidatively sensitive functional groups and that the sulfur atom is selectively oxidized.

Table 4. MTO-Catalyzed Hydrogen Peroxide Oxidation of Various Sulfides Having Functional Group[a]

Entry	Sulfide	H_2O_2[b]	MTO	Time	Conv	Yield/ %[c]	
		Mol amt.	mol%	min	%	Sulfoxide	Sulfone
1		1.1	1	60	95	89	4
2		2.2	2	180	100	0	97
3		1.1	1	30	100	97	0
4		2.2	2	150	100	0	95
5		1.1	1	60	97	93	4
6		2.2	2	180	100	0	99
7		1.1	1	60	>99	85	0
8		2.2	2	120	100	0	84
9		1.1	1	120	>99	81	2
10		2.2	2	180	100	0	97

a) At room temperature. b) 1.0 M H_2O_2/EtOH solution. c) Isolated yield based on starting sulfide.

Experimental

General. Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-3 spectrophotometer. ^{1}H and ^{13}C NMR were recorded on a JEOL EX-90 spectrometer at 90 and 22.5 MHz with tetramethylsilane as an internal standard. The progress of the reaction was monitored by TLC analysis on silica gel (Merck Silica Gel 60 F_{254}) or by GC analysis on a Shimadzu GC-14A with a Spelco SPB-50 (30 m×0.53 mm) wide bore capillary column. Column chromatography was performed using silica gel (Wakogel C-200). MTO was prepared from Re_2O_7 and $Sn(CH_3)_4$ in the presence of perfluoroglutaric anhydride.[20)] All the sulfides used in this research were commercially available and were used without further purification.

Preparation of Oxidation Solution (Hydrogen Peroxide-Ethanol Solution). EtOH (290 mL) was mixed with 30% H_2O_2 (30 mL). The solution was stirred with anhydrous $MgSO_4$ (25 g) for 3 h, and then filtered. The obtained oxidation solution was titrated (1.0 M, M = mol dm^{-3}) and the result was stored in a refrigerator. The concentration has not changed for months. The oxidation solutions in other solvents (Table 1) were prepared in a same manner.

General Procedure for Synthesis of Sulfoxide. A sulfide (4.0 mmol) was dissolved in ethanolic H_2O_2 (4.4 mL, 4.4 mmol, 1.0 M). MTO (10 mg, 0.040 mmol) was added to the solution. The reaction was carried out in a round-bottom flask under magnetic stirring at room temperature. The temperature of the mixture rose and came down within a few minutes. The progress of the reaction was monitored by TLC or GC. When no more sulfide was present (or when the reaction was stopped), the mixture was poured into aqueous $NaHSO_3$ to decompose excess H_2O_2. The aqueous solution was extracted with CH_2Cl_2 (10mL×3; in the cases of Table 3, Entry 5, and Table 4, Entry 3, salting out was requisite for the complete extraction). The combined extract was dried over anhydrous $Na_2SO_4/MgSO_4$ (50/50 volume mixture), and the solvent was removed by rotary evaporation. The pure product was isolated by open column chromatography on silica gel eluted with mixed solvent (CH_2Cl_2 and diethyl ether).

In the cases of dibenzyl sulfide and bis(phenylthio)methane, the oxidations were carried out in 0.25 M and 0.20 M H_2O_2/EtOH solution respectively, because the solubility of the sulfides in ethanol was low.

The sulfoxides were identified by comparison of physical data with literature results (di-*t*-butyl sulfoxide,[19,21)] pentamethylene sulfoxide,[22)] phenyl phenylthiomethyl sulfoxide,[23,24a)] bis(phenylsulfinyl)methane,[24)] 2-(phenylsulfinyl)ethanol,[25)] and diallyl sulfoxide[26)]) or with commercial samples (diphenyl sulfoxide, dibutyl sulfoxide, dibenzyl sulfoxide, methyl phenyl sulfoxide, chloromethyl phenyl sulfoxide, phenylsulfinylacetic acid ethyl ester, and phenyl vinyl sulfoxide).

Oxidation of Bis(4-nitrophenyl) Sulfide to Bis(4-nitrophenyl) Sulfoxide. The oxidation of bis(4-nitrophenyl) sulfide (1.0 mmol) was performed in 0.025 M H_2O_2/CH_3CN solution (1.1 mmol, 44 mL), because the solubility of the sulfide in ethanol was very low. The oxidation was carried out at 50 °C for 5 h in the presence of 5 mol% MTO. After treatment of the reaction mixture with aqueous $NaHSO_3$, the aqueous solution was extracted with ethyl acetate (10mL×3). After evaporation of solvent, the solid residue was separated by column chromatography on silica gel eluted with CH_2Cl_2. First, unreacted sulfide (2%), and then bis(4-nitrophenyl) sulfone (10%), and finally bis(4-nitrophenyl) sulfoxide was obtained (88%).

Bis(4-nitrophenyl) Sulfoxide: Mp 176—177 °C; IR (KBr) 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 7.90$ (d, $J = 9$ Hz, 4H), 8.35 (d, $J = 9$ Hz, 4H); ^{13}C NMR ($CDCl_3$) $\delta = 124.92$, 125.40, 151.56.

General Procedure for Synthesis of Sulfone. The sulfide (4.0 mmol) was dissolved in ethanolic H_2O_2 (8.8 mL, 8.8 mmol, 1.0 M). MTO (20 mg, 0.080 mmol) was added to the solution. The mixture was stirred at room temperature. The temperature of the mixture rose and came down within a few minutes. The reaction was monitored by TLC or GC. When no more sulfide and/or sulfoxide was present, the mixture was poured into aqueous $NaHSO_3$ to decompose excess H_2O_2. The aqueous solution was extracted with CH_2Cl_2 (10mL×3; in the cases of Table 3, Entry 6, and Table 4, Entry 4, salting out was necessary for the complete extraction). The combined extract was dried over anhydrous $Na_2SO_4/MgSO_4$ (mixture), and evaporated under reduced pressure. Generally the obtained residue was almost pure sulfone (checked by TLC, GC, and NMR).

The oxidations of dibenzyl sulfide and bis(4-nitrophenyl) sulfide were carried out in 0.50 M H_2O_2/EtOH and 0.10 M H_2O_2/CH_3CN solution, respectively, because the solubility of the sulfides was low.

The sulfones were identified by comparison of physical data with literature results (pentamethylene sulfone,[27)] 2-(phenylsulfonyl)ethanol,[28)] phenylsulfonylacetic acid ethyl ester,[29)] and diallyl sulfone[30)]) or with commercial samples (diphenyl sulfone, dibutyl sulfone, benzyl sulfone, methyl phenyl sulfone, bis(4-nitrophenyl) sulfone, chloromethyl phenyl sulfone, and phenyl vinyl sulfone).

Di-*t*-butyl Sulfone: Mp 126—127 °C; IR (KBr) 1265, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 1.52$ (s, 18H); ^{13}C NMR ($CDCl_3$) $\delta = 26.05$, 64.74.

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