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Rhenium-Catalyzed Oxidation of Sulfides with Phenyl Sulfoxide

Jeffrey B. Arterburn* and Sherry L. Nelson

Department of Chemistry and Biochemistry,
New Mexico State University, Box 30001/3C,
Las Cruces, New Mexico 88003

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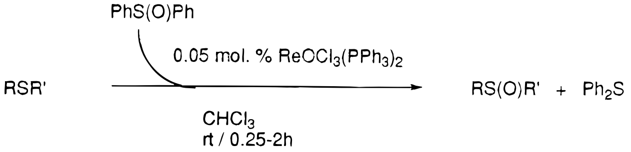
Sulfoxides are valuable functional groups in organic chemistry and are typically prepared by the oxidation of sulfides. A variety of reagents are capable of this oxidation; however, many of these are useful only within a limited range of sulfide structures.[1,2] Overoxidation of sulfides, resulting in formation of sulfones, and undesired reactions of other functional groups are common problems, particularly when preparing biologically relevant sulfoxides. In principle, oxygen atom transfer from a sulfoxide oxidant could provide a very mild method for oxidizing sulfides. The oxidation of sulfides by dimethyl sulfoxide has been reported, although this reaction is limited to sulfides with unusual structural features and conditions involving high temperatures or acid catalysts.[3] Sulfoxides are capable of oxidizing transition metals, and it has been observed that metal-catalyzed oxygen atom transfer from sulfoxides to phosphines occurs with a variety of complexes.[4,5] Bryan and Mayer et al. observed the rapid equilibrium exchange of an oxygen atom between dimethyl sulfoxide and dimethyl sulfide that was catalyzed by a rhenium(V) oxo complex $Re(O)Cl_3(Me_2S)(OPPh_3)$ (**I**).[6] Complex **I** was easily prepared from the reaction of dimethyl sulfoxide and $Re(O)Cl_3(PPh_3)_2$ (**II**). The accessibility of Re(V) oxo complexes and the potential for using sulfoxides as safe, inexpensive oxidants led us to investigate this chemistry further. We report here an exceedingly mild, catalytic oxidation of sulfides using diphenyl sulfoxide as the co-oxidant (Scheme 1). This procedure is effective for a wide range of sulfides, it is compatible with a variety of functional groups, and it is very practical for preparing hydrophilic sulfoxides.

Our initial experiments focused on determining the scope of rhenium catalyzed sulfide oxidations using Me_2SO-d_6 as the oxidant. Both Re(V) oxo complexes $Re(O)Cl_3(Me_2S)(OPPh_3)$ (**I**) and $ReOCl_3(PPh_3)_2$ (**II**) react with excess Me_2SO-d_6 to give a pale green, catalytically active reaction mixture, spectroscopically consistent with the known complex $Re(O)_2(Me_2SO)_2Cl$.[7] The presence of free $O{=}PPh_3$ was indicated by $^{31}P\{^1H\}$ NMR, and the solution ^1H NMR, UV/vis, and FT-IR spectra of the catalytically active reaction mixture from both precursors were identical. The rate of oxygen transfer between Me_2SO-d_6 (10 equiv) and Me_2S (1 equiv) in $CDCl_3$ was measured by ^1H NMR and found to be the same for reactions using 0.05 mol % of either precursor **I** or **II**. The synthetic and commercial availability of $ReOCl_3(PPh_3)_2$ (**II**)[8] make it the preferred catalyst precursor; therefore, **II** was used in all of the subsequent reactions. Reactions were carried out in organic solvents without precautions to exclude O_2 or H_2O; however, the activity of the catalytic system decreases slowly after several hours at ambient conditions and eventually produces inert Re(VII) perrhenate salts $[ReO_4]^-$.[7] Control experiments showed no sulfide oxidation occurs in the absence of catalyst.

Scheme 1



A series of sulfides were then reacted with $ReOCl_3(PPh_3)_2$ (**II**) (0.05 mol %) and an excess of Me_2SO-d_6 (10 equiv) in C_6D_6, and the results are presented in Table 1 (method A). Simple dialkyl sulfides such as methyl and *n*-butyl sulfide were oxidized efficiently with Me_2SO (entries 1 and 2, Table 1), while the reaction of the bulky *tert*-butyl sulfide gave only partial conversion to sulfoxide and the remainder as unreacted starting sulfide (entry 3, Table 1). Propylene sulfide (entry 4, Table 1) was unreactive under these conditions, while the 5-membered cyclic sulfide tetrahydrothiophene (entry 5, Table 1) was oxidized efficiently. Aryl sulfides were essentially unreactive using these conditions (entries 7 and 8, Table 1). Dialkyl sulfides possessing alcohol and protonated amine groups gave 77% and 44% conversion, respectively, without affecting these functional groups (entries 8 and 9, Table 1). (Methylthio)methyl acetate was unreactive under these conditions. No sulfide overoxidation products such as sulfones were detected in the crude reaction mixtures.

In order to improve the efficiency and extend this oxidation chemistry to aryl sulfides, we investigated diphenyl sulfoxide (Ph_2SO) as an oxidant.[9] The oxidations of a variety of sulfides using this procedure are reported in Table 1 (method B). Cyclic and acyclic alkyl sulfides were converted to sulfoxides nearly quantitatively with Ph_2SO and required shorter reaction times for completion than when Me_2SO was used (entries 1−3 and 5, Table 1), however, propylene sulfide (entry 4, Table 1) was unreactive using these conditions. The rhenium-catalyzed oxidation of the monoaryl sulfide thioanisole (entry 6, Table 1) with Ph_2SO was rapid and proceeded to 96% conversion. The reaction of phenyl vinyl sulfide (entry 7, Table 1) using these same conditions resulted in only 60% conversion after 15 min at ambient temperature. No further conversion occurred

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[1] (a) Madesclaire, M. *Tetrahedron* **1986**,*42*, 5459. (b) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Synthesis of Sulphoxides*; John Wiley & Sons, Ltd.: New York, 1994; p 109.

[2] The oxidation of sulfides with CH_3ReO_3/H_2O_2 has been reported: (a) Adam, W.; Mitchell, C. M.; Saha-Moller, C. R. *Tetrahedron* **1994**, *50*, 13121. (b) Vassell, K. A.; Espenson, J. H. *Inorg. Chem.* **1994**, *33*, 5491.

[3] (a) Hsu, F. L.; Szafraniec, L. L.; Beaudry, W. T.; Yang, Y. C. *J. Org. Chem.* **1990**, *55*, 4153. (b) Miotti, U. *J. Chem. Soc., Perkin Trans. 2* **1991**, 617.

[4] Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401.

[5] Kukushkin, V. Y. *Coord. Chem. Rev.* **1995**, *139*, 375.

[6] Bryan, J. C.; Stenkamp, R. E.; Tulip, T. H.; Mayer, J. M. *Inorg. Chem.* **1987**, *26*, 2283.

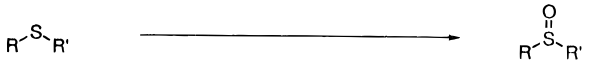
[7] Grove, D. E.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1224. The complex $ReO_2(Me_2SO)_2Cl$ is known to hydrolyze to $HReO_4$, and our attempted sulfide oxidations in neat Me_2SO or H_2O were unsuccessful. The organic soluble perrhenate salt $Bu_4N[ReO_4]$ also was not catalytically active. The addition of excess pyridine to the active catalyst results in a yellow solution, consistent with the Re(V) dioxo complex $[ReO_2(NC_5H_5)_4]Cl$ that has been reported from the reaction of (**I**) with pyridine. This complex was also not catalytically active for sulfide oxidation.

[8] Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145. Trichlorooxobis(triphenylphosphine)rhenium (**II**) is also commercially available from the Aldrich Chemical Co.

[9] For the gas-phase reaction: $Ph_2SO + Me_2S \rightarrow Ph_2S + Me_2SO$; $\Delta H = -2.6$ kcal/mol. Holm has introduced a thermodynamic scale of oxo transfer reactivity based on the correlation between ΔH values for gas-phase reactions and ΔG values. Holm, R. H.; Donahue, J. P. *Polyhedron* **1993**, *12*, 571.

0022-3263/96/1961-2260$12.00/0

Table 1. Synthesis of Sulfoxides by Rhenium-Catalyzed Sulfide Oxidations

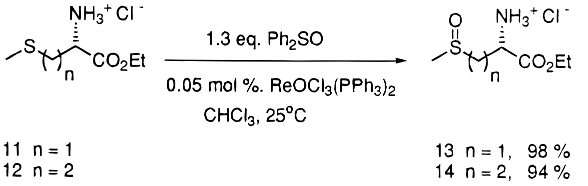


entry	substrate	method[a]	time (h)	yield (%)
1	R, R′ = −CH$_3$	A	0.5	86
		B	0.1	96
2	R, R′ = −^{n}Bu	A	2.0	86
		B	0.5	98
3	R, R′ = −^{t}Bu	A	2.5	50
		B	1.0	96
4	R, R′ = −CH$_2$CH(CH$_3$)−	A	24	0
		B	24	0
5	R, R′ = −CH$_2$CH$_2$CH$_2$CH$_2$−	A	1.0	80
		B	1.0	98
6	R = −Ph	A	5.0	10
	R′ = −CH$_3$	B	0.3	96
7	R = −Ph	A	24	0
	R′ = −CH=CH$_2$	B	0.3	60, 75[b]
8	R = −CH$_2$CH$_3$	A	4.0	77
	R′ = −CH$_2$CH$_2$OH	B	1.5	98, 96[c]
9	R = −CH$_2$CH$_3$	A	2.5	44
	R′ = −CH$_2$CH$_2$NH$_3$Cl	B	0.3	98,97[c]
10	R = −CH$_3$	A	24	0
	R′ = −CH$_2$OAc	B	0.3	77, 61[c]

[a] Reaction conditions: method A, 0.05 mol % of ReOCl$_3$(PPh$_3$)$_2$, 10 equiv of Me$_2$SO-d_6, 1 equiv of RSR′ in C$_6$D$_6$ at 25 °C; method B, 0.05 mol % of ReOCl$_3$(PPh$_3$)$_2$, 1.3 equiv of Ph$_2$SO, 1 equiv of RSR′ in CDCl$_3$ at 25 °C. [b] 2.6 equiv of Ph$_2$SO. [c] Preparative scale in CHCl$_3$.

after the addition of more catalyst precursor, and decomposition of the sulfoxide product became evident with longer reaction times.[10] When the reaction was performed using a larger excess of Ph$_2$SO (2.6 equiv), the sulfoxide yield was improved to 75%. Dialkyl sulfides possessing alcohol and protonated amine groups (entries 8 and 9, Table 1) were oxidized faster and more efficiently using Ph$_2$SO and without affecting these functional groups. (Methylthio)methyl acetate, which was unreactive with Me$_2$SO, gave 77% conversion to sulfoxide using Ph$_2$SO as the oxidant. The workup for the preparative scale reactions of the functionalized sulfoxides (entries 8−10, Table 1) was very simple, since the product sulfoxides were obtained easily by aqueous extraction.[11] No sulfones were detected in the reaction mixtures.

The sulfoxides of methionine and *S*-methylcysteine are of interest because of their biological activity, for protection of the sulfide group during peptide synthesis, as chiral ligands, and as synthetic intermediates.[12] We investigated the rhenium-catalyzed oxidation of *S*-methyl-L-cysteine and L-methionine ethyl ester derivatives with Ph$_2$SO to further test the functional group tolerance and preparative value of this reaction (eq 1).[11] The

 (1)

oxidation of *S*-methyl-L-cysteine ethyl ester hydrochloride (**11**) gave the sulfoxide (**13**) in 98% yield, and similar reaction with the methionine derivative (**12**) gave the sulfoxide (**14**) in 94% yield. No diastereoselectivity was evident in the formation of the sulfoxide stereocenter in these products.

In conclusion, the rhenium-catalyzed oxidation of alkyl and aryl sulfides with Ph$_2$SO is mild, efficient, and rapid. This oxidation reaction is compatible with a variety of functional groups and devoid of sulfone byproducts common with other oxidants. Catalytic oxygen atom transfer from sulfoxides provides a desirable alternative to traditional peroxide-based organic oxidations. Mechanistic studies, further synthetic applications of this reaction, and the potential for developing stereoselective oxidations are currently being investigated.

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Supporting Information Available: Experimental details and spectroscopic data for all compounds (5 pages).

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(10) The structures of these decomposition products have not yet been identified; however, the fact that no sulfone forms is significant.

(11) **General Procedure.** The catalyst precursor **II** (42 mg, 50 μmol) was added to a solution of the sulfide (1.0 mmol) and diphenyl sulfoxide (286 mg, 1.3 mmol) in CHCl$_3$ (4 mL) and the mixture shaken briefly to solubilize and then allowed to stand at 22 °C for 1.5−2 h. Aqueous extraction (3 × 4 mL) provided the sulfoxides free of unreacted starting compounds and reaction byproducts (Ph$_2$S and Ph$_3$PO); concentration and drying *in vacuo* gave the corresponding sulfoxides.

(12) The oxidation of methionine to methionine sulfoxide using aqueous Me$_2$SO/HCl has been reported: Shechter, Y. *J. Biol. Chem.*, **1986**, *261*, 66.