Rhenium-Catalyzed Oxidation of Thiols and Disulfides with Sulfoxides

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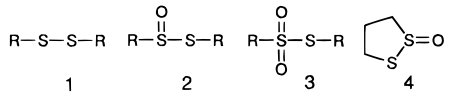
Oxidation reactions of organosulfur compounds hold continuing fascination for chemists because of their fundamental roles in biochemical and industrial processes and the variety of mechanistic pathways involved.[1] The oxidation of thiols to disulfides **1** is a characteristic reaction, and further oxidation to disulfide *S*-oxides (thiosulfinates **2**) and 1,1-dioxides (thiosulfonates **3**) is also possible. Weak S−S bonds in these compounds impart high reactivity,[2] and in natural products, these moieties and related cyclic analogues **4** are associated with



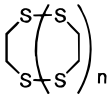
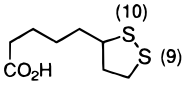
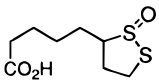
interesting biological activity and DNA-cleaving properties.[3−5] Direct oxidation of disulfides has been accomplished using peroxides,[6] periodate,[7] dimethyldioxirane,[8] and perborate,[6c] although careful control of oxidant stoichiometry and reaction conditions are necessary to avoid overoxidation and S−S bond cleavage.

We recently reported a mild method for oxidizing dialkyl and monoaryl sulfides to sulfoxides using a rhenium catalyst [$Re(O)Cl_3(PPh_3)_2$, **I**][9] and phenyl sulfoxide (Ph_2SO).[10] Sulfoxides are intriguing as oxidants because of their greater stability relative to peroxides and their suitability for safer, environmentally benign oxidation processes.[11] The oxidizing abilities of sulfoxides have been harnessed by molybdenum-containing oxotransferase enzymes such as dimethyl sulfoxide reductase,[12] and it has been hypothesized that thiols could function as external reductants.[13] Thiols are powerful reductants in vivo and are oxidized by sulfoxides to disulfides (eq 1) at high temperatures[14] or under acid/base catalysis.[15] On the basis of these observations, we investigated the possibility of rhenium-catalyzed oxidation of thiols and disulfides with sulfoxides. We report here a remarkably effective method for oxidizing thiols to disulfides using methyl sulfoxide (Me_2SO) and the catalyst precursor **I**. This system also exhibits synthetically valuable oxygen atom transfer chemistry, producing cyclic thiosulfinate **4** directly from reactions of 1,3-propanedithiol. The catalytic $Re(Ph_2SO)$ system was found to be even more effective for oxo transfer reactions, reacting with a variety of alkyl, aryl, and cyclic disulfides.

$$2R{-}SH + R'_2SO \rightarrow R{-}S{-}S{-}R + R'_2S + H_2O \quad (1)$$

A series of thiols were oxidized to disulfides rapidly by the catalytic $Re(Me_2SO)$ system (Table 1). Primary alcohol, carboxylic acid, ester, and protonated amine functional groups were unaffected during the oxidation of the thiols. Dithiols were particularly interesting substrates for the catalytic $Re(Me_2SO)$ oxidation, given the propensity of **I** toward formation of dithiolate complexes[16] and general interest in metal−thiolate complexes.[17] Slow addition of 1,2-, 1,3-, and 1,4-dithiols to the catalytic $Re(Me_2SO)$ reaction mixture resulted in the products shown in Table 1. Catalytic $Re(Me_2SO)$ oxidation of

Table 1. Catalytic $Re(Me_2SO)$ Oxidation of Thiols[a] and Dithiols[b]

entry	substrate	product	yield (%)
1	R-SH	R-S-S-R	
	(a) R = CH_3CH_2-		92[c]
	(b) $HO\text{-}CH_2CH_2$-		96[c]
	(c) $HO_2CCH_2CH_2$-		97[d]
	(d) $EtO_2CCH(NH_3Cl)CH_2$-		69[d]
	(e) C_6H_5-		100[c]
2	$HS\text{-}CH_2CH_2\text{-}SH$	 n = 1	29[cf]
		n = 2	13
		n = 3	9
		n = 4	13
		$H(\text{-}S\text{-}CH_2CH_2\text{-}S\text{-})_m$	36
3			94[e]
4			82[e]
5		 + S(9)-oxo	89[cf]

[a] Reaction conditions: **I**:Me_2SO:thiol = 0.05:2:2, 25 °C. [b] 0.05:2:1, 25 °C, slow addition of dithiol/CH_2Cl_2. [c] Product isolated by column chromatography. [d] Product isolated by recrystallization from MeOH/Et_2O. [e] Product isolated by bulb-to-bulb distillation. [f] Ratio determined by ^1H NMR.

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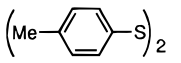
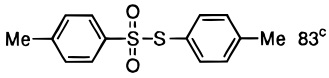
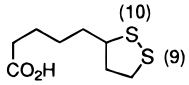
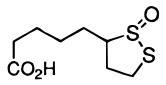
Table 2. Catalytic Re(Ph_2SO) Oxidation of Disulfides[a]

entry	substrate	product(s)	yield (%)
1	$(MeS)_2$	$Me-S(=O)-S-Me$	83[b]
2	$(MeS)_2$ + $(EtS)_2$	$Me-S(=O)-S-R$ and $Et-S(=O)-S-R$; R = Me, Et : (1 : 1 : 1 : 1)	100[d]
3			83[c]
4			84[b]
5	 (10) (9)	 + S(9)-oxo	90[c,d]

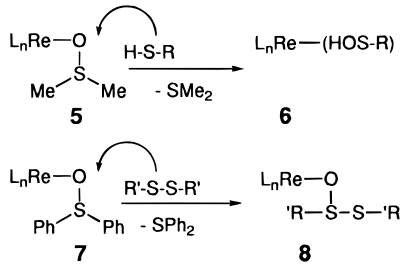
[a] Reaction conditions: **I**:Ph_2SO:disulfide = 0.05:2.2:1, 25 °C in CH_2Cl_2. [b] Product isolated by bulb-to-bulb distillation. [c] Product isolated by column chromatography. [d] Ratio determined by ^1H NMR.

1,2-ethanedithiol produced oligomeric cyclic disulfides[18] and an insoluble polymeric disulfide that precipitated directly from the reaction mixture. Intramolecular cyclization of 1,4-butanedithiol gave the stable, six-membered 1,2-dithiane ring. Unexpectedly, the catalytic Re(Me_2SO) oxidation of 1,3-propanedithiol produced 1,2-dithiolane *S*-oxide (**4**) in high yield. The intermediacy of the unstable five-membered disulfide 1,2-dithiolane[19] in this oxidation is suggested by the similar reactivity of (±)-α-lipoic acid, which was also rapidly oxidized to thiosulfinate products (entry 5). Thiosulfinates were not detected in the reaction mixtures in other thiol oxidations with Me_2SO.

Changing the sulfoxide component of the catalytic system from Me_2SO to Ph_2SO resulted in rapid oxidation of disulfides to the products indicated in Table 2. Thiosulfonate products were isolated from the catalytic Re(Ph_2SO) oxidation of acyclic alkyl and aryl disulfides.[20] Methyl methanethiosulfinate was observed as an intermediate by ^1H NMR during the oxidation of dimethyl disulfide $(MeS)_2$ with Re(Ph_2SO). The oxidation of $(MeS)_2$ with 1 equiv of Ph_2SO gave a mixture of thiosulfonate and starting $(MeS)_2$. The oxidation of a 1:1 mixture of $(MeS)_2$ and $(EtS)_2$ yielded a mixture of thiosulfonates, indicating that cleavage and recombination of the sulfur−sulfur bond occurred under these conditions (entry 2). Cyclic five- and six-membered disulfides were oxidized only to the corresponding thiosulfinate with the Re(Ph_2SO) system and did not react further with excess Ph_2SO.

The observed differences in reactivity for methyl and phenyl substituents suggests a mechanism where nucleophilic attack of the organosulfur compound occurs on a coordinated sulfoxide ligand,[21] rather than an oxo−metal complex as shown in Scheme 1.[22] This metal-mediated oxo-transfer reactivity differs significantly from the chemistry of sulfoxides activated by strong acids or electrophiles where nucleophiles react at sulfur.[11] The reaction of thiols with the Re(Me_2SO) system **5** would give a

Scheme 1



neutral, coordinated sulfenic acid intermediate **6**.[23] Inter- or intramolecular reaction between the second thiol and **6** would produce the observed disulfide products and H_2O, allowing the catalytic cycle to resume upon coordination of another Me_2SO ligand. Only the five-membered cyclic disulfides reacted with Re(Me_2SO), consistent with their lower oxidation potentials (0.70−0.75 V) relative to other disulfides.[24] All of the disulfides investigated were oxidized by the catalytic Re(Ph_2SO) reagent **7**. The enhanced oxo-transfer chemistry[25] of Ph_2SO compared with Me_2SO does not correlate with their relative S−O bond strengths, since aryl sulfoxide S−O bonds are typically stronger than alkyl ones (1−3 kcal mol^{-1}).[26] This unfavorable enthalpic component can be overcome by the electron-accepting ability of the aryl group in coordinated phenyl sulfoxide, lowering the energy necessary for cleavage of the sulfur−oxygen bond, resulting in an earlier transition state and a more reactive oxo-transfer reagent.

The formation of acyclic thiosulfonate products from the catalytic Re(Ph_2SO) oxidation most likely results from disproportionation of the initially formed, but unstable, acyclic thiosulfinates.[27] This proposal is supported by the high yields of stable cyclic thiosulfinates which do not disproportionate under these conditions.[6h] The observed mixed thiosulfonate products would result from exchange during disproportionation. An alternative reaction sequence involving two consecutive direct oxygen atom-transfer steps would also lead to thiosulfonate products.[28] The fact that cyclic thiosulfinates were not further oxidized here suggests that direct oxo transfer from the catalytic Re(Ph_2SO) to acyclic thiosulfinates does not occur.

In conclusion, catalytic Re sulfoxide systems have been shown to oxidize thiols and dithiols to disulfides under very mild conditions. The selective oxidation of cyclic disulfides to thiosulfinates should be well suited for the synthesis of natural products containing these sensitive subunits. Further mechanistic studies, the use of this synthetic methodology, and efforts to develop other selective rhenium-catalyzed oxidations with sulfoxides are currently in progress.

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Supporting Information Available: Synthetic procedures (7 pages). See any current masthead page for ordering and Internet access instructions.

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