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Deoxygenation of Sulfoxides to Sulfides with Thionyl Chloride and Triphenylphosphine: Competition with the Pummerer Reaction

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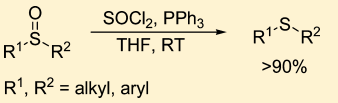
Supporting Information

ABSTRACT: Although a number of methods have been developed to reduce sulfoxides to sulfides, many of these processes are limited by side reactions, low yields, poorly available reagents, or harsh reaction conditions. We recently studied the reaction of various sulfoxides with $SOCl_2$ and Ph_3P. We were able to obtain the corresponding sulfides in excellent yields (>90%) when aliphatic and aromatic sulfoxides were treated with $SOCl_2$ as a catalyst and Ph_3P in THF at room temperature.



The Pummerer reaction is one of the most useful reactions in organic synthesis.[1] Originally, Pummerer reported that an alkyl sulfoxide rearranges to yield an α-acyloxy thioether in the presence of acetic anhydride.[2,3] In this reaction, sulfur is reduced while the adjacent carbon is oxidized. Later, thionyl chloride was used as an activator to generate and trap sulfonium ion **A** to give α-chloride thioether **2** through thionium ion **B** according to the same mechanism (Scheme 1).[4]

Recently, we have become interested in using thionyl chloride ($SOCl_2$) and triphenylphosphine (Ph_3P) as reagents at the same time because of the high reactivity of thionyl chloride to heteroatom nucleophiles and the high nucleophilicity of triphenylphosphine to reactive oxygen atom. In addition, both are the widely used reagents in organic reactions. We envisioned that the treatment of a sulfoxide with $SOCl_2$ would provide sulfonium ion **A**, as in the Pummerer reaction (Scheme 1). Then, Ph_3P might attack the oxygen atom of the original sulfoxide in the sulfonium ion **A** to afford deoxygenated sulfide **3** and phosphonium ion **C**. Subsequently, another sulfoxide might attack the sulfur atom in phosphonium ion **C** to generate sulfonium ion **A** and give triphenylphosphine oxide as a byproduct.

The deoxygenation of sulfoxides to the corresponding sulfides is a fundamental and significant functional group transformation in organic synthesis. During the last few decades, many types of methods have been developed to reduce sulfoxides.[5−43] Among them, a variety of metal complexes including molybdenum (Mo),[6−14] rhenium (Re),[11,15−18] zinc (Zn),[19−21] samarium (Sm),[22,23] iron (Fe),[24] copper (Cu),[25] niobium (Nb),[26−28] and other metals[29−34] have been widely employed for the deoxygenation of sulfoxides. Other reagents such as phosphorus compounds,[35−38] cyanuric chloride,[39] triflic anhydride,[40] acid chloride,[32,41] and halogen molecules[42] as activators were also used. However, many of these methods are limited by side reactions, low yields, poorly available reagents, or harsh reaction conditions. In particular, $ReOCl_3(PPh_3)_2$ was used as an efficient catalyst without any reducing agent although the reaction was performed under reflux conditions and long reaction time.[15] In addition, Ph_3P/CCl_4 combination generated very reactive phosphonium ylide ($Ph_3P{=}CCl_2$) as an intermediate under reflux conditions.[43] Only a few procedures allow mild deoxygenation with inexpensive and common laboratory reagents. For these reasons, the search for alternative efficient and convenient methods based on readily available reagents for the reduction of sulfoxides remains an important goal in organic synthesis.

Inspired by our consideration of the deoxygenation of sulfoxides to sulfides, as shown in Scheme 1, we initially examined the deoxygenation of methyl phenyl sulfoxide with 0.5 equiv of $SOCl_2$ and 1.5 equiv of Ph_3P at room temperature in CH_2Cl_2 (entry 1 in Table 1). The reaction afforded the desired methyl phenyl sulfide in 77% yield and the undesired chloromethyl phenyl sulfide in 23% yield. After obtaining this promising result, we carried out the reactions in different solvents including THF (entry 2), Et_2O (entry 3), and CH_3CN (entry 4). The best result was obtained in THF, with a 94% yield of the desired product (entry 2). When the amount of $SOCl_2$ was changed to 0.2 and 1 equiv in THF, the yields of the desired product decreased to 60% (entry 5) and 81% (entry 6), respectively. These results indicate that the use of the $SOCl_2$/Ph_3P combination is a new mild method for the deoxygenation of sulfoxides to the corresponding sulfides and that $SOCl_2$ participates in the reaction as a catalyst.

Next, the generality of this $SOCl_2/Ph_3P$ combination as reagents for the deoxygenation of sulfoxides was investigated, as shown in Table 2. First, a variety of aryl methyl sulfoxides were treated with $SOCl_2$ (0.5 equiv) and Ph_3P (1.5 equiv) in THF at room temperature. In the cases of methyl *p*-tolyl sulfoxide (entry 2) and 4-methoxyphenyl methyl sulfoxide (entry 3), the deoxygenation reactions afforded the corresponding sulfides in 92 and 98% yields, respectively, under the same reaction conditions as those used for methyl phenyl sulfoxide (entry 1). Although other aryl methyl sulfoxides with aromatic rings bearing electron-withdrawing groups, such as chloro (entry 4), cyano (entry 5), and acetyl groups (entry 6), required little longer reaction times, all substrates were converted into sulfides in excellent yields. When dioctyl sulfoxide was reacted with 0.5 equiv of $SOCl_2$, however, the desired sulfide was obtained in only

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Scheme 1. Plausible Mechanism of Deoxygenation with $SOCl_2$ and Ph_3P

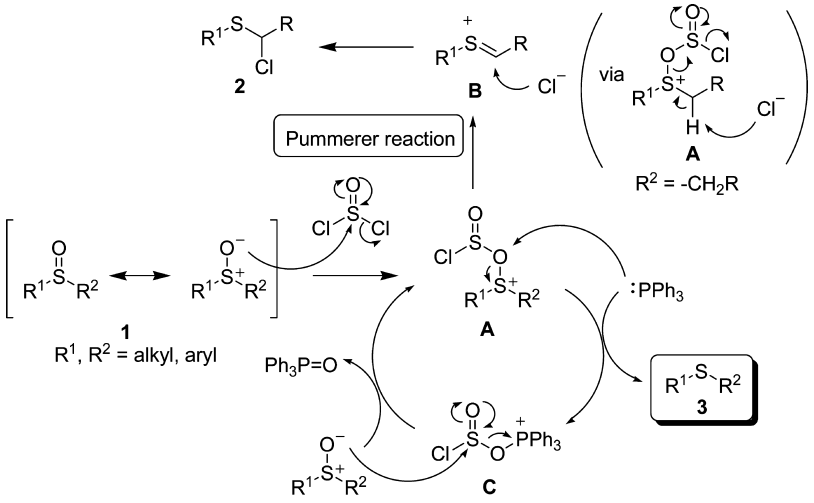
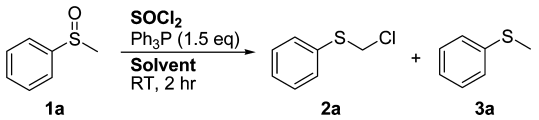


Table 1. Deoxygenation of Methylphenyl Sulfoxide (1a) in Various Solvents



1a 2a 3a

			yield (%)[a]	
entry	solvent	amount of $SOCl_2$ (equiv)	2a	3a
1	CH_2Cl_2	0.5	23	77
2	THF	0.5	6	94
3	Et_2O	0.5	10	90
4	CH_3CN	0.5	47	53
5[b]	THF	0.2	5	60
6	THF	1.0	19	81

[a]The yield was calculated by ^1H NMR. [b]35% unreacted sulfoxide was observed.

a 65% yield, with α-chloro sulfide, which is the Pummerer rearrangement product, in 33% yield. To increase the yield of the desired sulfide, we performed the reaction using different amounts of $SOCl_2$. When 0.2 equiv of $SOCl_2$ was used, the reaction afforded the desired sulfide in 94% yield with a trace of α-chloro sulfide (entry 7). Another dialkyl sulfoxide, dibenzyl sulfoxide, was converted into dibenzyl sulfide in 93% yield under the same reaction conditions (entry 8). Interestingly, when diphenyl sulfoxide was treated with 1.0 equiv of $SOCl_2$, the reaction proceeded very slowly. In this case, we used 1.5 equiv of $SOCl_2$ because there was no possibility of the Pummerer rearrangement. The reaction provided diphenyl sulfide in 97% yield (entry 9). Other diaryl sulfoxides, such as di(*p*-tolyl) sulfoxide (entry 10), di(4-methoxyphenyl) sulfoxide (entry 11), and di(4-chlorophenyl) sulfoxide (entry 12), were converted into the desired corresponding sulfides in excellent yields under the same reaction conditions. Clearly, the addition of Ph_3P to the Pummerer reaction furnished the corresponding sulfides as products from all types of sulfoxides in excellent yields. The role of Ph_3P is assumed that it works as a reductant by trapping the oxygen of sulfoxide and leads the catalytic cycle by forming the reactive intermediate **C** according to the proposed mechanism, as shown Scheme 1, which was supported by ^1H NMR kinetic study (see Supporting Information). It seems that the difference in the amount of $SOCl_2$ required for the deoxygenation reaction results from the nucleophilicity of the oxygen in the sulfoxide toward $SOCl_2$. Accordingly, because the reactivity of dialkyl sulfoxides is much higher than that of diaryl sulfoxides,[44] the $SOCl_2$ catalyst was used in a much lower amount with the dialkyl sulfoxides than with the diaryl sulfoxides.

In conclusion, we could obtain the corresponding sulfides in excellent yields when aliphatic and aromatic sulfoxides were treated with $SOCl_2$ and Ph_3P in THF at room temperature. Notably, $SOCl_2$ was used as a catalyst in this deoxygenation reaction. This protocol should be very useful in organic synthesis because of the ease of operation, the mild reaction conditions, the use of cheap reagents, and its wide scope.

EXPERIMENTAL SECTION

General Procedure for Deoxygenation of Sulfoxides Using $SOCl_2$ and Ph_3P. To a solution of sulfoxide (2.0 mmol) and Ph_3P (3.0 mmol) in dry THF (20 mL) was added dropwise $SOCl_2$ (0.4, 1.0, or 3.0 mmol according to the sulfoxide). The resulting solution was stirred under Ar atmosphere until the sulfoxide was consumed completely by TLC monitoring at room temperature and then concentrated in vacuo. The residue was subjected to column chromatography with only hexanes or hexanes/EtOAc (20:1−12:1) as eluent to afford the corresponding sulfide.

Thioanisole (Table 2, entry 1): colorless oil; TLC (100% hexanes) R_f = 0.35; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.36 (m, 4H), 7.25 (m, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.6, 126.4, 124.8, 15.6.

Methyl p-Tolyl sulfide (Table 2, entry 2): colorless oil; TLC (100% hexanes) R_f = 0.33; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 134.6, 129.5, 127.1, 20.8, 16.4.

4-Methoxythioanisole (Table 2, entry 3): white solid; TLC (hexanes/ethyl acetate = 17/1) R_f = 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 130.1, 128.7, 114.5, 55.3, 18.0.

4-Chlorothioanisole (Table 2, entry 4): colorless oil; TLC (100% hexanes) R_f = 0.39; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 130.7, 128.8, 127.7, 15.9.

4-(Methylthio)benzonitrile (Table 2, entry 5): white solid; TLC (hexanes/ethyl acetate = 9/1) R_f = 0.39; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 132.1, 125.4, 119.0, 107.6, 14.6.

4-(Methylthio)acetophenone (Table 2, entry 6): white solid; TLC (hexanes/ethyl acetate = 9/1) R_f = 0.35; ^1H NMR (400 MHz, $CDCl_3$) δ

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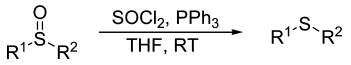
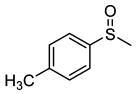
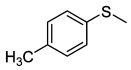
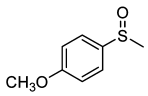
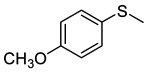
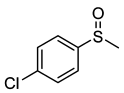
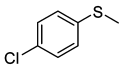
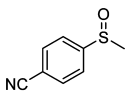
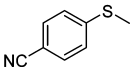
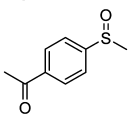
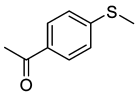
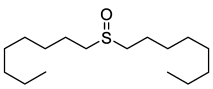
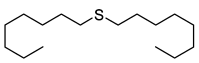
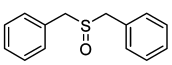
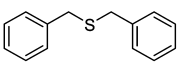
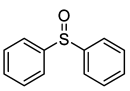
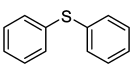
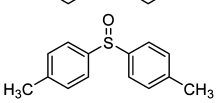
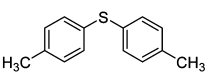
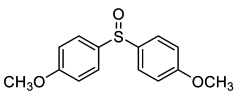
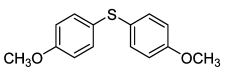
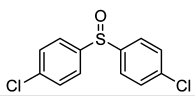
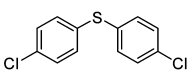
Table 2. Deoxygenation of Various Sulfoxides under the Optimized Reaction Conditions[a]



Entry	Substrate	Product	Amount of $SOCl_2$ (equiv.)	Reaction time	Yield (%)	Selectivity (product:α-chloro sulfide)[b]
1			0.5	2 hr	93	(94:6)
2			0.5	2 hr	92	(94:6)
3			0.5	2 hr	98	(98:2)
4			0.5	3 hr	95	(95:5)
5			0.5	3 hr	93	(95:5)
6			0.5	3 hr	92	(95:5)
7			0.2	3 hr	94	(96:4)
8			0.2	3 hr	93	(93:7)
9			1.5	4 hr	97	
10			1.5	4 hr	99	
11			1.5	4 hr	99	
12			1.5	4 hr	96	

[a]For all reactions, 1.5 equiv of Ph_3P was used. [b]The ratio was calculated by ^1H NMR.

7.83 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 2.53 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 145.8, 133.4, 128.7, 124.9, 26.4, 14.7.

Dioctyl Sulfide (Table 2, entry 7): colorless oil; TLC (100% hexanes) R_f = 0.53; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, J = 7.4 Hz, 2H), 1.58−1.51 (m, 2H), 1.36−1.24 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 31.8, 29.7, 29.2, 29.1, 28.9, 22.6, 14.1.

Dibenzyl Sulfide (Table 2, entry 8): white solid; TLC (hexanes/ethyl acetate = 17/1) R_f = 0.42; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.17 (m, 10H), 3.53 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 129.0, 128.4, 126.9, 35.5.

Diphenyl Sulfide (Table 2, entry 9): white solid; TLC (100% hexanes) R_f = 0.42; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.15 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 131.0, 129.2, 127.0.

Di(p-tolyl) Sulfide (Table 2, entry 10): white solid; TLC (100% hexanes) R_f = 0.27; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 4H), 7.03 (d, J = 8.0 Hz, 4H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 132.6, 131.0, 129.9, 21.1.

Di(4-methoxyphenyl) Sulfide (Table 2, entry 11): white solid; TLC (hexanes/ethyl acetate = 12/1) R_f = 0.36; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.8 Hz, 4H), 6.75 (d, J = 8.8 Hz, 4H), 3.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 132.7, 127.3, 114.7, 55.3.

Di(4-chlorophenyl) Sulfide (Table 2, entry 12): white solid; TLC (100% hexanes) R_f = 0.49; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.16 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 133.4, 132.2, 129.4.

■ ASSOCIATED CONTENT

Supporting Information

Kinetic ^1H NMR data for the proposed mechanism and ^1H NMR and $^{13}C\{^1H\}$ NMR spectra for all sulfides presented in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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