Selective and Efficient Oxidation of Sulfides and Thiols with Benzyltriphenylphosphonium Peroxymonosulfate in Aprotic Solvent

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Abstract: Benzyltriphenylphosphonium peroxymonosulfate could be used for selective oxidation of aromatic and aliphatic sulfides and thiols to their corresponding sulfoxides and disulfides under nonaqueous and aprotic conditions without catalyst.

Compounds containing a sulfoxide moiety are useful synthetic intermediates for the construction of various chemically and biologically significant molecules.[1] Oxidation of sulfides is a very useful route for preparation of sulfoxides. Several methods are available for conversion of sulfides to sulfoxides.[2−17] However, some of the existing methods use sophisticated reagents, complex catalysts, toxic metallic compounds, or rare oxidizing reagents that are difficult to prepare.[2−13] Otherwise overoxidation of sulfides resulting in sulfone formation and undesired reactions of other functional groups are common problems, particularly when preparing biologically relevant sulfoxides. Therefore, there is a need for a simple, less expensive, and safer method for conversion of sulfides to sulfoxides. Selective oxidative coupling of thiols to disulfides is of interest from both a biological[18] and a synthetic point of view.[19] Thiols are among functional groups which can be easily over oxidized and therefore extensive methods have been reported for their controlled oxidation.[12,20] Most of the existing methods involve the use of metal catalysts or reagents such as halogens and always suffer with effluents due to these reagents.

Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) is an inexpensive, water-soluble, and stable oxidizing reagent that is commercially available, but this reagent is insoluble in organic solvents and buffering is needed due to its acidity.[21] Recently, we have reported benzyltriphenylphosphonium peroxymonosulfate **1** ($PhCH_2Ph_3PHSO_5$) as a mild, inexpensive, and efficient oxidizing reagent for the oxidative deprotection of trimethylsilyl and tetrahydropyranyl ethers and of ethylene acetals under nonaqueous conditions[22a] or microwave irradiation,[22b] conversion of oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones, and semicarbazones to the parent carbonyl compounds in aprotic solvent,[22c] oxidation of alcohols to aldehydes and ketones under solvent-free[22d] or aprotic conditions,[22e] oxidation of urazoles to triazolinediones in a solvent-free system,[22f] and dethioacetalization of 1,3-dithiolanes and 1,3-dithianes.[22g] In the course of our studies on the oxidation of organic sulfur compounds,[14] we explored the utility of **1** as a mild and selective oxidizing reagent for oxidation of sulfides **2** and thiols **4** to their corresponding sulfoxides **3** and disulfides **5** under nonaqueous conditions.

Benzyltriphenylphosphonium peroxymonosulfate **1**, a mild, efficient, stable, and cheap reagent, is a white powder that is quite soluble in dichloromethane, chloroform, acetone, and acetonitrile and insoluble in nonpolar solvents such as carbon tetrachloride, *n*-hexane, and diethyl ether. This reagent is readily prepared by the dropwise addition of an aqueous solution of Oxone to an

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TABLE 1. Oxidation of Methyl Phenyl Sulfide with Different Amounts of Reagent 1 at Reflux Acetonitrile[a]

entry	substrate/oxidant (equiv)	time (h)	yield (%)
1	1/1	18	66
2	1/1.2	18	71
3	1/1.3	10	85
4	1/1.5	2	100

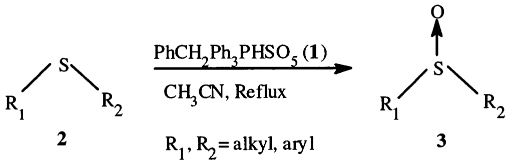
[a] Monitored by TLC and ^{1}H NMR analysis.

TABLE 2. Oxidation of Sulfides 2 to Sulfoxides 3 with Reagent 1 in Refluxing Acetonitrile[a,b]

entry	R_1	R_2	time (h)	yield[c] (%)
1	Ph	Me	2	91
2	Ph	*n*-Bu	2.5	92
3	Ph	$PhCH_2$	12	88
4	$PhCH_2$	Me	6	90
5	$PhCH_2$	*n*-Bu	6	90
6	4-MeC_6H_4	Me	3	86
7	4-ClC_6H_4	Me	3	89
8	C_4H_9	C_4H_9	12	78

[a] Confirmed by comparison with authentic samples.[2-17] [b] Substrate/oxidant (1:1.5). [c] Yield of isolated pure products.

SCHEME 1



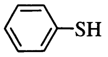
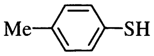
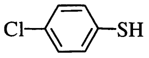
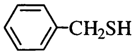
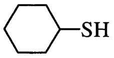
aqueous solution of benzyltriphenylphosphonium chloride in quantitative yield at room temperature and could be stored for months without losing its potency.[22] The amounts of HSO_5^- in this reagent have been determined by an iodometric titration method[23] and the measurements are consistent with almost 99 wt % of active oxidizing agent.

At first, the oxidation of methyl phenyl sulfide as the model compound in various solvents was examined. The solvents examined were dichloromethane, chloroform, and acetonitrile. The reactions were carried out by stirring the model compound with 1.5 molar amount of **1** at reflux condition. Dichloromethane and chloroform were inferior solvents to acetonitrile because the reaction stopped at lower conversions in these solvents than that in acetonitrile. Next, the effects of the amount of the oxidant **1** were examined with the model compound (1 mmol) under nonaqueous conditions in refluxing acetonitrile without catalyst. The results are summarized in Table 1.

The optimum ratio of sulfide to oxidant **1** (1:1.5) is found to be ideal for complete conversion of sulfides **2** to sulfoxides **3** while the reaction remains incomplete with lesser ratio of substrate and oxidant, for example 1:1 and 1:1.2. By using this oxidation system, a wide variety of alkyl aryl and dialkyl sulfides **2** were oxygenated to their corresponding sulfoxides **3** in high yields within mild reaction periods (Table 2 and Scheme 1). In this method, oxidation of a sulfide is achieved by stirring a mixture of a sulfide and the reagent **1** under reflux condition. The reaction time is usually between 2 and 12 h. The sulfoxides are isolated by filtering the reaction mixture and washing the filter cake with appropriate solvent. Evaporation of filtrate under vacuum often produces pure sulfoxide without any purification. All the reactions occurred with complete selectivity for sulfoxide formation, no overoxidation products such as sulfones were detected in the reaction mixtures. This method offers a simple, general, selective and highly efficient route for converting sulfides to the corresponding sulfoxides in the absence of complex catalyst.

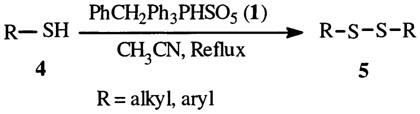
TABLE 3. Oxidative Coupling of Thiols 4 to Disulfides 5 with Reagent 1 in Refluxing Acetonitrile[a,b]

Acetonitrile[a,b]

entry	thiol	time (h)	yield (%)[c]
1		1	99
2		1	98
3		1	97
4		1.5	95
5[d]		2.5	90
6[d]	$CH_3(CH_2)_3SH$	2.5	91

[a] Confirmed by comparison with authentic samples.[12,20] [b] v-Substrate/oxidant (1:1). [c] Yield of isolated pure products. [d] Substrate/oxidant (1:1.5).

SCHEME 2



Benzyltriphenylphosphonium peroxymonosulfate **1** was also used to transform thiols **4** to disulfides **5** at reflux condition. A variety of aromatic and aliphatic thiols were converted into symmetrical disulfides **5** upon simple admixing with the reagent **1**. The process involves stirring the thiol **4** with reagent **1** in acetonitrile under reflux condition. In most cases investigated, the optimum mole ratio between the thiol and the oxidant is found to be 1:1, which produces pure disulfides **5** in high yields (Table 3 and Scheme 2). Aromatic thiols could be selectively oxidized within 1h to the corresponding disulfides in quantitative yields. Thiophenol, 4-chlorothiophenol and 4-methylthiophenol (Table 3, entries 1−3) exhibited a similar reactivity leading to the corresponding disulfides respectively, in high yields with no detectable influence of the substituent. Benzylthiol underwent oxidation with **1** in refluxing acetonitrile to afford dibenzyl disulfide in quantitative yield (Table 3, entry 4). The aliphatic thiols (Table 3, entries 5 and 6) afforded only traces of disulfides **5** even after 12 h under these

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conditions. These reactions could be completed, however, by increasing the oxidant/thiol ratio (Table 3). The presented oxidative coupling of thiols by reagent **1** is a convenient alternative to the reported reagents in terms of the reaction time, the yields of the disulfides, mild reaction conditions, no necessary to catalyst and the amount of the oxidant required.[20] In addition to the greater safety in handling and ease use of **1**, the product can be isolated by simple filtration and removal of the solvent. To demonstrate the utility of the procedure described here, a 10-fold scale oxidation was carried out with **1** for the oxidative coupling of thiophenol, and the corresponding disulfide was obtained in 99% yield within 1 h.

In conclusion, this new method for converting sulfides and thiols to their corresponding sulfoxides and disulfides offers the following advantages: (a) the reagent **1** is a cheap, selective, and safe oxidant, (b) the procedure is simple and occurs in aprotic solvent, (c) the yield of sulfoxide and disulfide is high, and (d) unlike previous oxygenation methods, this one requires neither an aldehyde nor a transition metal complex.

Experimental Section

Yields refer to isolated pure products. The oxidation products were characterized by comparison of their spectral (IR, ^{1}H NMR) and physical data with the authentic samples. All $_1$H NMR spectra were recorded at 90 MHz. All reactions were carried out in refluxing acetonitrile. The reagent **1** was prepared according to our previously reported procedures.[22]

Typical Procedure for Oxidation of Sulfides 2 to Sulfoxides 3 with Reagent 1. To a solution of thioanisole (1 mmol, 0.124 g) in acetonitrile (5 mL) in a 25 mL round-bottomed flask which was equipped with a condenser and a magnetic stirrer was added reagent **1** (1.5 mmol, 0.7 g). The reaction mixture was refluxed for 2 h. After disappearance of the starting sulfide monitored by TLC using EtOAc/cyclohexane (2:8), the mixture was filtered through a sintered glass funnel and the solid residue was washed with acetonitrile (10 mL). Evaporation of the filtrates gave methyl phenyl sulfoxide as a colorless oil in 91% yield as revealed from ^{1}H NMR analysis: mp 30−32 °C (lit.[16] mp 32−33 °C); ^{1}H NMR (CDCl$_3$, 90 MHz) δ 2.7 (s, 3H), 7.48−7.56 (m, 3H), 7.64−7.67 (m, 2H); IR (film) ν 692, 754, 954, 1046, 1092, 1415, 1446, 1477, 2915, 3000, 3062 cm^{-1}.

Typical Procedure for 10-Fold Scale Oxidative Coupling of Thiols 4 to Disulfides 5 with Reagent 1. In a round-bottomed flask (250 mL) equipped with a condenser and a magnetic stirrer was prepared a solution of thiophenol (10 mmol, 1.1 g) in acetonitrile (50 mL). Reagent **1** (10 mmol, 4.66 g) was added to the solution, and the resulting mixture was stirred magnetically under reflux conditions for 1 h. After completion of the reaction, monitored by TLC using EtOAc/cyclohexane (2:8), the reaction mixture was filtered and the solid material was washed with acetonitrile (50 mL). The removal of solvent under reduced pressure afforded pure diphenyl disulfide in 99% yield without any purification: mp 59−61 °C (lit.[12b] mp 58−61 °C); ^{1}H NMR (CDCl$_3$, 90 MHz) δ 7.62−7.48 (m, 4H), 7.42−7.20 (m, 6H); IR (KBr) ν 459, 470, 687, 734, 1435, 1474, 1572, 3050 cm^{-1}.

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