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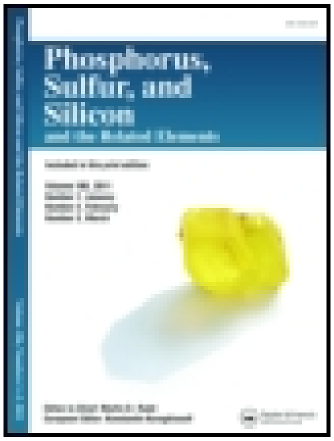

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A Selective Solid State Oxidation of Sulfides and Thiols with Benzyltriphenylphosphonium Peroxymonosulfate

A. R. Hajipour [a], S. E. Mallakpour [a] & H. Adibi [a]
[a] Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan, Iran

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A SELECTIVE SOLID STATE OXIDATION OF SULFIDES AND THIOLS WITH BENZYLTRIPHENYLPHOSPHONIUM PEROXYMONOSULFATE

A. R. Hajipour, S. E. Mallakpour, and H. Adibi
Pharmaceutical Research Laboratory, College of Chemistry,
Isfahan University of Technology, Isfahan, Iran

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*Benzyltriphenylphosphonium peroxymonosulfate **1** could be used for oxidation of sulfides **2** and thiols **4** to their corresponding sulfoxides **3** and disulfides **5** under solid-phase conditions.*

Keywords: Benzyltriphenylphosphonium peroxymonosulfate; disulfides; oxidation; sulfides; sulfoxides; thiols

INTRODUCTION

Sulfoxides play an important role in organic chemistry.[1] They have been utilized extensively in carbon-carbon bond formation reactions.[2] Oxidation of sulfides is a very useful route for preparation of sulfoxides. Several methods are available for conversion of sulfides to sulfoxides.[3–18] However, some of the existing methods which have been reported, use expensive, toxic or rare oxidizing reagents that are difficult to prepare.[3–10,16a] Many of these procedures also suffer from poor selectivity. Therefore, there is a need for a simple, less expensive, and safer method for conversion of sulfides to sulfoxides.

Disulfide bond formation is important in organic synthesis in biologically active molecules and for protein stabilization and in peptides.[19] There are several various methods[11,16,20] for the coupling of thiols but most of the reagents involve metal ions and solvents that are toxic in

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Address correspondence to S. E. Mallakpour, Pharmaceutical Research Laboratory, College of Chemistry, Mutah University, Isfahan University of Technology, Isfahan 84156, Iran. E-mail: mallakpour@cc.iut.ac.ir

nature. Recently, various methods have been reported for this transformation in dry media.[21]

Oxone ($2KHSO_5.KHSO_4.K_2SO_4$) is a strong, inexpensive, water-soluble, and versatile oxidizing agent that is commercially available. It has some disadvantages: It is insoluble in organic solvents and buffering is needed due to its acidity.

In recent years, there has been an increasing interest on reactions that employ environmentally friendly reagents or proceed in the absence of solvents.[22] Because of our interest in development of solvent-free reactions,[23] we now report on benzyltriphenylphosphonium peroxymonosulfate **1** as a mild and selective oxidizing reagent for oxidation of sulfides **2** and thiols **4** to their corresponding sulfoxides **3** and disulfides **5** respectively under solvent-free conditions. This reagent is readily prepared by reaction of an aqueous solution of Oxone with an aqueous solution of benzyltriphenylphosphonium chloride.[24] Filtration and drying of the precipitates resulted in a white powder, which could be stored for months without losing its oxidizing ability. The amounts of HSO_5^- in this reagent have been determined by an iodometric titration method.[25] The measurements are consistent with almost 99% by weight of active oxidizing agent. Unlike Oxone, this reagent is readily soluble in various organic solvents such as methylene chloride, chloroform, acetone, and acetonitrile and insoluble in non-polar solvents such as carbon tetrachloride, n-hexane, and ether. Very recently, we have reported the synthetic utility of $PhCH_2Ph_3P^+HSO_5^-$ **1** for some organic transformations.[24]

RESULTS AND DISCUSSION

At first, the effects of the amount of the oxidant **1** were examined with methyl phenyl sulfide as the substrate (1 mmol) under solvent-free conditions without catalyst. The results are summarized in Table I. 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

TABLE I Oxidation of Methyl Phenyl Sulfide with Different Amounts of Reagent **1** under Solvent-Free Conditions[a]

Entry	Substrate/Oxidant (mmol)	Time (min)	Yield (%)
1	1/1	20	60
2	1/1.2	20	70
3	1/1.3	15	85
4	1/1.5	10	100

[a] Monitored by TLC analysis.

TABLE II Oxidation of Sulfides **2** to Sulfoxides **3** with Reagent **1** under Solvent-Free Conditions[a,b]

Entry	R_1	R_2	Time (min)	Yield (%)[c]
1	Ph	Me	10	98
2	Ph	*n*-Bu	20	88
3	Ph	$PhCH_2$	25	85
4	$PhCH_2$	Me	15	92
5	$PhCH_2$	*n*-Bu	25	90
6	$PhCH_2$	$PhCH_2$	30	70
7	$4\text{-}MeC_6H_4$	Me	10	86
8	$4\text{-}ClC_6H_4$	Me	20	89
9[d]	C_4H_9	C_4H_9	35	79

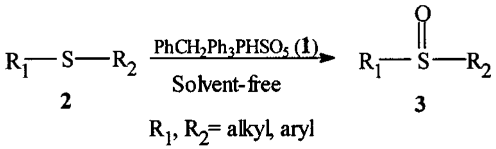
[a] Confirmed by comparison with authentic samples.[3–18]

[b] Substrate/oxidant (1:1.5).

[c] Yield of isolated pure products.

[d] Substrate/oxidant (1:2).

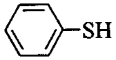
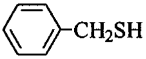
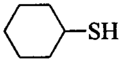
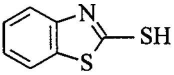
incomplete with lesser amounts for example 1:1 and 1:1.2. By using this oxidation system, a wide variety of alkyl aryl, dialkyl, and diaryl sulfides **2** were transformed to their corresponding sulfoxides **3** in high yields within short reaction periods (Table II and Scheme 1). In this method, oxidation of a sulfide is achieved by grinding a mixture of a sulfide and the reagent **1** in a mortar under solvent-free condition at room temperature. The reaction time is usually between 10 and 40 min. The sulfoxides are isolated by washing the reaction mixture with solvent followed by filtering the mixture. Evaporation of filtrate under vacuum often produces pure sulfoxide. Overoxidation is not a problem in our method. This method offers a simple, general, selective, and highly-efficient route for converting sulfides to the corresponding sulfoxides.



SCHEME 1

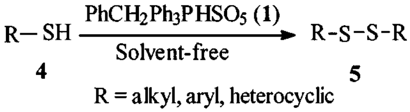
Benzyltriphenylphosphonium peroxymonosulfate **1** was also used to transform thiols **4** to disulfides **5** under solvent-free conditions at room temperature. A variety of thiols, aromatic and heterocyclic, are converted into symmetrical disulfides **5** on simple admixing with the reagent **1**. The process in its entirety involves grinding the thiol **4** with reagent **1** in an ambient air atmosphere. In most cases investigated,

TABLE III Oxidative Coupling of Thiols **4** to Disulfides **5** with Reagent **1** under Solvent-Free Conditions[a,b]

Entry	Thiol	Time (min)	Yield (%)[c]
1		5	98
2		10	95
3		10	98
4		20	90
5[d]		25	88
6[d]	$CH_3(CH_2)_3SH$	25	80
7[d]		40	80

[a] Confirmed by comparison with authentic samples.[11,16,20,21]
[b] Substrate/oxidant (1:1).
[c] Yield of isolated pure products.
[d] Substrate/oxidant (1:2).

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 III and Scheme 2). The fused ring heterocyclic (Table III, entry 7) and alkyl thiols (Table III, entries 5, 6) afforded only traces of disulfides **5** even after 2 h under these conditions. These reactions could be completed, however, by increasing the oxidant/thiol ratio (Table III). In addition from economical and environmental points of view, the presented solvent-free oxidation by reagent **1** can be compared by other methods in the literature in terms of the reaction time, the yields of the disulfides, mild reaction conditions and the amount of the oxidant.[21]

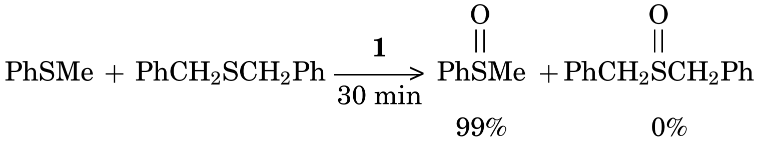


$$\underset{\mathbf{4}}{R\text{–}SH} \xrightarrow[\text{Solvent-free}]{PhCH_2Ph_3PHSO_5\ (\mathbf{1})} \underset{\mathbf{5}}{R\text{-}S\text{-}S\text{-}R}$$

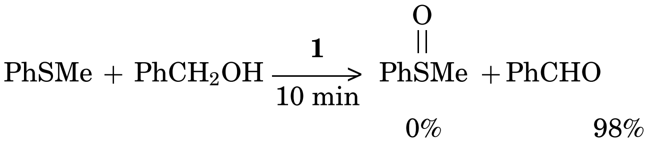
R = alkyl, aryl, heterocyclic

SCHEME 2

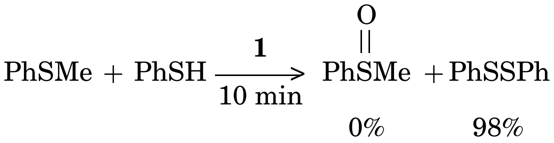
In order to evaluate the selectivity of reagent **1**, the competitive reactions shown in Eq. 1–3 were carried out. When an equimolar amount of thioanisole (1 mmol) and dibenzyl sulfide (1 mmol) was treated with 1.5 molar ratio of reagent **1**, only thioanisole was selectively oxidized to methyl phenyl sulfoxide (Eq. 1).Treatment of benzyl alcohol (1 mmol) with 1.5 molar ratio of reagent **1** in the presence of an equimolar amount of thioanisole for 10 min, led to exclusive oxidation of benzyl alcohol to benzaldehyde (Eq. 2). We also tried the competitive reaction between thioanisole (1 mmol) and thiophenol (1 mmol) with reagent **1** (1 mmol), and observed that only thiophenol was selectively oxidized to diphenyl disulfide (Eq. 3).



$$\mathrm{PhSMe + PhCH_2SCH_2Ph \xrightarrow[30\ min]{\mathbf{1}} \underset{99\%}{Ph\overset{O}{\overset{\|}{S}}Me} + \underset{0\%}{PhCH_2\overset{O}{\overset{\|}{S}}CH_2Ph}} \qquad (1)$$



$$\mathrm{PhSMe + PhCH_2OH \xrightarrow[10\ min]{\mathbf{1}} \underset{0\%}{Ph\overset{O}{\overset{\|}{S}}Me} + \underset{98\%}{PhCHO}} \qquad (2)$$



$$\mathrm{PhSMe + PhSH \xrightarrow[10\ min]{\mathbf{1}} \underset{0\%}{Ph\overset{O}{\overset{\|}{S}}Me} + \underset{98\%}{PhSSPh}} \qquad (3)$$

In order to show the strong and weak points of our method, we have compared the results of oxidation of thioanisole and thiophenol by our method with some of those reported in the literature under solvent-free conditions (Table IV).

TABLE IV Comparison of Oxidation of Thioanisole and Thiophenol by Our Method with Some of Those Reported in the Literature under Solvent-Free Conditions

Reagent (Substrate/oxidant)	Substrate	Time (min)/Yield (%)
$MnO_2/H_2SO_4/SiO_2$/Neat (1:2)[16c]	PhSMe	60/80
$NaIO_4/SiO_2$/*MW* (1:1.7)[13]	PhSMe	2/80
$Fe(NO_3)_3.9H_2O$/Neat (1:2)[16a]	PhSMe	75/92
$PhCH_2Ph_3PHSO_5$ (1:1.5)	PhSMe	10/98
NH_4NO_3/Clay/*MW* (1:3)[21a]	PhSH	0.5/98
Active MnO_2/Neat (1:1)[22d]	PhSH	6/97
$BaMnO_4$/Neat (1:1)[22d]	PhSH	6/97
$(NH_4)_2S_2O_8$/Grinding (1:1.1)[21b]	PhSH	10/79
$PhCH_2Ph_3PHSO_5$/Grinding (1:1)	PhSH	5/98

In conclusion, this new method for converting sulfides and thiols to their corresponding sulfoxides and disulfides offers the following advantages: (1) the reagent **1** is a cheap, selective and safe oxidant; (2) the procedure is simple and occurs under solvent-free condition; (3) the yield of sulfoxide and disulfide is high; and (4) the cost of the solvent has been eliminated.

EXPERIMENTAL

General

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.[3–21] All ^{1}H-NMR spectra were recorded at 90 MHz in $CDCl_3$ relative to TMS (0.00 ppm) and IR spectra were recorded on Shimadzu 435 IR spectrometer. All reactions were carried out under solvent-free conditions. The reagent **1** was prepared according to our previously reported procedures.[24]

Oxidation of Sulfides 2 to Sulfoxides 3 with Reagent 1 under Solvent-Free Conditions

Typical Procedure

Thioanisole (1 mmol, 0.124 g) was added to **1** (1.5 mmol, 0.7 g), and the mixture was ground with a pestle in a mortar until TLC showed complete disappearance of starting material, which required 10 min (Table II). Carbon tetrachloride (2 × 10 ml) was added to the reaction mixture and after vigorous stirring the mixture was filtered and the solvent was evaporated. The methyl phenyl sulfoxide was obtained in 98% yield as revealed from ^{1}H-NMR analysis, m.p. 30–32°C [Lit.[15] m.p. 32–33°C].

Oxidative Coupling of Thiols 4 to Disulfides 5 with Reagent 1 under Solvent-Free Conditions

Typical Procedure

Thiophenol (1 mmol, 0.11 g) and reagent **1** (1 mmol, 0.47 g) were mixed thoroughly using a pestle and mortar. The reaction mixture was placed in air at room temperature with further mixing for 5 min. On completion of the reaction, monitored by TLC, the product was extracted into carbon tetrachloride (2 × 10 ml). The removal of solvent under reduced pressure afforded pure diphenyl disulfide in 99% yield, m.p. 59–61°C [Lit.[16e] m.p. 58–61°C].

Competitive Reaction

Typical Procedure

A mixture of benzyl alcohol (1 mmol, 0.11 g), thioanisole (1 mmol, 0.12 g) and oxidizing reagent **1** (1.5 mmol, 0.7 g) in a mortar by pestle was ground, until TLC showed complete disappearance of benzyl alcohol (10 min). The crude reaction mixture was extracted into carbon tetrachloride (2 × 15 ml) and the solvent was evaporated. The benzaldehyde and methyl phenyl sulfoxide were obtained in 98% and 0% yields respectively as revealed from ^{1}H-NMR analysis. The other competitive reactions for Eqs. 1 and 3 are the same as above.

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