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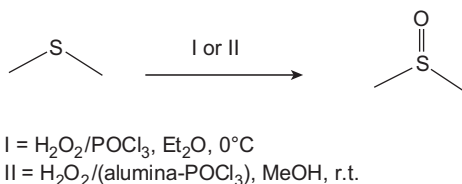
Alumina-supported monopero-phosphoric acid for selective oxidation of sulfides to sulfoxides

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Selective oxidation of aromatic and aliphatic sulfides to the corresponding sulfoxide was achieved by using $\text{POCl}_3/\text{H}_2\text{O}_2$ and (alumina-supported phosphorus oxychloride)/ H_2O_2 . A versatile procedure for the oxidation of sulfides to sulfoxides without any over-oxidation to sulfones has been reported. It is noteworthy that the reaction is clean and tolerates oxidatively sensitive functional groups and the sulfur atom is selectively oxidized.



Keywords: sulfide; sulfoxide; hydrogen peroxide; phosphorus oxychloride; oxidation; peracid

1. Introduction

The convenient synthesis of sulfoxides is of high interest in organic chemistry because of the importance of sulfoxides as synthetic intermediates for the construction of various chemically and biologically active molecules (1).

To date, the most important methods of sulfoxide preparation involve the oxidation of sulphides and various oxidizing agents have been introduced for this purpose (2–13). Unfortunately, many of these reagents are not satisfactory for medium- to large-scale operations for several reasons. The main reasons are the low content of the effective oxygen that is available for the oxidation, generation of environmentally unfavorable by-products and high cost. Another reason is the undesirable over-oxidation of sulfoxides to sulfones during the oxidation.

Indeed, selective oxidation of sulfides to sulfoxides remains a challenging task and constitutes an active research on its own, particularly with the emphasis on “green chemistry”. In this direction, the use of aqueous hydrogen peroxide as an oxidizing agent is highly preferred in view of an

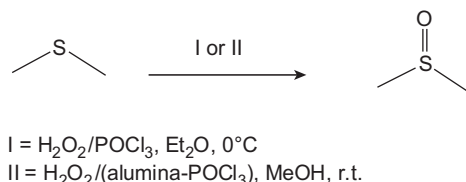
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effective oxygen content (47%) (14), simplified operation after reaction, cleanness that produces only harmless water by reaction (15), safety in storage and operation and the low cost of production transportation (16). However, aqueous hydrogen peroxide is a moderate oxidant and requires the use of a catalyst (13, 17–19). These features have already stimulated the development of useful procedures to promote the H_2O_2 oxidation.

Solid and polymer supports have been extensively studied as a reagent and a catalyst for many reactions and have found industrial application in several processes (17, 18). More recently, solid and polymer supports have attracted much attention because of their enhanced selectivity, milder reaction conditions and associated ease of manipulation (19, 20). As the study continued on the activation of hydrogen peroxide, we have now found that various sulfides are readily oxidized to the corresponding sulfoxides in excellent yields under mild conditions by alumina-supported and -unsupported monoperphosphoric acid which is generated *in situ* by the treatment of phosphorus oxychloride and hydrogen peroxide.

2. Results and discussion

We disclosed that $\text{H}_2\text{O}_2/\text{POCl}_3$ and $\text{H}_2\text{O}_2/\text{alumina-supported POCl}_3$ systems can be used for the gentle, efficient and selective oxidation of a wide range of sulfides at mild reaction conditions. The route for the synthesis of sulfoxides is shown in Scheme 1.



Scheme 1. Oxidation of sulfide to sulfoxide.

In order to determine what organic solvent would be most suitable, we studied the oxidation of methyl phenyl sulfide in the presence of common organic solvents such as THF, acetone, Et_2O , 1,4-dioxane, CH_3CN and MeOH for both reaction conditions (I and II). The results showed that Et_2O and MeOH are generally the best solvents both in terms of yield and reaction period for conditions I and II, respectively.

To explore the role of phosphorus oxychloride, we performed a set of preliminary experiments on methyl phenyl sulfide as a model substrate using 30% aqueous hydrogen peroxide in the presence of different amounts of phosphorus oxychloride in Et_2O at 0°C . The results are depicted in Table 1. It is found that a 1:1.7:1.7 ratio of sulfide/ $\text{H}_2\text{O}_2/\text{POCl}_3$ is required to achieve a quantitative yield of corresponding sulfoxides.

It is proposed that the treatment of H_2O_2 with POCl_3 produces monoperphosphoric acid (21). We presume that the electrophilicity of monoperphosphoric acid is higher than H_2O_2 which can easily transfer active oxygen to the sulfide (Scheme 2). The by-product of the oxidation reaction of sulfides with this oxidizing system is H_3PO_4 which is separated from the reaction mixture by neutralization with Na_2CO_3 .

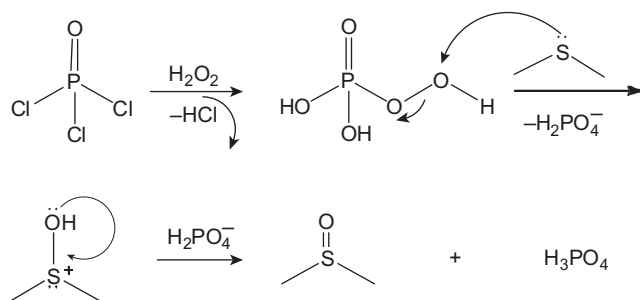
The yield of oxidation reaction was low at higher temperatures due to the thermal decomposition of the *in situ*-generated monoperphosphoric acid. To overcome this drawback, we decided to immobilize the monoperphosphoric acid on alumina. Practically, on treatment of alkali alumina with POCl_3 , a non-hygroscopic free-flowing powder was obtained, which could be easily used even at higher temperatures for the activation of H_2O_2 (Scheme 3). Then, we attempted a set

Table 1. Effect of POCl₃ on the H₂O₂ oxidation of methyl phenyl sulfide.^a

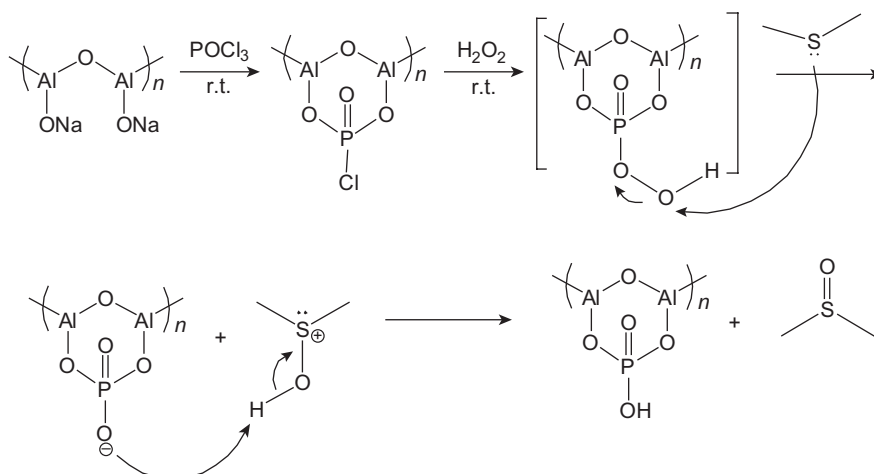
Entry	POCl ₃ (mmol)	H ₂ O ₂ (mmol)	Yield (%) ^b
1	1	0.5	20
2	1	1	68
3	1	2	58
4	1	3	50
5	1.5	1.5	83
6	1.6	1.6	91
7	1.7	1.7	97
8	1.8	1.8	93

Notes: ^aReactions were performed with methyl phenyl sulfide (1 mmol), within 10 min at 0 °C.

^bIsolated yields.

Scheme 2. Mechanistic pathway for the oxidation of sulfide using H₂O₂/POCl₃.

of similar experiments on methyl phenyl sulfide using 30% aqueous hydrogen peroxide in the presence of different amounts of alumina-supported POCl₃ in MeOH at room temperature.

Scheme 3. Proposed mechanism for the oxidation of sulfide using H₂O₂/alumina-POCl₃.

A ratio of 1:1:0.6 g of sulfide/H₂O₂/(alumina-supported POCl₃) was found to be optimum for complete conversion of sulfides to sulfoxides. The results are summarized in Table 2.

Table 2. Effect of alumina- POCl_3 on the H_2O_2 oxidation of methyl phenyl sulfide.^a

Entry	Alumina- POCl_3 (g)	H_2O_2 (mmol)	Yield (%) ^{a,b}
1	0.6	1	99
2	0.6	2	93
3	0.6	3	90
4	0.3	1	65
5	0.4	1	87
6	0.5	1	96

Notes: ^aReactions were performed with methyl phenyl sulfide (1 mmol), at room temperature. ^bIsolated yields.

To extend the scope of the reaction and to generalize the procedure, we investigated the sulfoxidation of a variety of organic sulfide including diallyl, dibenzyl, alkyl benzyl, dialkyl and heterocyclic sulfides under the optimized reaction conditions (Table 3).

To evaluate the effect of alumina supported POCl_3 , we studied the oxidation of methyl phenyl sulfide in the presence of H_2O_2 and alumina alone. The results showed that conversion is restricted to 30–40% over 24 h. We have also studied the effect of H_3PO_4 on the possible activation of H_2O_2 in the oxidation of sulfide and the conversion was less than 5% within 24 h.

All the reactions occurred with complete selectivity for sulfoxide formation, no over-oxidation products such as sulfones were detected in the reaction mixtures. The chemoselectivity of the procedure was noteworthy. Under these conditions, various functional groups including olefin, alcohol, ester, nitrile and aldehyde groups were tolerated (Table 3, entries 5, 6, 9, 10 and 12). These substrates selectively underwent oxidation at the sulfur atom without undergoing further structural changes in their functional groups.

Finally, the results of sulfoxidation were compared with those of previously reported oxidation methods in Table 4.

On comparison of the available reagents for such oxidation, the *in situ*-generated monoperphosphoric acid and the alumina-supported oxidizing agents possess certain features that over-oxidation can be avoided, mild reaction condition are used and the reagents are environmentally safe and easy to handle. The inherent advantages such as cost, smoothness, high yields of pure product and its environmental compatibility justify the use of *in situ*-generated monoperphosphoric acid as an efficient reagent for selective oxygenation of the thioethers.

Table 3. Oxidation of sulfides to sulfoxides with H_2O_2 in the presence of alumina- POCl_3 .^a

Entry	R ¹	R ²	(I), yield (%) ^{b,c}	(II), yield (%) ^b /time (min)
1	Ph	Me	97	99/20
2	Ph	PhCH ₂	98	98/25
3	PhCH ₂	PhCH ₂	89	97/30
4	–CH ₂ CH ₂ CH ₂ CH ₂ –		96	98/15
5	CH ₂ =CHCH ₂	CH ₂ =CHCH ₂	90	95/15
6	Ph	CH ₂ CH ₂ OH	98	98/120
7	4-BrC ₆ H ₄	PhCH ₂	96	96/180
8	<i>n</i> -Bu	<i>n</i> -Bu	91	95/10
9	Ph	CH ₂ COOEt	95	97/300
10	Me	CH ₂ CH ₂ CHO	88	93/18
11	4-BrC ₆ H ₄	4-BrC ₆ H ₄ CH ₂	95	96/240
12	Ph	CH ₂ CN	94	97/320

Notes: ^aThe products were characterized by comparison of their spectroscopic and physical data with those reported in the literature (23). ^bYields refer to pure isolated products. ^cThe reactions were completed within 10 min.

Table 4. Comparison of our reagents with those reported in the literature.

Substrate	Reagent/conditions	Yield (%)	Reference
PhSMe	Ca(OCl) ₂ , wet alumina/CH ₂ Cl ₂ , r.t./40 min	90	(23)
PhSMe	CAN, SiO ₂ hydrated/CH ₂ Cl ₂ /1 h	100	(24)
PhSMe	Fe ₂ O ₃ /O ₂ , RCHO/1 h	81	(25)
PhSMe	H ₂ O ₂ (35%), Mont.K ₁₀ /CH ₃ OH, r.t./2.5 h	97	(19)
PhSMe	H ₂ O ₂ (35%), Amberlyst 15/CH ₃ OH, r.t./3 h	98	(26)
PhSMe	H ₂ O ₂ (35%), Amberlite IR-400/CH ₃ OH, r.t./3 h	98	(26)
PhSMe	H ₂ O ₂ (30%)/POCl ₃ , EtOH, 50 °C/8 min	98	(27)
PhSMe	POCl ₃ /H ₂ O ₂ (30%)/Et ₂ O, 0 °C/10 min	97	–
PhSMe	(POCl ₃ -alumina)/H ₂ O ₂ (30%)/CH ₃ OH, r.t./20 min	99	–
(<i>n</i> -Bu) ₂ S	Ca(OCl) ₂ , wet alumina/CH ₂ Cl ₂ , r.t./40 min	88	(23)
(<i>n</i> -Bu) ₂ S	CAN, SiO ₂ hydrated/CH ₂ Cl ₂ /40 min	90	(24)
(<i>n</i> -Bu) ₂ S	Wet silica gel, MMPP/CH ₂ Cl ₂ /1 h	99	(28)
(<i>n</i> -Bu) ₂ S	UHP/Ti-beta/acetone, 20 °C/2 h	94	(29)
(<i>n</i> -Bu) ₂ S	H ₂ O ₂ (35%), Mont.K ₁₀ /CH ₃ OH, r.t./2 h	98	(19)
(<i>n</i> -Bu) ₂ S	H ₂ O ₂ (35%), Amberlyst 15/CH ₃ OH, r.t./2 h	98	(26)
(<i>n</i> -Bu) ₂ S	H ₂ O ₂ (35%), Amberlite IR-400/CH ₃ OH, r.t./2 h	95	(26)
(<i>n</i> -Bu) ₂ S	H ₂ O ₂ (30%)/POCl ₃ , EtOH, 50 °C/11 min	95	(27)
(<i>n</i> -Bu) ₂ S	POCl ₃ /H ₂ O ₂ (30%)/Et ₂ O, 0 °C/10 min	91	–
(<i>n</i> -Bu) ₂ S	(POCl ₃ -alumina)/H ₂ O ₂ (30%)/CH ₃ OH, r.t./10 min	95	–

3. Conclusions

Summing up, we have found that POCl₃ and alumina-supported phosphorus oxychloride with commercially available 30% aqueous hydrogen peroxide are efficient and convenient oxidizing reagents for the mild and selective oxidation of sulfides to their corresponding sulfoxides.

4. Experimental

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. A number of sulfides were prepared using the standard synthesis method (22). All sulfoxides were separated and purified by chromatographic techniques and also identified by comparison of their mp, IR and NMR with those reported in the literature (23).

4.1. General procedure for the oxidation of sulfide by POCl₃/H₂O₂

The appropriate sulfide (1 mmol), Et₂O (2 ml) and 30% H₂O₂ (0.17 mmol) were mixed in a round-bottomed flask. Then POCl₃ (0.17 mmol) was added dropwise and the mixture stirred electromagnetically at 0 °C. After 10 min, the mixture was quenched by adding 10% aqueous Na₂CO₃. The product was extracted with EtOAc (4×5 ml) and the combined extracts were dried (Na₂SO₄). The filtrates were evaporated and the corresponding crude sulfoxides were purified by chromatography on silica gel plate to afford the corresponding pure sulfoxides in 88–98% yield.

4.2. Preparation of alumina-supported POCl₃

A 50 ml suction flask was equipped with a constant-pressure dropping funnels containing phosphorus oxychloride (5.13 g, 0.034 mol) and gas inlet tube for conducting HCl gas over an adsorbing solution, *i.e.* water. Basic alumina (10 g) was charged into the flask. Phosphorus oxychloride was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately which removed through suction. Then the mixture was shaken for 30 min.

The white solid was washed with dry dichloromethane (DCM) and dried *in vacuo* for 4 h. Finally, alumina-supported POCl₃ was obtained in 89% yield (13.61 g) as free-flowing powder. Selected spectroscopic data: IR (KBr cm⁻¹): 1143 (P–O) st, 1259 (P=O) st, 650 (P–Cl) st.

4.3. General procedure for the oxidation of sulfides by (alumina-supported POCl₃)/H₂O₂

In a round-bottomed flask equipped with a magnetic stirrer, a mixture of sulfides (1 mmol) and 30% H₂O₂ (1 mmol) in MeOH (2 ml) was prepared. Then alumina-POCl₃ (0.6 g) was added and stirred at room temperature for the appropriate reaction times (Table 3). On completion of the reaction (monitored by TLC), the mixture was diluted with EtOAc and filtered. The organic layer was washed with (5%) Na₂CO₃ solution and then was dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure to give the corresponding sulfoxides in pure form.

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