Molybdatophosphoric acid as an efficient catalyst for the catalytic and chemoselective oxidation of sulfides to sulfoxides using urea hydrogen peroxide as a commercially available oxidant

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Abstract: An efficient procedure for the chemoselective oxidation of alkyl (aryl) sulfides to the corresponding sulfoxides using urea hydrogen peroxide (UHP) in the presence of a catalytic amount of molybdatophosphoric acid at room temperature is described. The advantages of described method are: generality, high yield and chemoselectivity, short reaction time, low cost and compliment with green chemistry protocols.

Keywords: molybdatophosphoric acid; urea hydrogen peroxide (UHP); chemoselective; oxidation; sulfides; sulfoxides.

INTRODUCTION

The development of efficient catalytic systems for selective organic transformations is currently one of the challenging tasks in synthetic organic chemistry.[1] In recent years, the search for environmentally benign chemical processes or methodologies has received much attention from chemists, because they are essential for the conservation of the global ecosystem. From this viewpoint, catalytic oxidation is a valuable process because the use of stoichiometric reagents, which are often toxic, poses inherent limitations from both economical and environmental viewpoints regarding product purification and waste management.[2]

Heteropolyacids (HPAs) are more active catalysts than conventional inorganic and organic acids for a variety of organic reactions.[3] They have been used as the catalyst for several types of reactions such as Freidel–Crafts acylation,[4] hetero-Michael addition reaction[5] and the oxidation of anilines to their nitro com-

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pounds.[6] Among heteropolyacids, molybdatophosphoric acid is a good promoter due to its high acid strength, thermal stability, low reducibility and atom economy.[7]

Concentrated H_2O_2 is very dangerous to handle and not readily available. Hence this reagent has been replaced by its more stable and safe complexes. The strongly H-bonded urea hydrogen peroxide (UHP, $H_2NCONH_2 \cdots H_2O_2$),[8] is nowadays commercially available,[9] and its applications in organic and analytical chemistry, as well as in industry, are quickly widening. Its stability at room temperature, high hydrogen peroxide content (36.2 %) and the potential for releasing it in a controlled manner, as well as its solubility in organic solvents, make it a good and safe substitute as a "dry carrier" of the hazardous and unstable hydrogen peroxide in most oxidation reactions. Moreover, selectivity can be achieved by replacing the potentially explosive hydrogen peroxide with the safer crystalline UHP for the controlled release of the oxidant and it is a well-recognized source of oxygen.[10]

The selective oxidation of organic sulfides to sulfoxides without any over-oxidation to sulfones is a challenging research topic in synthetic organic chemistry, partly because of the importance of sulfoxides as intermediates in a range of biologically active molecules, including therapeutic agents such as anti-ulcer, antibacterial, antifungal, anti-atherosclerotic, antihypertensive and cardiotonic agents as well as psychotropic and vasodilators.[11] There are many reagents available for the oxidation of sulfides to sulfoxides.[12–23] However, most of the existing methods use sophisticated reagents, complex catalysts, toxic metallic compounds, or rare oxidizing agents that are difficult to prepare. Many of these procedures also suffer from poor selectivity or undesirable products, such as aromatic halogennation, C–S bond cleavage and over-oxidation to sulfone. Hence, for the facile conversion of sulfides to sulfoxides, careful selection of the oxidizing agent and the reaction conditions are prerequisites.

Before commencing the results and discussion section, a list of the employed abbreviations is given in Table I.

TABLE I. List of abbreviations

Abbreviation	Name
UHP	Urea hydrogen peroxide
MPA	Molybdatophosphoric acid
TPA	Tungstophosphoric acid
BTPPDC	*n*-Butyltriphenylphosphonium dichromate
CAN	Ceric ammonium nitrate
CPCC	3-Carboxypyridinium chlorochromate
NBS	*N*-Bromosuccinimide
THF	Tetrahydrofuran
DMF	Dimethylformamide

RESULTS AND DISCUSSION

In continuation of our interest in the development of synthetic methods for the transformation of organic functional groups, in particularly the application of heteropolyacids, H_2O_2 adducts and catalytic oxidation reactions,[24] urea hydrogen peroxide is introduced in this report as a safe and eco-friendly oxidant for the selective conversion of sulfides to sulfoxides in the presence of a catalytic amount of molybdatophosphoric acid (Scheme 1).

$$R-S-R' \xrightarrow[\text{Cat., Solvent, r.t.}]{\text{UHP}} R-\overset{O}{\underset{||}{S}}-R'$$

Cat.: Molybdatophosphoric acid   Scheme 1.
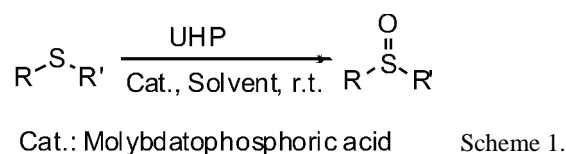
In order to optimize the reaction conditions, the oxidation of benzyl phenyl sulfide using urea hydrogen peroxide (UHP) in methanol was chosen as a model reaction to provide the corresponding sulfoxide (Scheme 2).

$$\text{PhCH}_2\text{-S-Ph} \xrightarrow[\text{Cat. CH}_3\text{OH, r.t.}]{\text{UHP}} \text{PhCH}_2\text{-S(=O)-Ph}$$

Scheme 2.
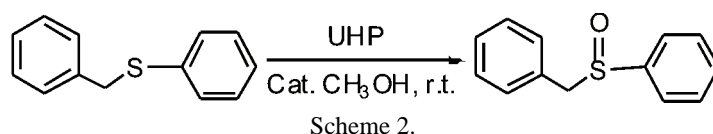
The obtained results are summarized in Table II. First, a model run was performed with benzyl phenyl sulfide and UHP in the absence of catalyst in methanol at room temperature (Table II, Entries 1 and 2). It was found that the reaction did not go to completion even using a ten-fold excess of UHP and a long reaction time (4 h). Thus, the effect of various activators as promoter or catalyst on the reactivity of UHP for the oxidation of model compound was studied, Scheme 2. The results are summarized in Table II, from which it can be seen that although tungstophosphoric acid gave a good yield of benzyl phenyl sulfoxide (Table II, entry 8), an excellent yield of the product was obtained in the presence of molybdatophosphoric acid in a shorter reaction time (Table II, entry 3). The other tested catalysts or activators had one or more of the following disadvantages: long reaction time, low yield and selectivity and the use of large amount of activator. Therefore, molybdatophosphoric acid (MPA) is an effective catalyst for the oxidation of sulfide to sulfoxide and it was used as catalyst for all subsequent reactions. In this study, the effects of various amounts of molybdatophosphoric acid and various amounts of UHP were investigated (see, Table II, entries 3–7). The highest yield in an appropriate reaction time for the sulfoxidation reaction was obtained when 0.1 mmol MPA was used for the reaction of 1 mmol benzyl phenyl sulfide with 2 mmol UHP in 5 mL CH_3OH at room temperature (Table II, entry 3).

TABLE II. Oxidation of benzyl phenyl sulfide (1 mmol) to the corresponding sulfoxide using UHP in the presence of various catalysts/activators in CH_3OH (5 mL) at room temperature

Entry	Catalyst (amount)	UHP, mmol	Time	Yield of sulfoxide, %[a]
1	Abs[b]	2	4 h	trace
2	Abs	10	4 h	30
3	MPA (0.1 mmol)	2	17 min	100
4	MPA (0.2 mmol)	2	10 min	100
5	MPA (0.05 mmol)	2	2 h	97
6	MPA (0.1 mmol)	1	3 h	80
7	MPA (0.1 mmol)	1.5	2 h	86
8	TPA[c] (0.1 mmol)	2	3 h	80
9	TPA (0.3 mmol)	2	2 h	90
10	$AlCl_3$ (0.5 mmol)	2	3 h	nc[d]
11	$Al(HSO_4)_3$ (0.5 mmol)	2	3 h	nc
12	Na_2HPO_4 (0.5 mmol)	2	3 h	trace
13	$ZnCl_2$ (0.3 mmol)	2	3 h	30
14	$CaCl_2.2H_2O$ (0.5 mmol)	2	3 h	20
15	Al_2O_3 (0.5 g)	2	3 h	trace
16	SiO_2 (0.5 g)	2	3 h	20
17	$ZrCl_4$ (0.2 mmol)	2	3 h	trace
18	$NaHSO_4$	2	3 h	trace
19	ZnO (0.5 mmol)	2	3 h	trace
20	MgO (0.5 mmol)	2	3 h	trace
21	NH_2SO_3H	2	3 h	nc

[a]Isolated yield; [b]in the absence of catalyst; [c]tungstophosphoric acid; [d]reaction did not go to completion
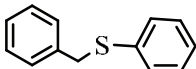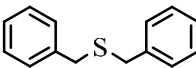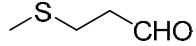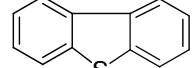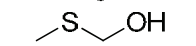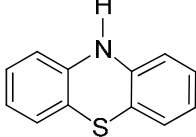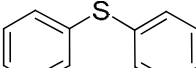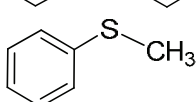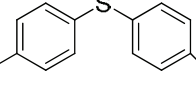
In the next step, the effect of various solvents on the progress of the reactions was investigated. As illustrated in Table III, methanol was the solvent of choice for the above-mentioned reaction.
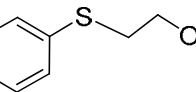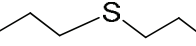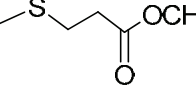
TABLE III. Solvent effect on the oxidation of benzyl phenyl sulfide using UHP in the presence of MPA as catalyst

Entry	Solvent	Time	Conversion, %
1	CH_2Cl_2	6 h	0
2	$CHCl_3$	5 h	0
3	EtOAc	3 h	70
4	Acetone	6 h	50
5	*n*-Hexane	5 h	0
6	THF	5 h	45
7	CH_3CN	3 h	60
8	DMF	3 h	45
9	CH_3OH	17 min	100
10	C_2H_5OH	2 h	65
11	H_2O	2 h	0

To determine the scope of this procedure, the oxidation of other sulfides to sulfoxides was studied. A wide range of substrates, *i.e*., aryl alkyl, diaryl and di-alkyl sulfides were selectively oxidized to their corresponding sulfoxides (Table IV).

TABLE IV. Chemoselective oxidation of sulfide (1.0 mmol) to the corresponding sulfoxide using UHP (2.0 mmol) in the presence of MPA (0.10 mmol) as catalyst in CH_3OH at room temperature

Entry	Substrate	Time	Yield, %[a]
1		17 min	100
2		10 min	90
3		18 min	91
4		6.5 h	95[c]
5		15 min	90
6		10 min	udp[b]
7		3 h	100
8		13 min	100
9		17 min	92
10		40 min	80
11		90 min	91
12		20 min	87

[a]Isolated yields, UHP (1 mmol), MPA (0.2 mmol), 50 °C; [b]undesired products

It is noteworthy that sulfides containing functional groups, such as alcohol, aldehyde and ester, were selectively oxidized without any interference from these

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groups (Table IV, entries 5, 9 and 11). To further determine the chemoselectivity of the described system, some competitive reactions were designed. Thus, the competitive oxidation of sulfides in the presence of sulfoxide, aldehyde, oxime, nitrile, benzylic alcohol and alkene was monitored. These observations clearly show that the method is applicable for the chemoselective oxidation of sulfides to sulfoxides in the presence of the previously mentioned functional groups and can be considered as a useful practical method for the oxidation of sulfides to sulfoxides without general oxidation (Scheme 3).
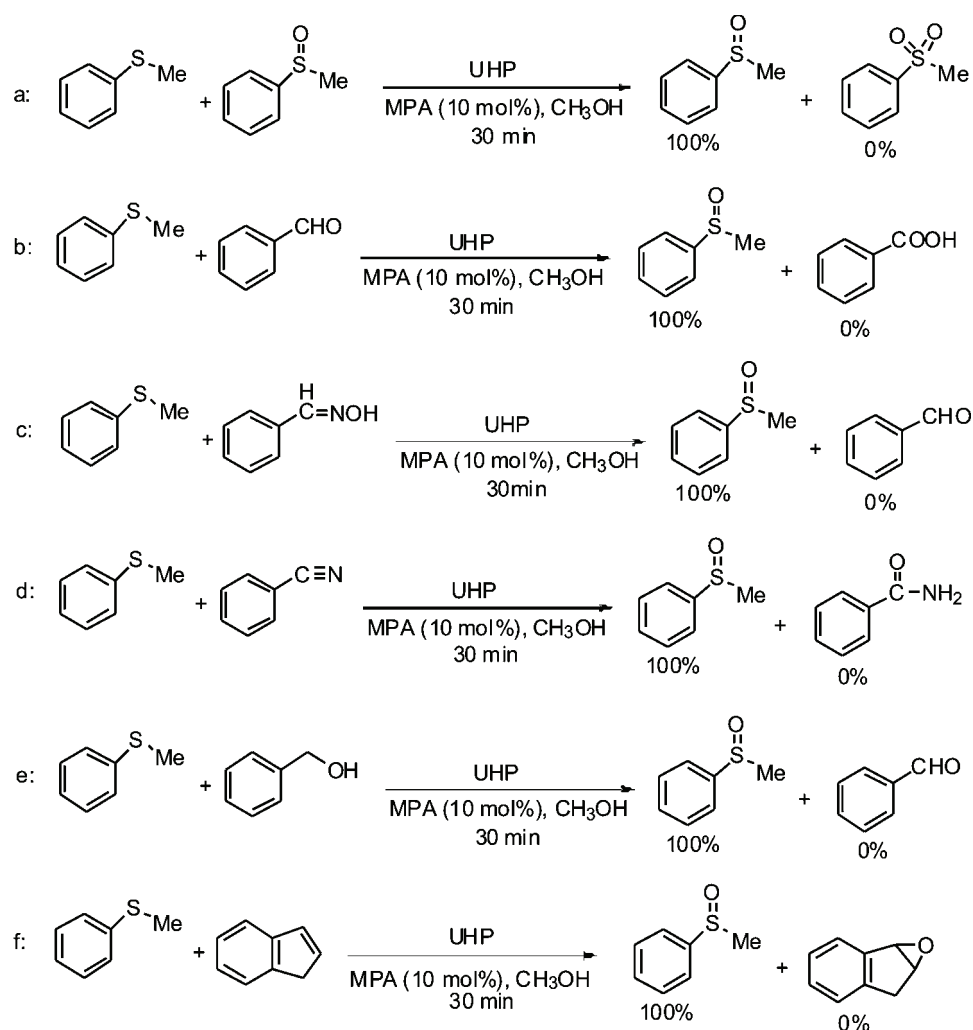
Scheme 3.

In order to assess the capability of the present method with respect to the reported methods for the oxidation of sulfide to sulfoxide, the oxidation of benzyl phenyl sulfide by the present method was compared with oxidation by the reported methods (Table V). It is clear from Table V that the present method is superior to some previously reported methods in terms of chemoselectivity, yield, reaction time and amount of the catalyst and reagent required for successful oxidation without having to resort to complex catalysts, a hazardous and unstable oxidant, microwave heating or toxic metallic compounds.

TABLE V. Comparison of the oxidation of benzyl phenyl sulfide (1.0 mmol) by UHP/MPA with some reagents reported in the literature

Entry	Reagent (oxidant/substrate)	Time	Yield, %		Ref.
			Sulfoxide	Sulfone	
1	UHP/MPA/CH$_3$OH/rt (2:0.1)	17 min	100	0	–
2	BTPPDC/AlCl$_3$/CH$_3$CN/reflux (1.5:1)	90 min	93	nr[a]	14
3	BTPPDC/AlCl$_3$/MW (1.2:1)	2 min	94	nr	14
4	NaIO$_4$/wet SiO$_2$/MW (1.7:1)	2.5 min	83	nr	15
5	PhCH$_2$PPh$_3$HSO$_5$/CH$_3$CN/reflux (1.5:1)	12 h	88	nr	16
6	Ba(MnO$_4$)$_2$/CH$_3$CN/reflux (6:1)	4 h	88	nr	13
7	CAN/wet SiO$_2$/CH$_2$Cl$_2$/rt (2:1)	45 min	96	nr	17
8	BTPPDC/AlCl$_3$/MW (2.5:1)	2.5 min	nr	97	14
9	CPCC/AlCl$_3$/CH$_3$CN/reflux (1:1)	75 min	93	nr	18
10	CPCC/AlCl$_3$/MW (0.8:1)	1.5 min	92	nr	18
11	H$_2$O$_2$/Silica sulfuric acid/CH$_3$CN/rt (1:0.1 g)	40 min	96	nr	19
12	H$_2$O$_2$/Amberlyst 15/CH$_3$OH/rt (2:0.5)	6.5 h	95	nr	20
13	H$_2$O$_2$/Amberlyst IR-400/CH$_3$OH/rt (3:0.5)	7.5 h	92	nr	20
14	HIO$_3$/wet SiO$_2$/ solvent-free 50 °C (1:3)	170 min	93	nr	21
15	H$_2$O$_2$/Silica-based tungstate/CH$_2$Cl$_2$:CH$_3$OH (4:0.1)	3 h	85	nr	22
16	H$_2$O$_2$/NBS/CH$_3$CN (3:0.1)	15 h	90	nr	22[b]
17	H$_2$O$_2$/ZrCl$_4$/CH$_3$OH (7:2)	2 min	96	nr	23

[a]Not reported

The observation that the oxidation of benzyl phenyl sulfide and dibenzyl sulfide yields the corresponding sulfoxide (Table IV, entries 1 and 2) indicates that the reaction proceeds *via* an oxygen transfer mechanism. If the reaction involved electron transfer instead of oxygen transfer, substantial amounts of benzaldehyde would have been formed.[25] According to a literature survey,[26–33] a reasonable mechanism for the oxidation of sulfide to the corresponding sulfoxide using UHP in the presence of MPA is outlined in Scheme 4. This observation

probably indicates that molybdenum ions generate Mo^{5+}-peroxo species on interaction with UHP, which is possibly the active intermediate species.[26] Then the reaction can proceed *via* the 1,3-dipolar mechanism.
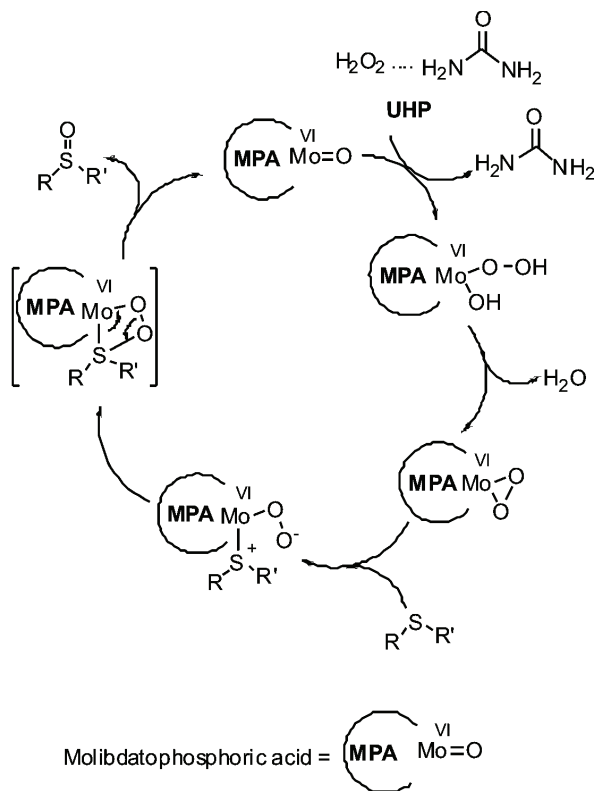
Scheme 4.

EXPERIMENTAL

General

The employed chemicals were purchased from Fluka, Merck or Aldrich. The quoted yields refer to isolated pure products. The oxidation products were characterized by comparison of their spectral (IR and ^{1}H-NMR) and physical data with those of authentic samples, which were synthesized by other reported procedures.[12-23]

General procedure for the oxidation of sulfides

A mixture of sulfide (1.0 mmol), UHP (2.0 mmol) and molybdatophosphoric acid (0.10 mmol) in methanol (5.0 mL) was vigorously stirred for the required time (see Table III). The progress of the reaction was monitored by TLC. After completion of the reaction, the CH_3OH was evaporated and the crude product was purified by short column chromatography on silica gel with EtOAc/*n*-hexane (1:5 to 1:2) as the eluent.

CONCLUSIONS

In summary, it was found that molybdatophosphoric acid efficiently catalyzed the selective oxidation of sulfides to sulfoxides by the urea hydrogen peroxide adduct (UHP) at room temperature. This method offers the following advantages: a) the procedure is highly efficient, b) the yield of sulfoxide is high, c) the reagent is cheap, safe, and available and d) the selectivity of the method is remarkable with regards to sulfides. Also, its compatibility with sensitive functionalities, such as ester, aldehyde, oxime, nitrile and double bonds, with regards to economic and ecological considerations allows the belief that this method represents a valuable alternative to the existing reagents reported in the literature for the oxidation of sulfides to sulfoxides.

ИЗВОД

МОЛИБДАТОФОСФОРНА КИСЕЛИНА КАО ЕФИКАСАН КАТАЛИЗАТОР ЗА КАТАЛИТИЧКУ И ХЕМОСЕЛЕКТИВНУ ОКСИДАЦИЈУ СУЛФИДА У СУЛФОКСИДЕ КОРИШЋЕЊЕМ АДУКТА УРЕЕ И ВОДОНИК-ПЕРОКСИДА КАО КОМЕРЦИЈАЛНО ДОСТУПНОГ ОКСИДАНТА

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