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Highly Efficient Selective Oxygenation of Sulfides to Sulfoxides by Oxalic Acid Dihydrate in the Presence of H_2O_2

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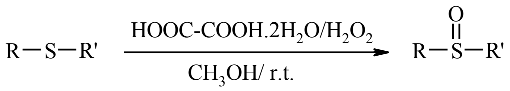
Abstract: A highly efficient method for the oxidation of sulfides to sulfoxides using oxalic acid dihydrate in the presence of hydrogen peroxide has been developed. A versatile procedure for the oxidation of sulfides to sulfoxides without any over-oxidation to sulfones has been reported. This procedure cleanly oxidizes sulfides to the corresponding sulfoxides in excellent yields at ambient temperature.

Keywords: Oxidation, Oxalic acid dehydrate, Sulfides, Sulfoxides, Hydrogen peroxide.

Introduction

The ready oxidation of sulfur compounds by appropriate reagents is a key feature of organosulfur chemistry. Especially, sulfoxides deserved much attention as important chiral auxiliary in asymmetric synthesis[1]. However, this transformation is conventionally achieved using both organic and inorganic reagents[2-24], but most of are not suitable for medium to large scale operations and which also lead to large a volume of toxic wastes. Therefore, development of green, environmentally acceptable oxidative methodologies has emerged as an urgent task in this field. Furthermore, over oxidation of the sulfoxides to their sulfones is a common problem during the oxidation of sulfides. Also, the use of H_2O_2 as a final oxidant offers the advantages that it is a cheap and is a readily available reagent and produces water as the only by product[25]. Organocatalysis[26,27], has gained widespread attention as a result of the efficiency and selectivity of many organocatalytic reactions. Novel methods employing organic molecules are advantageous from both a practical and an environmental standpoint due to their ability to perform in wet solvents under an aerobic atmosphere and to avoid the possibility of metal contamination that may occur with traditional metal catalyst systems. Recently, oxalic acid was efficiently used as catalyst in variety of chemical reactions like, imino Diels-Alder reaction[28], Beckmann rearrangement[29], synthesis of coumarins[30], protection of carbonyl to thioacetal and deprotection of thioacetal to carbonyl as well[31].

In this research we introduce the use of oxalic acid dihydrate as an eco-friendly promoter for oxidation of sulfides to sulfoxides by hydrogen peroxide at room temperature (Scheme 1). The use of oxalic acid dihydrate/H_2O_2 system offers the advantages that it is an inexpensive, environmentally benign and easy available reagent.



$$R{-}S{-}R' \xrightarrow[CH_3OH/\ r.t.]{HOOC\text{-}COOH.2H_2O/H_2O_2} R{-}\overset{\overset{O}{\|}}{S}{-}R'$$

Scheme 1

Experimental

All chemicals were purchased from Merck chemical company. A number of sulfides were prepared using the standard synthetic method.[32] Melting points were recorded on an electro thermal melting point apparatus. The NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker advance DRX 400 MHz spectrometer. IR spectra were determined on a SP-1100, P-UV-Com instrument. Purity determination of the products was accomplished by TLC on silica gel poly gram SIL G/UV 254 plates. Products were separated and identified by comparison IR and ^1H NMR spectra, with those reported for authentic samples.

Typical Procedure for Oxidation of Sulfides

A solution of sulfide (1 mmol) and 35% hydrogen peroxide (3 mmol) in 5 mL mehtanol was prepared. Oxalic acid dihydrate (0.5 mmol) was added to the solution and the reaction mixture was stirred for 2-3 h at room temperature until TLC analysis showed that no sulfide remained. Then, the mixture of reactions was extracted with dichloromethane (20 mL) and the combined organic fraction was washed with 3% $NaHSO_3$ and dried over Na_2SO_4. Evaporation of the solvent gave the corresponding sulfoxide in 88-98% yields.

Results and Discussion

To select the best solvent, the oxidation of methylphenyl sulfide was studied in a variety of organic solvents such as methanol, acetonitrile, n-hexane and dichloromethane. Among them, methanol was found to be the best solvents for oxidation of sulfides to sulfoxides (Table 1). So, a protic solvent such as methanol is required to facilitate the oxygenation of sulfide to give the corresponding sulfoxide in excellent yield. To show the role of the oxalic acid dihydrate in this oxidation reaction, the oxidation of methylphenyl sulfide was carried out in the absence of the catalyst. The oxidation was very slow and a low yield of corresponding sulfoxide was formed. As seen in Table 2, the optimized stoichiometric ratio of RSR′:H2O2 for the conversion of sulfides to sulfoxides was found to be 1:3 using 0.5 mmol of the oxalic acid in methanol at room temperature. We examined the oxidation reaction of structurally different sulfides with an oxalic acid/H2O2 system in methanol at room temperature. All reactions were carried out under the optimized conditions and the results are summarized in Table 3.

Table 1. Oxidation of methylphenyl sulfide to corresponding sulfoxide in different solvents[a].

Entry	Sulfide, 1 mmol	Solvent	Time, h	Yield, %[b]
1	PhSMe	CH_2Cl_2	4	38
2	PhSMe	CH_3OH	1.5	96
3	PhSMe	CH_3CN	3	78
4	PhSMe	*n*-hexane	3.5	56

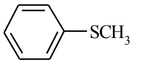
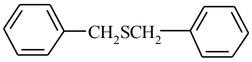
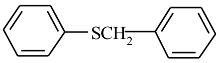
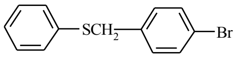
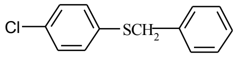
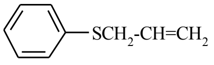
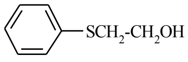
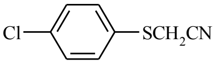
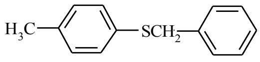
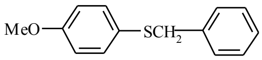
[a] *All reactions were carried out using 0.5 mmol oxalic acid and 3 mmol of* H_2O_2. [b] *The yield was determined by GC analysis of the crude product.*

Table 2. Effect of oxalic acid on oxidation of methylphenyl sulfide[a].

Entry	Sulfide	H_2O_2, mmol	Oxalic acid, mmol	Yield, %[b]
1	PhSMe	1	0. 25	42
2	PhSMe	2	0. 25	58
3	PhSMe	3	0. 25	78
4	PhSMe	1	0.5	56
5	PhSMe	2	0.5	84
6	PhSMe	3	0.5	96

[a] *Reactions were carried out in methanol at room temperature in 1.5 h.* [b] *The yield was determined by GC analysis of the crude product.*

Table 3. Oxidation of sulfides to sulfoxides using oxalic acid dihydrate/H_2O_2[a,b].

Entry	Sulfides	Time/h	Yield, %[c]	M.P.°C (Lit.)[11,14]
1		1.5	96	33-34 (31-33)
2		2	98	130-132 (131-133)
3		1.5	96	121-123 (122-123)
4		2.5	96	178-180 (178-179)
5		2	97	129-131 (128-130)
6		2	90	oil
7		2	96	150-152 (151-152)
8		2	93	69-71 (70-71)
8		1.5	94	137-139 (136-137)
9		2	97	104-106 (105-107)
10	$(CH_2{=}CH\text{-}CH_2)_2S$	2	88	39-41 (40-41)
11	$(CH_3CH_2CH_2)_2S$	2	94	oil
12	$(CH_3CH_2CH_2CH_2)_2S$	2	94	oil

[a] *All the products were characterized by IR,* ^{1}*H-NMR spectra and comparison with authentic samples.* [b] *Reaction conditions: sulfide (1 mmol), oxalic acid dihydrate (0.5 mmol),* H_2O_2 *(3 mmol),* CH_3OH*, r.t.* [c] *All yields refer to isolated products.*

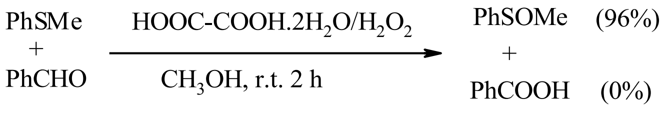
It is clear that sulfide bearing sensitive to oxidation such as hydroxy and carbon–carbon double bonds are completely unaffected under the reaction conditions (Table 3, entry 6, 7, 10). In order to show the advantages and disadvantages of our method, some of our results in oxidation of sulfides were compared with some of those reported in literature (Table 4).

Table 4. Comparison of HOOC-COOH.2H_2O/H_2O_2 with some other catalyst for oxidation of PhSMe.

Entry	Reagent	Conditions	Time	Yield (%)[a]	Ref.
1	Silica-Based Ammonium Tungstate /H_2O_2 (30%)	CH_2Cl_2/MeOH, r.t.	1.5 h	82	6
3	Mont. K10/H_2O_2 (35%)	MeOH, r.t	2.5 h	95	11
4	$Ce(OTf)_4 \cdot xH_2O/H_2O_2$ (50%)	THF, r.t	42 min	93	12
5	$CuBr_2$/*t*-BuOOH	MeCN/reflux	45 min	94	13
6	DBUH-Br_3/H_2O_2 (30%)	MeCN, r.t.	1 h	95	15
7	$Ca(OCl)_2$/moist Alomina	CH_2Cl_2, r.t.	40 min	90	16
8	N_2O_4/Charcoal	CH_2Cl_2, r.t.	3 h	93	17
9	$PhCH_2Ph_3PHSO_5$	MeCN/ reflux	2 h	91	18
10	$(Bu_4N)[PMo_{12}O_{40}]$/ UHP	4 °C	72 h	85	19
11	2-PSBA or 2-IBA/ H_2O_2	MeOH, r. t	5 h	87	20
12	$HAuCl_4.4H_2O$	r.t.	1 h	92	21
12	Cyclohexylidenebishydroperoxide	CH_2Cl_2, r.t.	0.5 h	89	22
13	Thiourea dioxide/ *t*-BuOOH	CH_2Cl_2, r.t.	3.5 h	95	23
14	fluorous thiourea/H_2O_2 (30%)	CH_2Cl_2, r.t.	12 h	95	24
15	HOOC-COOH.2H_2O/H_2O_2 (35%)	MeOH, r.t	1.5 h	96	-

[a] *Yield refers to the corresponding sulfoxide.*

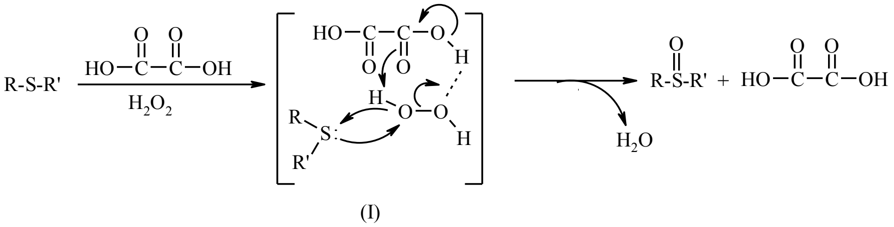
It is evident that the oxalic acid dihydrate/H2O2 system allows these transformations to proceed with excellent selectivity, good yield and milder conditions. Furthermore, the use of oxalic acid dihydrate makes this method simple, inexpensive, more convenient and practical. Additionally, competitive oxalic acid dihydrate catalyzed oxidation reaction of equimolar amounts of methylphenyl sulfide and benzaldehyde at room temperature lead to the selective formation methylphenyl sulfoxide in good yield, whereas benzaldehyde remaind unchanged (Scheme 2).



$$\begin{array}{c} \text{PhSMe} \\ + \\ \text{PhCHO} \end{array} \xrightarrow[\text{CH}_3\text{OH, r.t. 2 h}]{\text{HOOC-COOH.2H}_2\text{O/H}_2\text{O}_2} \begin{array}{c} \text{PhSOMe (96\%)} \\ + \\ \text{PhCOOH (0\%)} \end{array}$$

Scheme 2

It is suggested that the acid interaction or hydrogen bonding of oxalic acid with hydrogen peroxide would enhance the electrophilicity and reactivity of hydroperoxy intermediate (I) much higher than inactivated hydrogen peroxide. At the same time, the deporting of water as a leaving group would be assisted by nucleophilic attack of sulfide (Scheme 3).



Scheme 3

Conclusion

In summary, we demonstrated oxalic acid dihydrate as a readily available, cheap and eco-friendly reagent that exhibits excellent selectivity toward oxygenation of sulfides to sulfoxides, in the presence of hydrogen peroxide under mild reaction conditions.

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