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A Mild, Efficient and Highly Selective Oxidation of Sulfides to Sulfoxides Catalyzed by Lewis Acid–Urea–Hydrogen Peroxide Complex at Room Temperature

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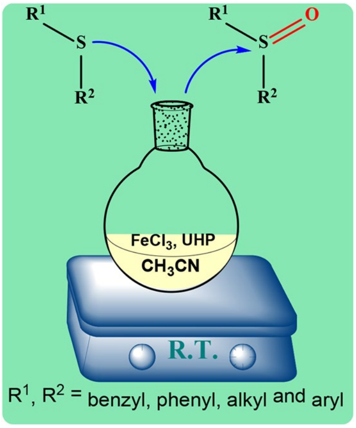
Abstract Alkyl and aryl sulfides were oxidized to the corresponding sulfoxides with urea–hydrogen peroxide (UHP) in the presence of $FeCl_3$ as a Lewis acid catalyst under simple and mild reaction conditions. The protocol is efficient and highly selective and sulfoxides were obtained as the sole oxidation products in high yields at room temperature.

Graphical Abstract



Keywords UHP · Oxidation · Sulfides · Sulfoxides · $FeCl_3$

1 Introduction

Organosulfur compounds, particular sulfoxides, are useful synthetic reagents in organic chemistry. The selective oxidation of sulfides to sulfoxides is a fundamental and important functional group transformation. The chemistry of sulfoxides has been attractive to organic chemists; because, they are valuable synthetic intermediates for the construction of chemically and biologically important significant molecules [1–5]. In addition, some of biologically active sulfoxides play an important role as therapeutic agents such as anti-ulcer [6–8], antibacterial [9] and anti-atherosclerotic [10, 11]. The increasing interest in and applications of sulfoxides have prompted investigations on novel methodologies for the preparation of these compounds. Even though, various approaches have been reported for the oxidation of sulfides to sulfoxides, such as H_2O_2/iron(III)–salen [12], *tert*-butyl hydroperoxide/Ti(*i*PrO)$_4$/1,2-diphenylethane-1,2-diol [13], $TaCl_5/H_2O_2$ [14], sodium perborate or 2,2,2-trifluoroacetophenone/H_2O_2 [15], 3-carboxypyridinium chlorochromate/$AlCl_3$ [16], ceric ammonium nitrate (CAN) supported on silica/$NaBrO_3$ [17], H_2O_2/*N*-hydroxysuccinimide [18], Some of these methods suffer from some disadvantages like long reaction time, expensive reagents and catalysts, difficulties in products isolation and formation of over-oxidation products.

The use of H_2O_2 as an oxidant has been studied extensively. Compared to catalytic methods that require other oxidants such as NaOCl, the use of aqueous H_2O_2 offers the advantage that it is a cheap, environmentally benign,

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readily available reagent and water is the only expected by-product [19–21]. In order to improve above-mentioned drawbacks and during the course of our studies on the development and introduce new routes and reagents for the oxidation reactions [22–24], we became interested to apply a new catalytic method for the conversion of sulfides to sulfoxides using urea–hydrogen peroxide (UHP)/$FeCl_3$ system in acetonitrile at room temperature.

2 Experimental

2.1 Materials and Methods

All chemicals were purchased from Merck and Aldrich chemical companies. Infrared spectra were recorded on ABB FTLA 2000 Bruker FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AQS 300 Avance spectrophotometer in $CDCl_3$ as the solvent and TMS as the internal standard. Preparative TLC was performed using silica gel Kieselgel 60 $PF_{254+366}$. All yields refer to isolated products.

2.2 General Procedure: Oxidation Reactions Catalyzed by UHP/$FeCl_3$ System in CH_3CN as Solvent

In a 25 round-bottomed flask, to a solution a sulfide (1 mmol) in CH_3CN (10 mL), UHP (1.5 mmol) and $FeCl_3$ (1 mmol) were added successively and the mixture was stirred magnetically at room temperature. The reaction progress was followed by TLC (eluent: *n*-hexane/ethyl acetate: 2:1). After completion of the reaction, the solvent was removed under vacuum and the residue was quenched by adding water (15 mL), extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and the solvent was removed in vacuum. The residue was purified by chromatography on silica gel (25–30 mesh), eluting with ethyl acetate/*n*-hexane to give pure sulfoxides.

All the products were known compounds and were identified by comparison of their melting points with those authentic literature samples, and also characterized by FT-IR, ^1H NMR and ^{13}C NMR spectral data analyses. Spectral data and physical properties of benzyl phenyl sulfoxide as a model reaction are as below:

2.2.1 *Spectral Data of a Selected Product*

2.2.1.1 Benzyl Phenyl Sulfoxide White crystalline solid, M.p.: 122 °C. IR (KBr): 3065, 2952, 1447, 1041, 744, 697 $cm^{-1.}$ ^1H NMR (300 MHz, $CDCl_3$) δ: 4.05 (d, 1H, J = 12.6 Hz), 4.24 (d, 1H, J = 12.6 Hz), 7.048–7.079 (m, 2H), 7.23–7.26 (m, 2H), 7.50 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.44, 125.62, 126.03, 128.43, 128.55, 128.63, 130.36, 132.02, 141.89.

3 Results and Discussion

The use of Lewis-acid catalyst in modern organic synthesis has been studied extensively during the last decade. The research is focused on the more versatile, more selective and more reactive catalyst [25, 26]. A large number of such oxidation reactions often require the use of metal reagents or catalysts. Recently transition metals extensively have been used as catalyst for beside H_2O_2 as oxidant. However, one of the problems frequently encountered in metal-catalyzed oxidation with peroxide is the concomitant decomposition of it, which makes the use of an excess amount of H_2O_2 necessary to reach full conversion [27, 28].

Because of the safety problems associated with the use of concentrated solution of H_2O_2 and overcoming above mentioned deficiency, it has been adducted with some carrier. Among these adducts, UHP is an inexpensive, stable, mild and easy to handle source of pure H_2O_2. In continuation of our studies on introducing of UHP as an ideal green reagent in organic synthesis, it was successfully utilized as a green oxidant due to its strength and lack of toxicity of by-products, mild oxidant due to the effective oxygen content, safety in storage and operation and environmentally-friendly character, for promotion of oxidation of sulfides to sulfoxides via this transformation [29, 30].

In this work, the applicability of the UHP/$FeCl_3$ system was examined for the oxidation of diaryl, dibenzyl, aryl benzyl, alkyl benzyl and dialkyl sulfides at room temperature. For further studies, benzylphenyl sulfide was selected as a model substrate and a variety of reaction conditions were performed to optimize the reaction conditions. For this reason different solvents, Lewis acid catalysts and relative amount of reagents were studied. Results are described below.

In general, hydrogen peroxide adducts are not able to oxidize organic compounds by themselves, therefore introduction of an inorganic catalyst or organic mediator for active oxygen transfer of these adducts is a necessity in oxidation systems where they are used. To illustrate the need of catalyst, an experiment was conducted in which the reaction of benzyl phenyl sulfide as model substrate was studied in the absence of Lewis-acid catalyst. As expected the reaction did not occur even after 14 h. Therefore, $FeCl_3$ is an essential component of the reaction. In order to investigate the reaction media, different solvents were examined in the model reaction. It was found that the reaction time in acetonitrile was very faster than other solvents (Table 1). Therefore, it was selected as the best solvent for further studies.

Table 1 Solvent optimization for the oxidation of benzyl phenyl sulfoxide (1 mmol)

Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_3CN	18	43
2	CH_2Cl_2	8	Trace
3	$CHCl_3$	10	13
4	CH_3OH	16	28
5	CH_3COCH_3	8	Trace
6	H_2O	8	Trace
7	C_2H_5OH	12	14

Reaction conditions: UHP (0.5 mmol), $FeCl_3$ (0.5 mmol), acetonitrile (10 mL), r.t.

[a] Isolated yields

After examination of different Lewis-acids, we also have observed that $FeCl_3$ was the best among others such as $AlCl_3$, $ZrCl_4$, $ZnCl_2$, $FeCl_2$, $MnCl_2$, $CoCl_2$ and $TiCl_3$. The results are shown in Table 2.

Then similar reactions were studied in the presence of various amounts of catalyst and oxidant. As shown in Table 3, a ratio of 1:1.5:1 mmol of sulfide/UHP/$FeCl_3$ was found to be optimum for complete conversion of sulfides to sulfoxides.

In order to investigate the generality and applicability of the present catalytic system in this new protocol synthesis of sulfoxides, a variety of products were synthesized under the optimized conditions. The results summarized in Table 4 indicate that all sulfoxide products were obtained selectively in good-to-excellent yields after appropriate reaction times at room temperature, and no over oxidation to sulfones were detected in the reaction mixtures.

Moreover, in order to examine the efficiency of this procedure, we compared the results of the oxidation of methylphenyl sulfide and diphenyl sulfide in the presence of UHP/$FeCl_3$ catalytic system with the previous methods in the literatures (see Tables S1 and S2 in Supporting Information). It is obvious that described procedure in this research project shows good reaction time than the other catalysts, which has been reported previously. Also this catalytic system is comparable in terms of price, non-toxicity, stability and easy separation.

Table 2 Lewis-acid optimization for the oxidation of benzyl phenyl sulfoxide (1 mmol)

Entry	Lewis acid	Time (h)	Yield (%)[a]
1	–	14	N.R.
2	$FeCl_2$	16	45
3	$MnCl_2$	16	35
4	$CoCl_2$	16	35
5	$FeCl_3$	16	69
6	$ZnCl_2$	12	17
7	$AlCl_3$	13	27
8	$ZrCl_4$	10	24
9	$TiCl_3$	12	20

Reaction conditions: UHP (1 mmol), $FeCl_3$ (0.5 mmol), acetonitrile (10 mL), r.t.

[a] Isolated yields and N.R. means no reaction

Table 3 Optimization of relative amount of catalyst and oxidant for the oxidation of benzyl phenyl sulfoxide (1 mmol) in acetonitrile (10 mL) at room temperature

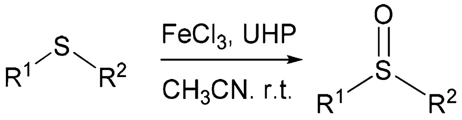
Entry	Oxidant (mmol)	$FeCl_3$ (mmol)	Time (h)	Yield (%)[a]
1	UHP (0.5)	0.5	18	43
2	UHP (1)	0.5	16	69
3	UHP (0.5)	1	21	48
4	UHP (1)	1	15	76
5	UHP (1.5)	0.5	10	89
6	UHP (2)	0.5	8	91
7	UHP (1.5)	1	2.5	96
8	UHP (2)	1	2.5	96
9	UHP (1.5)	1.5	2.5	96
10	UHP (1.5)	1	3.5	96
11	UHP (2)	1.5	3	96
12	UHP (2)	–	10	N.R.
13	H_2O_2 (1.5)	1	10	45
14	H_2O_2 (2)	–	10	N.R.

[a] Isolated yields and N.R. means no reaction

As it can be seen, the applicability of the UHP/$FeCl_3$ system was examined for the oxidation of diaryl, dibenzyl, aryl benzyl, alkyl benzyl and dialkyl sulfides at room temperature. In compare of other Lewis-acid catalysts, $FeCl_3$ has many advantages. It is cheap, nontoxic, and commercially available. Another significant advantage of this method is that only 1 mmol of the catalyst and 1.5 mmol of oxidant were required for sulfoxidation reaction while the oxidation of sulfides to sulfoxides by H_2O_2 mediated in the presence of $TiCl_3$ and $ZrCl_4$ was employed more than 1 equivalent of these catalysts per mole of sulfide and an excess of oxidant is used for the synthesis of sulfoxides [sulfide/30% H_2O_2/$ZrCl_4$; 2:14:4] [27].

Moreover, UHP as an inexpensive, commercially available, stable solid and anhydrous source of H_2O_2 has been used that is more selective and safer than H_2O_2. due to its effective oxygen content. Interestingly, herein, over oxidation of sulfides to sulfones was not detected in any of the reactions even by using additional amount of catalytic system or increasing the time (Table 3, entries 8–11). Therefore, the present method is highly selective to sulfoxide formation as the sole oxidation product in high yield and purity.

Table 4 Oxidation of sulfides to sulfoxides in the presence of $FeCl_3$/UHP



Entry	R^1	R^2	Time (min)	Yield (%)[a]	Melting point	
					Found	Reported
1	Ph	$PhCH_2$	150	96	122	121–122 [31]
2	4-Cl–C_6H_4	$PhCH_2$	150	96	128–129	126–127 [32]
3	4-Br–C_6H_4	$PhCH_2$	150	94	138–140	139–140 [33]
4	*n*-Octyl	$PhCH_2$	140	96	71–72	70–71.5 [34]
5	Ph	Ph	180	96	73.5	72–73 [35]
6	4-Me–C_6H_4	$PhCH_2$	135	97	123–125	121–122 [32]
7	$PhCH_2$	$PhCH_2$	120	97	133–134	133–135 [35]
8	4-Cl–C_6H_4	CH_3	120	95	44–45	45–46 [36]
9	*n*-Butyl	*n*-Butyl	115	92	Oil	Oil [32]
10	Ph	CH_3	120	94	Oil	Oil [32]
11	4-Br–C_6H_4	CH_3	125	93	73–75	72–75 [35]
12	4-Br–$PhCH_2$	$PhCH_2$	130	96	138–139	139–140 [27]

[a] Isolated yields

As shown in Fig. 1a, according to FT-IR spectrum, the presence of a strong absorption peak at near 1041 cm^{-1} is related to S=O stretching vibration that approved the formation of benzyl phenyl sulfoxide as a sole product. In addition, ^1H NMR spectrum clearly confirmed the successful conversion of benzyl phenyl sulfide to benzyl phenyl sulfoxide (Fig. 1b).

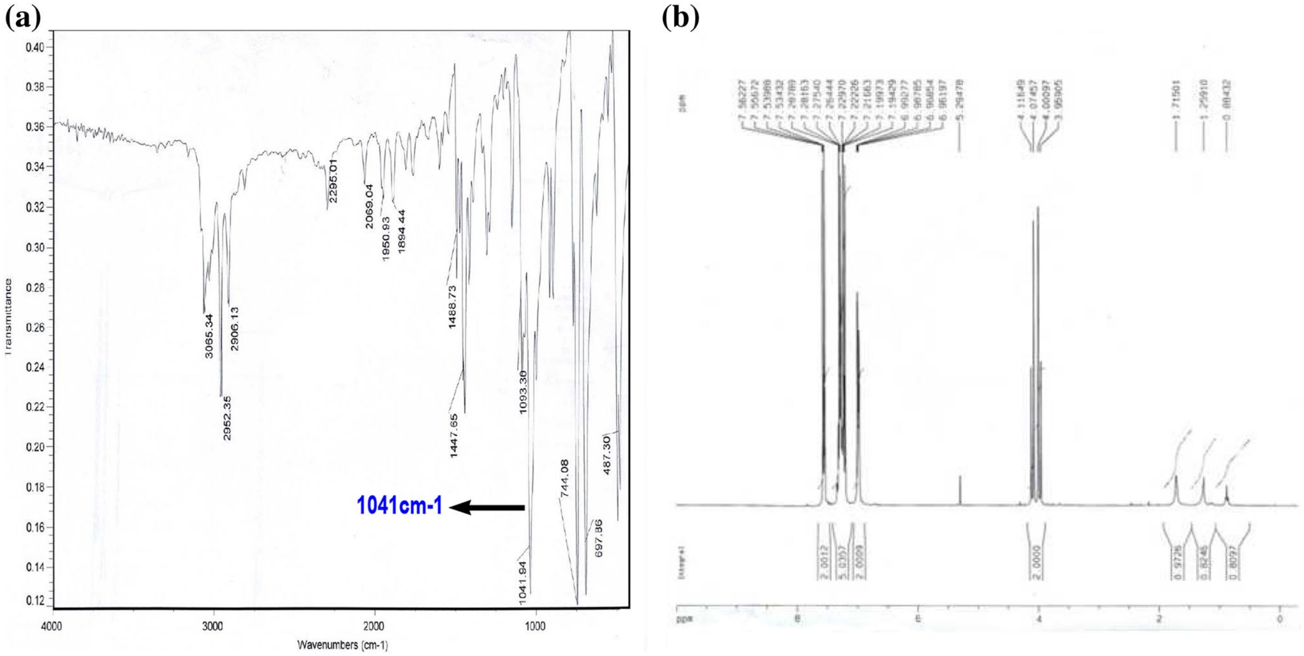


Fig. 1 FT-IR (**a**) and ^1H NMR (**b**) spectra of benzylphenyl sulfoxide

Obviously, in the case of sulfone formation, we must have seen the strong asymmetric and symmetric absorption peaks of SO_2 near 1300 and 1150 cm^{-1}, respectively. Therefore, the absence of these two absorption peaks and appearance of only one strong S=O stretching peak at near 1041 cm^{-1} confirms the selective oxidation of sulfide to sulfoxides.

4 Conclusion

In conclusion, we have introduced a simple, efficient, selective and eco-friendly procedure for the oxidation of various sulfides to sulfoxides using UHP catalyzed by $FeCl_3$ at room temperature. The method offers several noteworthy advantages including non-toxic, inexpensive catalyst, high-to-excellent yields of the products and easy work-up procedure.

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