A Novel, Practical Synthesis of Sulfonyl Chlorides from Thiol and Disulfide Derivatives

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Abstract: Hydrogen peroxide, in the presence of zirconium tetrachloride, is a very efficient reagent for the direct oxidative conversion of thiol and disulfide derivatives into the corresponding sulfonyl chlorides with high purity through oxidative chlorination. Excellent yields, very short reaction times, mild reaction conditions, and the avoidance of harsh reagents are the main advantages of this method.

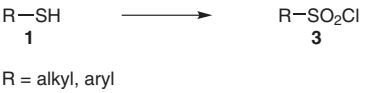
Key words: oxidative chlorination, sulfonyl chloride, thiol, disulfide, hydrogen peroxide, zirconium tetrachloride

With new pharmacological targets continuously being discovered, novel biologically active leads are urgently needed. This requirement has stimulated a search for techniques capable of providing large numbers of pharmaceutically interesting compounds. Oxidation is an important chemical process, which is prevalent throughout chemistry and leads to significant changes in the properties of organic and biological compounds.[1,2] Sulfonyl chlorides are precursors with extensive uses in organic synthesis.[3] The most typical method for the preparation of such compounds is the oxidative chlorination of sulfur moieties such as: thiols, sulfides, thioacetates and thiocarbamates, with aqueous chlorine,[4] although other oxidizing agents such as KNO_3/SO_2Cl_2,[5] cyanuric chloride,[6] HCl/Cl_2,[7] HCl/NCS,[8] and $TMSCl/KNO_3$[9] have also been used for this purpose. However, various drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious work up, use of expensive reagents, use of toxic agents and special efforts required to prepare the reagent, are associated with many of these methods. Owing to the wide range of biological activity of sulfonyl chlorides, the development of an alternative synthetic methodology is of paramount importance.

Zirconium tetrachloride ($ZrCl_4$) is a commercially available compound. Due to its low toxicity, low cost, ease of handling and high activity, zirconium tetrachloride has been widely used in organic reactions,[10] however, it has not been studied in the synthesis of sulfonyl chlorides until now.

Hydrogen peroxide (H_2O_2) is also an attractive and inexpensive oxidant that is widely used in laboratory and industry scale syntheses. From the view point of green chemistry, H_2O_2 has become increasingly popular with regard to the formation of water as a sole by-product.

As part of our continuing studies on the use of hydrogen peroxide in organic synthesis,[11] herein, we introduce for the first time $H_2O_2/ZrCl_4$ as valuable reagent system for the direct oxidative chlorination of thiol derivatives to the corresponding sulfonyl chlorides (Scheme 1).



Scheme 1

In order to evaluate the effect of solvent, the oxidative chlorination of 4-bromothiophenol was carried out under identical reaction conditions using various organic solvents such as chloroform, dichloromethane, acetonitrile and 1,4-dioxane. The course of the oxidative chlorination reaction was found to be strongly influenced by the nature of the solvent used in the reaction. For example, chlorinated solvents such as dichloromethane and chloroform furnished the sulfonyl chlorides in low yield, whereas, in contrast, polar organic solvents such as acetonitrile and 1,4-dioxane resulted in an excellent yield of the corresponding sulfonyl chlorides.

To optimize the reaction conditions, the reaction of 4-bromothiophenol was selected as a model with which to examine the effects of different amounts of H_2O_2 and $ZrCl_4$ in acetonitrile at room temperature. As shown in Table 1, the best result (98% yield) was obtained by carrying out the reaction with three equivalents of H_2O_2 in the presence of one equivalent of $ZrCl_4$ for one minute.

Using the above optimized reaction conditions, the reactions of various thiols were investigated. As shown in Table 2, aromatic thiols carrying either electron-donating or electron-withdrawing substituents afforded excellent yields of products with high purity (monitored by ^1H NMR). Heterocyclic thiols, such as 2-mercaptopyrimidine and 2-mercaptobenzimidazole, were also investigated. Under the same conditions, the desired products were obtained in excellent yields (Table 2, entries 10 and 11). Furthermore, aliphatic compounds such as cyclohexanethiol and 1-octanethiol, also afforded the sulfonyl chlorides in excellent yields (Table 2, entries 12 and 13).

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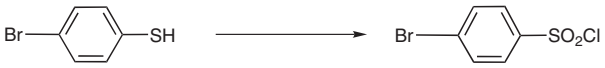
Table 1 Effect of the Amount of H_2O_2 and $ZrCl_4$ on Oxidative Chlorination of 4-Bromothiophenol[a]



Entry	$ZrCl_4$ (equiv)	30% H_2O_2 (equiv)	Yield (%)[b]
1	0.25	4	30
2	0.5	4	50
3	0.75	4	76
4	1	2	84
5	1	3	98
6	1	4	98

[a] Reaction conditions: 4-bromothiophenol (1 mmol), 1 min, 25 °C.
[b] Isolated yields.

Furthermore, the protocol is fairly general and several functionalities including nitro, ether and halide groups are able to survive the course of the reaction.

The limitation of this method is that this procedure fails to produce a clean oxidative chlorination reaction for furan-2-methanethiol. This thiol produced a mixture of products which were difficult to separate; after laborious separation, we obtained an unacceptable yield of the desired sulfonyl chloride.

An investigation into the mechanistic aspects of oxidative chlorination of thiols **1** showed the corresponding disulfide **2** is the main intermediate in this transformation. When the reaction of 4-methylthiophenol was carried out with 1:1 molar ratios of thiol to H_2O_2 in the presence of 1 mmol $ZrCl_4$ for 10 min, the desired disulfide was obtained as the major product (Figure 1).

In order to further verify the mediation of the disulfides in the oxidative chlorination of thiols, reactions were repeated with a range of symmetrical disulfides (Scheme 2). After optimizing the reaction in order to identify conditions that consistently produced excellent yields of sulfonyl chlorides, we found that the best reaction conditions required the presence of 30% H_2O_2 (2 mmol), $ZrCl_4$ (1 mmol) and disulfide (1 mmol) in acetonitrile at room temperature. The generality and the scope of the reaction were investigated and the results of the study are summarized in Table 3. As shown, all reactions resulted in the formation of the corresponding sulfonyl chlorides in excellent yields with high purity. This shows that successive oxidation of the sulfur atom, followed by S–S bond cleavage and subsequent chlorination, occurs during the direct conversion of thiols into the corresponding sulfonyl chlorides. Furthermore, the selectivity of the present method is fairly wide, as several functionalities remain unaffected under these reaction conditions.

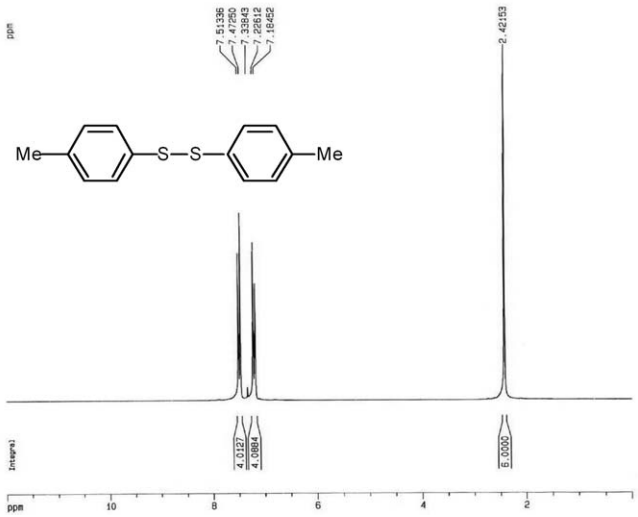
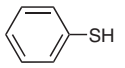
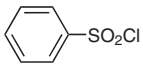
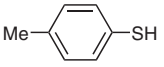
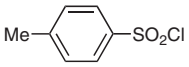
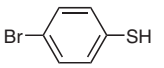
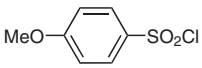
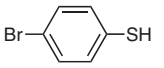
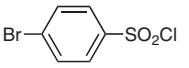
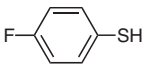
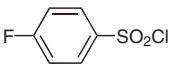
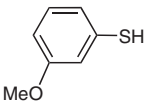
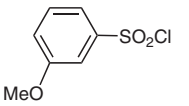
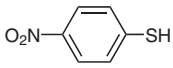
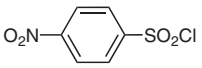
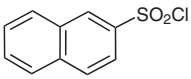
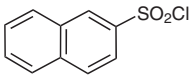
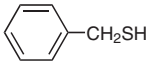
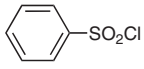
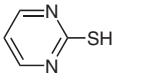
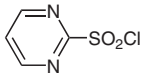
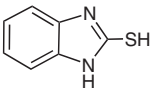
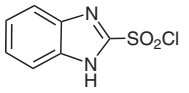
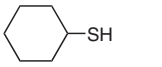
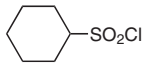
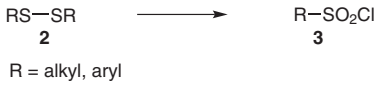


Figure 1 ^1H NMR spectrum (200 MHz) of 4-mehylphenyl disulfide in $CDCl_3$

Table 2 Oxidative Chlorination of Thiol Derivatives

Entry	Thiol **1**	Sulfonyl chloride **3**[a]	Time (min)	Yield (%)[b]
1			1	98
2			1	99
3			1	96
4			1	98
5			1	97
6			1	96
7			2	98
8			1	97
9			3	97
10			3	95
11			2	97
12			2	98
13	*n*-Octyl—SH	*n*-Octyl—SO_2Cl	2	95

[a] The purified products were characterized by mp, ^1H and ^{13}C NMR.
[b] Pure isolated products.



Scheme 2

Table 3 Oxidative Chlorination of Disulfide Derivatives

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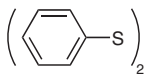
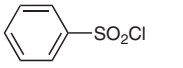
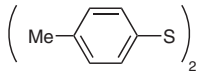
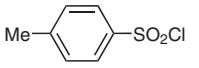
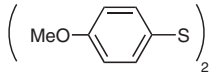
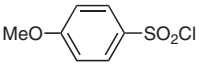
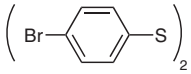
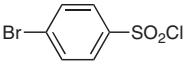
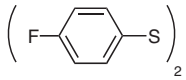
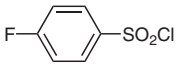
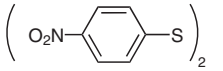
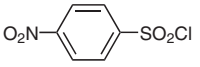
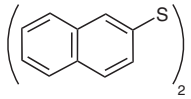
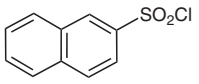
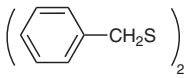
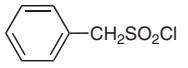
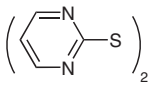
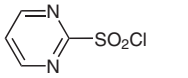
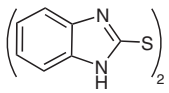
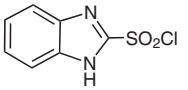
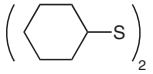
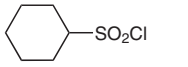
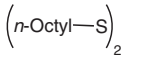
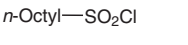
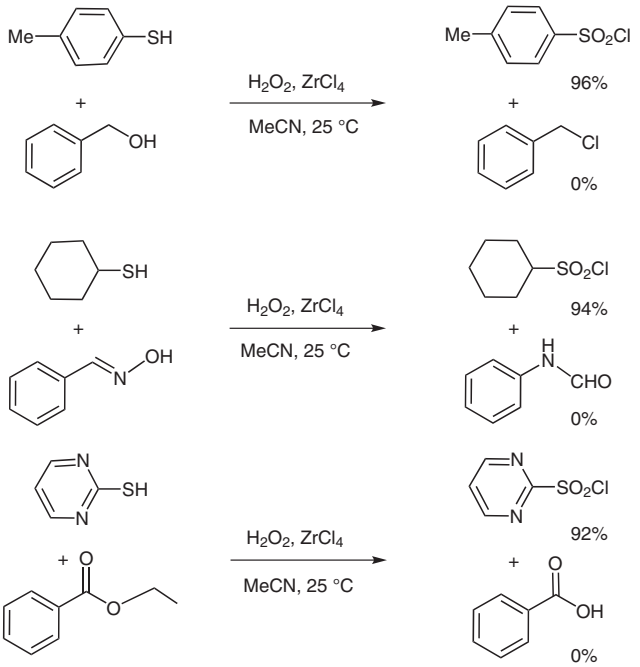
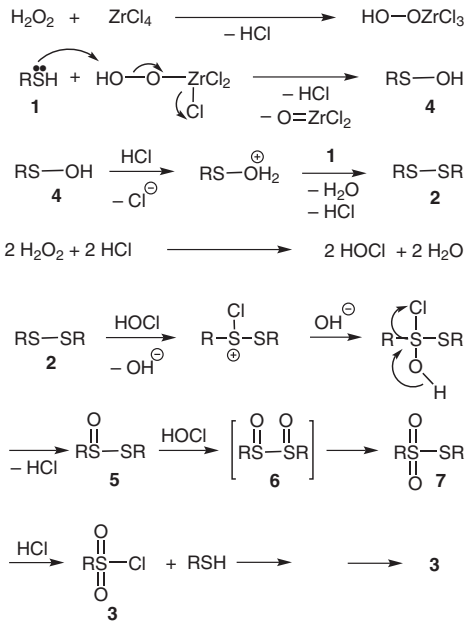
1			<1	95
2			<1	98
3			<1	96
4			<1	98
5			<1	94
6			<1	96
7			<1	98
8			2	96
9			2	94
10			1	95
11			<1	98
12			<1	96

[a] The purified products were characterized by mp, ^{1}H and ^{13}C NMR.
[b] Pure isolated product.

In order to evaluate the selectivity of this reagent system, we studied the oxidative chlorination of thiols in the presence of alcohols, oximes and esters; the results are depicted in Scheme 3. These observations suggest that this method can be applied to the oxidative chlorination of thiols in the presence of the functional groups mentioned above in multifunctional molecules.



Scheme 3 Selectivity of the oxidative chlorination reaction. *Reagents and conditions*: molar ratio of substrates to H_2O_2 to $ZrCl_4$ (1:1:3:1), MeCN, 25 °C.



Scheme 4 Proposed mechanism for oxidative chlorination with the $H_2O_2/ZrCl_4$ reagent system

The possible mechanism for this transformation is outlined in Scheme 4. It is acceptable to assume that nucleophilic attack of H_2O_2 on $ZrCl_4$ makes one of the oxygen atoms more electrophilic. Therefore, the mechanism may proceed through hydroxylation of thiol **1** leading to the formation of sulfenic acid **4**, which gives the corresponding symmetric disulfide **2**. Then, the successive oxidation of both sulfur atoms of the disulfide molecule by hypochlorous acid produces the intermediate **6**, which un-

dergoes rapid isomerization to the thiosulfonate **7**. The latter sulfonate can then easily furnish sulfonyl chloride **3**. Conversion of **6** into **7** has been well recognized and documented.[12]

In conclusion, $H_2O_2/ZrCl_4$ is an extremely efficient reagent system for the conversion of thiols and disulfides into sulfonyl chlorides.[13] The advantages are excellent yields, extremely fast reaction, low cost, and room temperature conditions. This methodology also overcomes the problem of unwanted by-product formation. We believe that the present approach could lead to new possibilities for medicinal chemistry and material sciences and could be an important addition to the existing methodologies.

Acknowledgment

We are thankful to the Razi University Research Council for partial support of this work.

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(13) Zirconium tetrachloride, hydrogen peroxide (30%) as well as all the thiol derivatives employed as substrates are commercial products (Merck chemical company) and were used without further purification. Disulfides were prepared according to our previously reported procedure.[14]
Melting points were determined in a capillary tube and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-200 NMR spectrometer using TMS as internal standard. The concentration of the commercial 30% H_2O_2 solution was checked iodometrically prior to use.
Synthesis of Sulfonyl Chlorides; General Procedure:
A mixture of thiol (1 mmol), 30% H_2O_2 (3 mmol, 0.3 mL) and $ZrCl_4$ (1 mmol, 0.233 g) was stirred in MeCN (5 mL) at 25 °C for the appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by adding H_2O (10 mL), and extracted with EtOAc (4 × 5 mL). The extract was dried with anhydrous $MgSO_4$ and the filtrate was evaporated under vacuum to afford the analytically pure product (Table 2). An identical procedure was employed using 30% H_2O_2 (2 mmol, 0.2 mL) and $ZrCl_4$ (1 mmol, 0.233 g) for the oxidative chlorination of disulfides (Table 3).
All of the products are known compounds and were easily characterized by comparison with authentic samples (^{1}H NMR, ^{13}C NMR, mp).
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