Simple Synthesis of Sulfonyl Chlorides from Thiol Precursors and Derivatives by $NaClO_2$-Mediated Oxidative Chlorosulfonation

Zhanhui Yang, Yongpeng Zheng, Jiaxi Xu*

State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, P. R. of China
Fax +86(10)64435565; E-mail: jxxu@mail.buct.edu.cn

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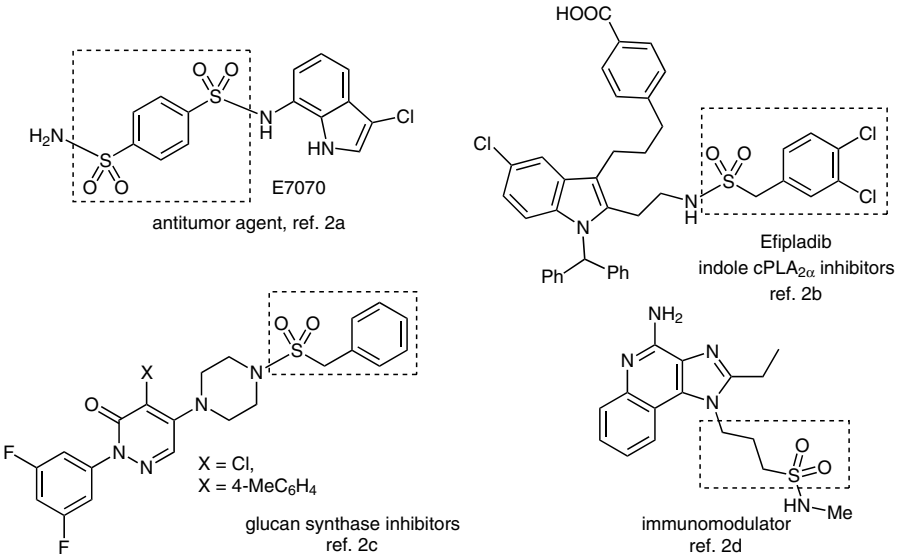
Abstract: A simple method to synthesize diverse sulfonyl chlorides through $NaClO_2$-mediated oxidative chlorosulfonation of *S*-alkyl isothiourea salts is presented. The approach features safe operation, environmental friendliness, convenient purification procedures, and delivers high yields of up to 96%. The procedure is also applicable to substrates such as thiols, disulfides, thioacetates, and xanthates. It is a versatile and convenient method for the synthesis of various sulfonyl chlorides from different thiol precursors and derivatives.

Key words: sulfonyl chloride, sodium chlorite, oxidative chlorosulfonation, synthetic methods, isothiourea

Sulfonyl chlorides are versatile building blocks for the synthesis of sulfonic acid derivatives and are important synthetic intermediates for the introduction of a sulfonyl group.[1] One representative type of sulfonic acid derivative is the sulfonamide group, which is commonly used in antibacterial medicines and enzyme inhibitors (Scheme 1).[2] The most efficient route toward the synthesis of sulfonamides is the coupling of sulfonyl chlorides and amines. Sulfonyl chlorides have also been widely applied in the production of fine chemicals, such as detergents, dyes, and herbicides.[1b,c]

With respect to their significant importance, sulfonyl chlorides have received increasing interest during the past centuries. Generally, the chlorination of sulfonic acids or their salts,[3] and oxidative chlorosulfonation of thiols and their precursors or derivatives,[4] are the two predominant methods for the synthesis of sulfonyl chlorides. The first method always suffers from the required use of reactive and hazardous reagents such as $SOCl_2$,[3a] PCl_3,[3b] PCl_5,[3c] $POCl_3$,[3d] oxalyl chloride,[3e] or phosgene.[3f] Modified, mild chlorinating reagents such as $PPh_3{\cdot}Cl_2$[3g] and cyanuric chloride[3h] generate large amounts of byproducts. Compared with the first methods, the second approach usually gives the desired products in high yields in a single step from thiols and their derivatives. Many relatively safe and mild oxidative chlorosulfonating reagents have been developed to replace chlorine gas.[4]Most of the substrates employed in the above conditions are thiols or their derivatives, which are not friendly to workers or the environment because of their strong and repulsive odors. Furthermore, compared with alkyl halides, thiols and their derivatives are either not easily available or expensive.[5] Thus, the preparation of sulfonyl chlorides in a simple and environmentally friendly way is of ongoing concern in the synthetic community.



Scheme 1 Representative important sulfonamides generated from sulfonyl chlorides as building blocks

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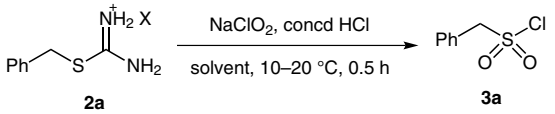
In our previous work,[6c] we modified the *N*-chlorosuccinimide-mediated synthesis of sulfonyl chlorides from the substrate aspect,[6] by using more convenient *S*-alkyl isothiourea salts instead of malodorous thiols and their derivatives. In that procedure, however, organic waste succinimide was generated in large amount and, consequently, contamination of the products, especially liquid products, was problematic. As an extension of our previous study,[6c] we wanted to solve that problem and find an easily accessible and worker-safe oxidative chlorosulfonating reagent, for which the reduction product does not cause contamination of the desired products. After numerous attempts, the commercially available, inexpensive reagent $NaClO_2$, which is a reagent widely applied in Pinnick oxidation or Lindgren oxidation, was identified.[7] Herein, for the first time, we present the $NaClO_2$-mediated oxidative chlorosulfonation of *S*-alkyl thiourea salts to prepare and purify sulfonyl chlorides in a simple procedure. The method can also be applied in the oxidative chlorosulfonation of thiols and their derivatives.

Optimization of the conditions commenced by treating *S*-benzyl isothiouronium chloride (**2a**) with solid $NaClO_2$ (2 equiv) and concentrated HCl (2 mL) in water, which is the most preferred solvent from the standpoint of green chemistry. However, since the yield was unsatisfactory (Table 1, entry 1), we replaced the water with acetonitrile, which is also a usable solvent in green chemistry according to Pfizer solvent selection guide;[8] use of this solvent dramatically improved the yield to 55% (Table 1, entry 2). Further optimization by using $NaClO_2$ (3 equiv) and concentrated HCl (3 mL) gave a satisfactory yield of 82% (Table 1, entry 3). Changing the addition sequence of $NaClO_2$ and concentrated HCl, or increasing their amount had little effect on the yield (Table 1, entries 4 and 5). However, when solid $NaClO_2$ was replaced by its water solution, the yield decreased from 82 to 62% (Table 1, entry 6). Prolonging the reaction time to two hours gave a yield of 71% (Table 1, entry 7).

Table 1 Optimizing Reaction Conditions[a]

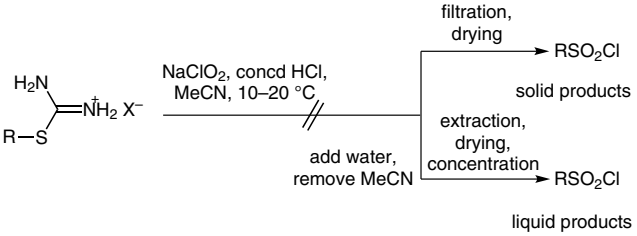


2a **3a**

Entry	$NaClO_2$ (equiv)	Concd HCl (mL)	Solvent	Yield (%)[b]
1	2	2	H_2O	31
2	2	2	MeCN	55
3	**3**	**3**	**MeCN**	**82**
4[c]	3	3	MeCN	79
5	4	4	MeCN	77
6[d]	3	3	MeCN	62
7[e]	3	3	MeCN	71

[a] Reaction conditions (5 mmol scale): To the solvent was sequentially added solid $NaClO_2$, concd HCl, and then *S*-alkyl isothiourea salt **2a**.
[b] Isolated yield after filtration.
[c] $NaClO_2$ solid was added after the addition of concd HCl.
[d] An aqueous solution of $NaClO_2$ (3 mL) was used instead of the solid.
[e] Reaction conducted for 2 h.

Under the optimized experimental conditions, starting material **2a** was almost completely consumed, and the by-product urea and NaCl are quite soluble in water; however, it was likely that there may be some sulfonic acid generated from the hydrolysis of the sulfonyl chloride. Since the sulfonic acid is strongly hydrophilic, we believed it would act like a surfactant and stay in the aqueous phase during the purification. Based on these considerations, we developed a convenient procedure with which to quickly and easily purify the benzylsulfonyl chloride. After completion of the reaction, water was added and the resulting solution was evaporated at less than 20 °C in vacuum to remove acetonitrile, upon which a large amount of white solid 'recrystallized' from the solution. Filtration of the solid and drying under infrared light afforded benzylsulfonyl chloride in analytical purity. This procedure was found to be general for the purification of solid sulfonyl chlorides. The procedure for the purification of liquid sulfonyl chlorides was also proposed as following: after removal of acetonitrile in the same way, the products could be obtained through a sequence of extraction with ethyl acetate (a preferred solvent in green chemistry), drying with Na_2SO_4, and removal of the solvent under vacuum (Scheme 2). The applicability of this procedure was confirmed in subsequent reactions.



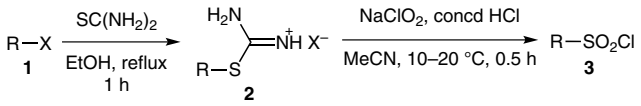
Scheme 2 Procedure for the purification of solid and liquid sulfonyl chlorides

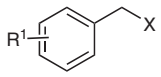
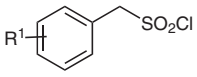
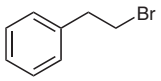
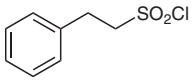
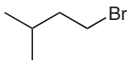
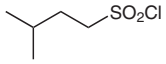
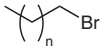
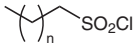
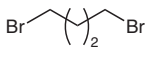
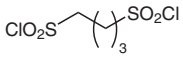
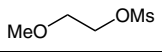
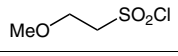
With the optimal conditions (Table 1, entry 3) and a convenient purification protocol established, we prepared some significantly important sulfonyl chlorides; the results are presented in Table 2. All the halo-substituted phenylmethanesulfonyl chlorides were prepared in good to excellent yields (Table 2, entries 2–6), regardless of the substituent positions (Table 2, entries 3–5). When strong electron-withdrawing groups such as cyano or nitro were introduced, the products were still afforded in 71 and 54% yields, respectively (Table 2, entries 7 and 8). The decrease in the yields was presumably caused by reactions of water with **3g** and **3h** either in the reaction mixture or during workup. The presence of an electron-donating group such as methyl at the *para*-position also led to the corresponding sulfonyl chloride **3i** in 65% yield (Table 2, entry 9). 2-Phenylethanesulfonyl chloride (**3j**) was readily

prepared in moderate yield (62%; Table 2, entry 10). Since alkanesulfonyl chlorides with long chains are important intermediates in the field of surfactants, we tested our method in the synthesis of these compounds. Gratifyingly, the desired compounds with straight and branched chains were generated in satisfactory to excellent yields (74 to 96%), regardless of the length of the chains (Table 2, entries 11–13). Surprisingly, butane-1,4-disulfonyl dichloride was also generated in excellent yield (94%; Table 2, entry 14). The β-functionalized sulfonyl chloride **3o** was readily prepared in good yield (87%; Table 2, entry 15). The successful preparation of the latter compound indicates that the substrate scope of this method is not limited to alkyl halides, with compounds containing other good leaving groups such as mesylates also being suitable substrates.

To establish the versatility of our method, thiols, thiophenol, and their derivatives, including disulfides, thioacetates, and xanthates, were directly subjected to the $NaClO_2$-mediated oxidative chlorosulfonation (Table 3). To our delight, the reactions of thiols **4a** and **4b** and thiophenol **4c** proceeded smoothly, and the desired products were obtained in satisfactory to good yields after purification (Table 3, entries 1–3). Even the active ethanesulfonyl chloride (**3s**) was obtained in 46% yield from disulfide **4d** in analytical purity (Table 3, entry 4). It is noteworthy that a one-pot procedure to synthesize sulfonyl chlorides was also presented.[5] Displacements of benzyl chloride with nucleophiles KSAc and KSCSOEt afforded the corresponding thioacetate **4e** and xanthate **4f**. In the same pot, subsequent oxidative chlorosulfonation of **4e** and **4f**, mediated by $NaClO_2$, gave rise to phenylmethanesulfonyl

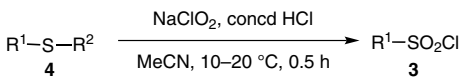
Table 2 Preparation of Structurally Diverse Sulfonyl Chlorides[a]



Entry	Substrate	1	Product	3	Yield (%)[b]
					
1	R^1 = H, X = Cl	**1a**	R^1 = H	**3a**	82
2	R^1 = 4-F, X = Cl	**1b**	R^1 = 4-F	**3b**	75
3	R^1 = 2-Cl, X = Cl	**1c**	R^1 = 2-Cl	**3c**	92
4	R^1 = 3-Cl, X = Cl	**1d**	R^1 = 3-Cl	**3d**	91
5	R^1 = 4-Cl, X = Cl	**1e**	R^1 = 4-Cl	**3e**	96
6	R^1 = 4-Br, X = Cl	**1f**	R^1 = 4-Br	**3f**	90
7	R^1 = 4-NC, X = Cl	**1g**	R^1 = 4-NC	**3g**	71
8	R^1 = 4-O_2N, X = Br	**1h**	R^1 = 4-O_2N	**3h**	54
9	R^1 = 4-Me, X = Cl	**1i**	R^1 = 4-Me	**3i**	65
10		**1j**		**3j**	62
11		**1k**		**3k**	74
					
12	n = 4	**1l**	n = 4	**3l**	96
13[c]	n = 14	**1m**	n = 14	**3m**	96
14[c,d]		**1n**		**3n**	94
15		**1o**		**3o**	87

[a] Reaction workup (5 mmol scale based on the alkyl halides or mesylate): compounds **3a–i**, **3m–n** were purified by filtration; others by concentration after extraction with ethyl acetate and drying with Na_2SO_4.
[b] Isolated yield of two steps.
[c] Reaction performed at 40–50 °C.
[d] The amounts of thiourea, $NaClO_2$, concd HCl, and MeCN were doubled.

Table 3 Synthesis of Sulfonyl Chlorides from Thiols and Derivatives[a]

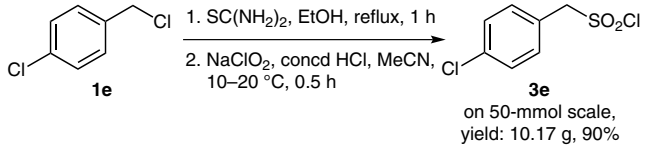


Entry	Substrate	4	Product	3	Yield (%)[b]
1	$PhCH_2SH$	**4a**	$PhCH_2SO_2Cl$	**3a**	82
2	*n*-BuSH	**4b**	*n*-$BuSO_2Cl$	**3p**	87
3	PhSH	**4c**	$PhSO_2Cl$	**3q**	82
4[c]	EtSSEt	**4d**	$EtSO_2Cl$	**3r**	46
5[d]	$PhCH_2SAc$	**4e**	$PhCH_2SO_2Cl$	**3a**	54[e]
6[d]	$PhCH_2SCSOEt$	**4f**	$PhCH_2SO_2Cl$	**3a**	73[e]

[a] Reaction workup (5 mmol scale, based on the substrate): Compounds **3p**–**r** were purified by concentration after extraction with ethyl acetate and drying over Na_2SO_4; compound **3a** was obtained by filtration.
[b] Isolated yield.
[c] The amounts of $NaClO_2$, concd HCl, and MeCN were doubled.
[d] One-pot procedure from benzyl chloride and KSAc or KSCSOEt.
[e] Yield over two steps.

chloride in 54 and 73% yield, respectively, over two steps. The purification procedures described above worked well in the workup of all the reactions.

The ability to scale up this method was confirmed by the preparation of (4-chlorophenyl)methanesulfonyl chloride (**3e**) on a 50-mmol scale (Scheme 3). In the large-scale production, oxidative chlorosulfonation proceeded smoothly to give the desired product in excellent yield (90%) and analytical purity after filtration and drying.



Scheme 3 Large-scale synthesis of (4-chlorophenyl)methanesulfonyl chloride

A plausible mechanism for the $NaClO_2$-mediated oxidative chlorosulfonation of *S*-alkyl isothiourea salts is depicted in Scheme 4. First, $NaClO_2$ undergoes a redox reaction with hydrochloric acid to generate a highly oxidative species: hypochlorous acid (HOCl; Scheme 4, eq. 1). Under acidic conditions, the hypochlorous acid initiates the oxidation of the *S*-alkyl isothiourea salt, leading to the corresponding alkanesulfonyl methanimidamide salt **5** after two consecutive oxidations. With the assistance of water, intermediate **5** undergoes elimination of urea to generate sulfinic acid **6**, which is further oxidized to the corresponding sulfonyl chloride **3** by another equivalent of hypochlorous acid (Scheme 4, eq. 2). Alternatively, chlorine could also be proposed as the highly oxidative intermediate species. The mechanism is similar to that involved in *N*-chlorosuccinimide-mediated oxidative chlorosulfonation.[6c]

In summary, a simple and reliable method for the preparation of sulfonyl chlorides has been developed.[9] The method features $NaClO_2$-mediated oxidative chlorosulfonation of *S*-alkyl isothiourea salts as well as thiols and their derivatives, such as thioacetates, xanthates, and disulfides. The use of *S*-alkyl isothiourea salts successfully circumvents problems caused by the strong and repulsive odors of thiols and their derivatives, making our method environment- and worker-friendly. We achieved the synthesis of various sulfonyl chlorides in satisfactory to excellent yields by this simple procedure, which involves convenient operation and straightforward purification.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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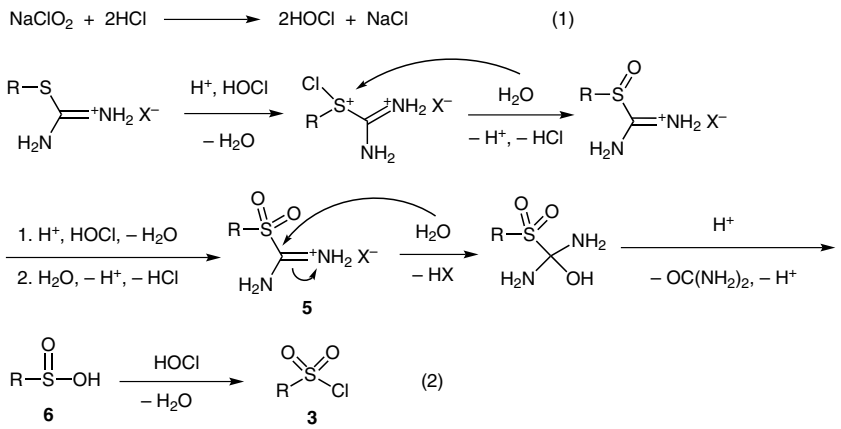
(1) (a) Hoyle, J. *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, In *The Chemistry of Functional Groups*;



Scheme 4 Plausible mechanism for $NaClO_2$-mediated oxidative chlorosulfonation of *S*-akyl isothiourea salts

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(9) **Synthesis of 3e; Typical Procedure:** (1) *p*-Chlorobenzyl chloride **1e** (0.805 g, 5 mmol) and thiourea (0.381 g, 5 mmol) were heated at reflux in EtOH (5 mL) for 1 h. After removal of the solvent under vacuum *S*-*p*-chlorobenzyl isothiouronium chloride (**2e**) was obtained as a white solid in quantitative yield. (2) A 50-mL three-necked flask equipped with a thermometer and a solid-addition funnel was immersed in an ice-bath. To the flask was sequentially added solid $NaClO_2$ (1.61 g, 15 mmol, 85% purity), MeCN (10 mL), and then concd HCl (3 mL) during 1 min, keeping the inner temperature below 10 °C. Then **2e** was slowly added through the solid-addition funnel to keep the inner temperature below 20 °C. After the addition, the resulting mixture was stirred for another 30 min, then H_2O (25 mL) was added, and the resultant mixture was evaporated in vacuum at 15 °C to remove MeCN. After addition of H_2O (100 mL), filtration on a Büchner funnel and drying under an infrared lamp, **3e** was afforded as colorless crystals. Yield: 1.080 g (96%); mp 91–93 °C (Lit.[6c] 90–92 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.41 (m, 4 H), 4.83 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8, 132.6, 129.5, 124.6, 70.0.

