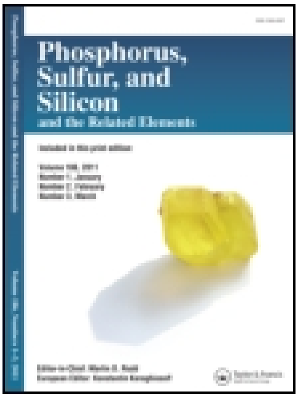

Phosphorus, Sulfur, and Silicon and the Related Elements

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# Trichloroisocyanuric Acid (TCCA) and N-Chlorosuccinimide (NCS) as Efficient Reagents for the Direct Oxidative Conversion of Thiols and Disulfides to Sulfonyl Chlorides

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# TRICHLOROISOCYANURIC ACID (TCCA) AND *N*-CHLOROSUCCINIMIDE (NCS) AS EFFICIENT REAGENTS FOR THE DIRECT OXIDATIVE CONVERSION OF THIOLS AND DISULFIDES TO SULFONYL CHLORIDES

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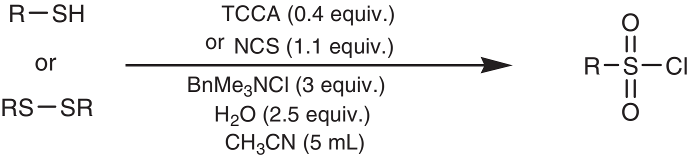
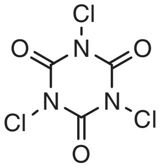
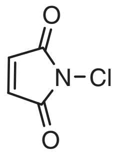
## GRAPHICAL ABSTRACT





TCCA



NCS

**Abstract** *Trichloroisocyanuric acid (TCCA) and N-chlorosuccinimide (NCS) were found to be mild and efficient reagents for the direct oxidative conversion of sulfur compounds to the corresponding arenesulfonyl chlorides in good-to-excellent yields through the oxidative chlorination. The overall process is simple and practical, and it provides convenient access to a variety of aryl or heteroarylsulfonyl chlorides. The mild reaction conditions and the broad substrate scope render this method attractive and complementary to existing syntheses of aryl or heteroarylsulfonyl chlorides.*

**Keywords** Oxidative chlorination; sulfonyl chloride; thiol; disulfide; *N*-chloro reagents

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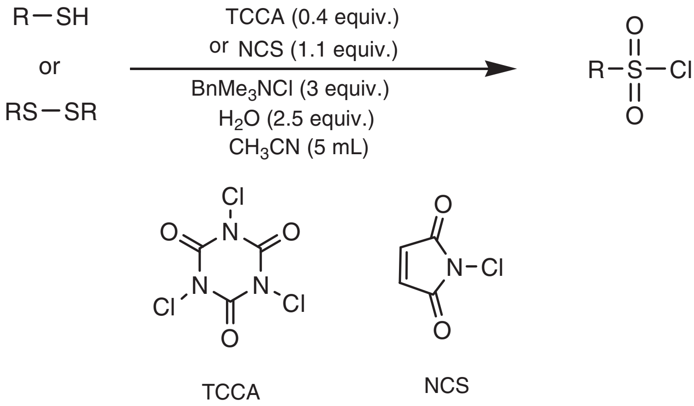
## INTRODUCTION

Aryl and heteroarylsulfonyl chlorides are an important class of compounds primarily used in the preparation of sulfonamides. Sulfonamide motifs are prevalent in a variety of biologically active compounds with a broad range of biological and pharmaceutical activities, including inhibition of carbonic anhydrase,[1] novel and selective cholecystokinin-2 receptor antagonists,[2] $\beta_3$-receptor agonists,[3] and HCV polymerase inhibitors.[4]

The development of simple, versatile, and environmentally friendly processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. Organic sulfur compounds are widespread in numerous natural products and widely used as various artificial chemicals. Sulfonyl chlorides, in particular, are precursors with extensive uses in organic synthesis.[5] The most typical method for the preparation of sulfonyl chlorides is the oxidative chlorination of sulfur compounds, thiols, sulfides, thioacetates, and thiocarbamates with aqueous chlorine,[6] although other oxidizing agents such as $KNO_3/SO_2Cl_2$,[7] cyanuric chloride,[8] $HCl/Cl_2$,[9] HCl/NCS,[10] $H_2O_2/ZrCl_4$,[11] $H_2O_2/SOCl_2$,[12] Oxone/$SOCl_2$,[13] $Br_2$-$Cl_3PO$,[14] and TMSCl/$KNO_3$[15] have also been used for this purpose. However, in spite of their potential utility, many of these methods involve various drawbacks such as the use of expensive or less easily available reagents, vigorous reaction conditions, long reaction time, tedious manipulations in the isolation of the pure products, and side reactions.

## RESULTS AND DISCUSSION

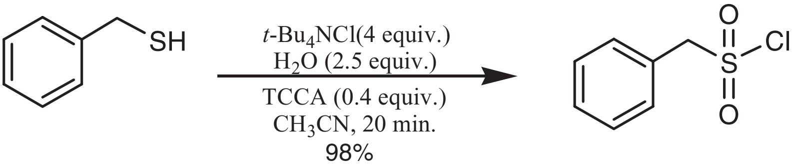
Owing to the drawbacks of oxidative chlorination with different oxidizing agents (mentioned previously), the discovery of milder and practical routes for the synthesis of sulfonyl chlorides is highly desirable. As part of our continuing studies on the use of *N*-halo reagents in organic synthesis,[16] herein we introduce for the first time trichloroisocyanuric acid (TCCA)/$BnMe_3NCl/H_2O$ or *N*-chlorosuccinimide (NCS)/$BnMe_3NCl/H_2O$ as valuable reagent systems for the direct oxidative chlorination of thiols and disulfides to the corresponding sulfonyl chlorides (Scheme 1).



**Scheme 1**

Initially, we surmised that it might be possible to generate controlled amounts of chlorine in nonprotic organic solvents by mixing a tetra-alkylammonium chloride salt with

TCCA. We were pleased to find that treatment of tetra-alkylammonium chloride (4 equiv.) and $H_2O$ (2.5 equiv.) with TCCA (0.4 equiv.) in $CH_3CN$ (20 min, r.t.) provided a light yellow solution that was suitable as a chlorinating oxidation system for the synthesis of benzylsulfonyl chlorides from benzyl thiol (1 equiv.) under mild conditions (Scheme 2).



Scheme 2

Under the abovementioned optimized reaction conditions, the reactions of various thiols were investigated in this study. As shown in Table 1, aromatic thiols carrying either electron-donating or electron-withdrawing substituents afforded excellent yields of products with high purity (monitored by $^1$H 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 1, entries 8 and 9). Furthermore, aliphatic compounds, such as cyclohexanethiol, also afforded the sulfonyl chloride in excellent yield (Table 1, entry 10).

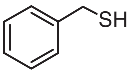
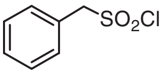
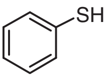
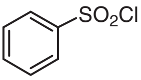
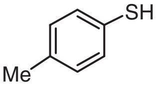
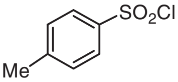
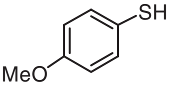
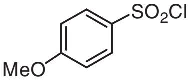
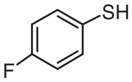
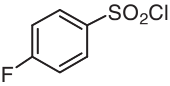
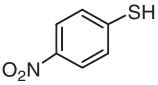
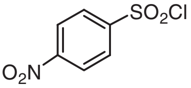
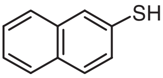
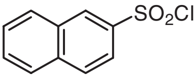
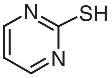
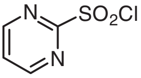
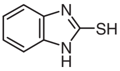
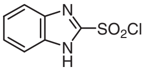
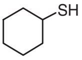
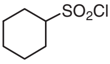
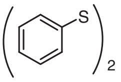
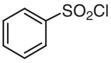
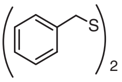
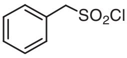
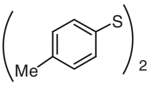
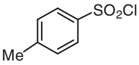
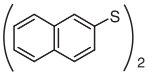
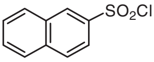
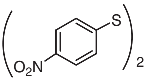
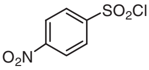
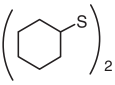
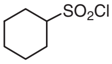
An investigation into the mechanistic aspects of oxidative chlorination of thiols showed the corresponding disulfide to be the main intermediate in this transformation. When the reaction of 4-methoxybenzyl thiol was carried out with 1:0.15 molar ratios of thiol to TCCA in the presence of tetra-alkylammonium chloride (1.5 equiv.) and $H_2O$ (1.5 equiv.) for 5 min, the desired disulfide was obtained as the major product.

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 1). 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 TCCA (0.4 mmol), TBAB (2 mmol), $H_2O$ (1.5 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 1 (entries 11–16). 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.

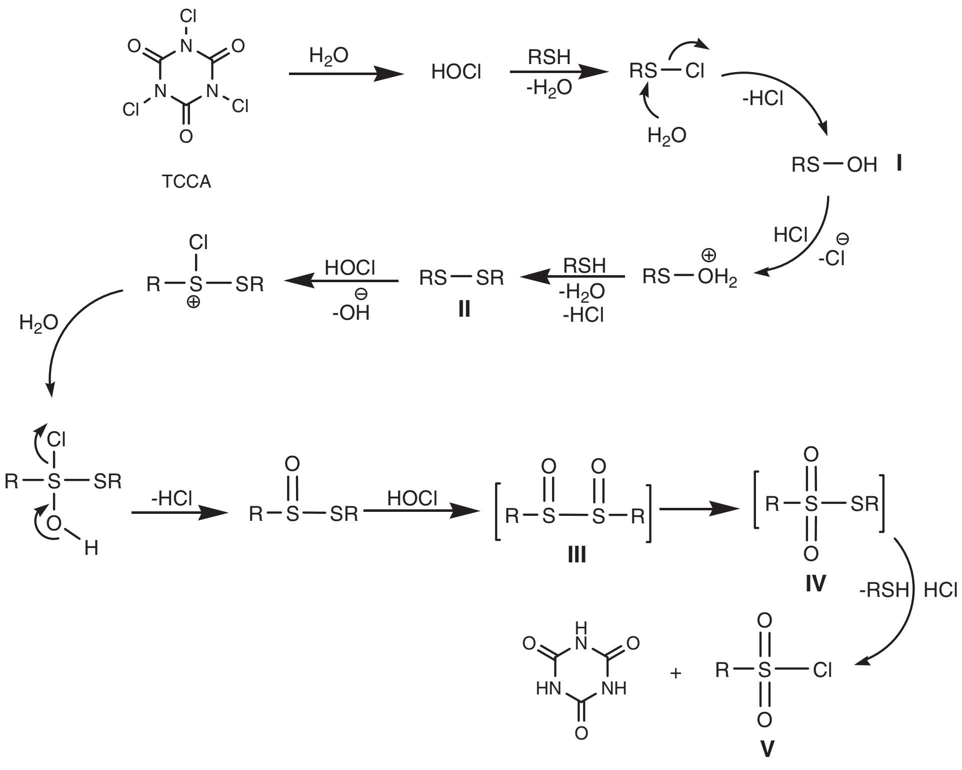
Also, we found that NCS was a suitable reagent for the conversion of thiols and disulfides into the corresponding sulfonyl chlorides in excellent yields under same conditions. The results were presented in Table 1 (entries 1–16).

The possible mechanism for this transformation is shown in Scheme 3.[12] It is acceptable to assume that the thiol is chlorinated in the presence of hypochlorous acid. Therefore, the mechanism proceeds through hydroxylation of the thiol under formation of a sulfenic acid (I), which gives the corresponding symmetric disulfide (II). Then, the successive oxidation of both sulfur atoms of the disulfide molecule by hypochlorous acid produces the intermediate (III), which undergoes rapid isomerization to form thiosulfonate (IV), which can easily furnish the sulfonyl chloride (V).

**Table 1** Oxidative chlorination of thiols and disulfides with TCCA and NCS

| Entry | Thiol | Sulfonyl chloride[a] | TCCA yield (%) | NCS yield (%) |
|---|---|---|---|---|
| 1 |  |  | 99 | 98 |
| 2 |  |  | 98 | 96 |
| 3 |  |  | 98 | 95 |
| 4 |  |  | 99 | 98 |
| 5 |  |  | 96 | 90 |
| 6 |  |  | 96 | 96 |
| 7 |  |  | 98 | 95 |
| 8 |  |  | 95 | 95 |
| 9 |  |  | 96 | 96 |
| 10 |  |  | 98 | 95 |
| 11 |  |  | 99 | 99 |
| 12 |  |  | 98 | 97 |
| 13 |  |  | 95 | 92 |
| 14 |  |  | 98 | 95 |
| 15 |  |  | 96 | 95 |
| 16 |  |  | 98 | 98 |

[a] Products were characterized by their physical properties and spectroscopic methods.



Scheme 3

To compare this method with a few previously published methods for the direct oxidative chlorination of thiols and disulfides to the corresponding sulfonyl chlorides, we carried out a few experimental runs, which are presented in Table 2. These results clearly demonstrate that our novel procedure is a good system for the preparation of sulfonyl chlorides.

**Table 2** Reaction times and yields for previously published methods

| Substrate | Product | Conditions | Time | Yield (%) |
|---|---|---|---|---|
| $C_6H_5SH$ | $C_6H_5SO_2Cl$ | TCCA/TBAC/$H_2O$/r.t. | 20 min | 98 |
| $C_6H_5SH$ | $C_6H_5SO_2Cl$ | 2,4-Dichloro-5,5-dimethyl-hydantoin $CH_3CN$-HOAc-$H_2O$ 5–20 °C | 60 min | 92[17] |
| $C_6H_5SH$ | $C_6H_5SO_2Cl$ | TMS-Cl/$MNO_3$/$CH_2Cl_2$/50 °C | 60 min | 85[8] |
| $C_6H_5SH$ | $C_6H_5SO_2Cl$ | Cyanuric chloride/$Et_3N$/reflux | 20 h | 90[15] |
| 4-Me-$C_6H_4SH$ | 4-Me-$C_6H_4SO_2Cl$ | TCCA/TBAC/$H_2O$/r.t. | 20 min | 98 |
| 4-Me-$C_6H_4SH$ | 4-Me-$C_6H_4SO_2Cl$ | 2,4-Dichloro-5,5-dimethyl-hydantoin $CH_3CN$-HOAc-$H_2O$ 5–20 °C | 60 min | 88[17] |
| 4-Me-$C_6H_4SH$ | 4-Me-$C_6H_4SO_2Cl$ | TMS-Cl/$MNO_3$/$CH_2Cl_2$/50 °C | 2 h | 85[8] |
| 4-Me-$C_6H_4SH$ | 4-Me-$C_6H_4SO_2Cl$ | Cyanuric chloride/$Et_3N$/reflux | 20 h | 90[15] |
| 2-Naphthothiol | 2-Naphthosulfonyl chloride | TCCA/TBAC/$H_2O$/r.t. | 20 min | 98 |
| 2-Naphthothiol | 2-Naphthosulfonyl chloride | 2,4-Dichloro-5,5-dimethyl-hydantoin $CH_3CN$-HOAc-$H_2O$ 5–20 °C | 60 min | 88[17] |
| 2-Naphthothiol | 2-Naphthosulfonyl chloride | Cyanuric chloride/$Et_3N$/reflux | 20 h | 88[15] |

## CONCLUSIONS

In conclusion, we have developed a simple and effective oxidative chlorination procedure for the synthesis of aryl and heteroaryl sulfonyl chlorides with TCCA or NCS as a safe and inexpensive equivalent to chlorine gas. Many aromatic thiols and disulfides can be converted to the corresponding arylsulfonyl chlorides in good-to-excellent yields, making it superior to the methods described previously.

## EXPERIMENTAL

All commercially available chemicals were obtained from Merck and Fluka and used without further purifications unless otherwise stated. $^1$H NMR spectra were recorded on a Jeol 90 MHz FT NMR spectrometer using TMS as internal standard and chemical shift were measured in $\delta$ (ppm). IR spectra were recorded on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

### General Procedure for the Conversion of Thiols and Disulfides to Sulfonyl Chlorides

To a stirred mixture of the thiol (1.0 mmol), $Bu_4NCl$ (4.0 mmol), and water (2.5 mmol) or the disulfide (1.0 mmol) $Bu_4NCl$ (2.0 mmol), and water (1.5 mmol) in $CH_3CN$ (5 mL) at 0 °C, TCCA (0.4 mmol) or NCS (1.1 mmol) was added as a solid in portions over 1–2 min. After the addition, the mixture was stirred at room temperature for 20 min until completion of the reaction. The mixture was filtered and the filtrate was evaporated under vacuum. Then, $CH_2Cl_2$ (10 mL) was added, and the insoluble reagent was removed by filtration. The filtrate was evaporated under vacuum to afford the product. All of the products are known compounds and characterized easily by comparison with authentic samples ($^1$H NMR, $^{13}$C NMR, m.p.).

## REFERENCES

1. Dudutiene, V.; Baranauskiene Matulis, D. *Bioorg. Med. Chem. Lett.* **2007,** 17, 3335-3339.
2. Allison, B. D.; Phuong, V. K.; McAtee, L. C.; Rosen, M.; Morton, M.; Prendergast, C.; Barrett, T.; Lagaud, G.; Freedman, J.; Li, L.; Wu, X.; Venkatesan, H.; Pippel, M.; Woods, C.; Rizzolio, M. C.; Hack, M.; Hoey, K.; Deng, X.; King, C.; Shanley, N. P.; Rabinowitz, M. H. *J. Med. Chem.* **2006,** 49, 6371-6375.
3. Mathvink, R. J.; Barritta, A. M.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. J.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999,** 9, 1869-1872.
4. Donner, P. L.; Xie, Q.; Pratt, J. K.; Maring, C. J.; Kati, W.; Jiang, W.; Liu, Y.; Koev, G.; Masse, S.; Montgomery, D.; Molla, A.; Kempf, D. L. *Bioorg. Med. Chem. Lett.* **2008,** 18, 2735-2740.
5. Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003,** 125, 15292-15295.
6. Watson, R. J.; Batty, D.; Baxter, A. D.; Hannah, D. R.; Owen, D. A.; Montana, J. G. *Tetrahedron Lett.* **2002,** 43, 683-686.
7. Gareau, Y.; Pellicelli, J.; Laliberté, S.; Gauvreau, D. *Tetrahedron Lett.* **2003,** 44, 7821-7825.
8. Blotny, G. *Tetrahedron Lett.* **2003,** 44, 1499-1501.
9. Meinzer, A.; Breckel, A.; Thaher, B. A.; Manicone, N.; Otto, H.-H. *Helv. Chim. Acta* **2004,** 87, 90-95.
10. Nishiguchi, A.; Maeda, K.; Miki, S. *Synthesis* **2006,** 4131-4134.
11. Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *Synlett* **2009,** 2773-2776.

12. (a) Humljan, J.; Gobec, S. *Tetrahedron Lett.* **2005,** 46, 4069-4072; (b) Ishii, A.; Kashiura, S.; Oshida, H.; Nakayama, J. *Org. Lett.* **2004,** 6, 2623-2626.
13. Kværnø, L.; Werder, M.; Hauser, B. A.; Carreira, E. M. *Org. Lett.* **2005,** 7, 1145-1149.
14. Meinzer, A.; Breckel, A.; Thaher, B. A.; Manicone, N.; Otto, H.-H. *Helv. Chim. Acta* **2004,** 8, 90-94.
15. Prakash, G. K. S.; Mathew, T.; Panja, C.; Olah, G. A. *J. Org. Chem.* **2007,** 72, 5847-5850.
16. (a) Veisi, H. *Synthesis* **2010,** 2631-2635; (b) Veisi, H. *Tetrahedron Lett.* **2010,** 51, 2109-2114; (c) Veisi, H.; Ghorbani-Vaghei, R.; Eskandari, H.; Hemmati, S.; Rezaei, A.; Hajinazari, S.; Heidari Far, M. R.; Entezari, A. *Phosphorus Sulfur Silicon Relat. Elem.* **2011,** 186, 213-219.
17. Pu, Y.-M.; Christesen, A.; Ku, Y.-Y. *Tetrahedron Lett.* **2010,** 51, 418-421.