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Synthesis of Sulfonic Acid Derivatives by Oxidative Deprotection of Thiols Using *tert*-Butyl Hypochlorite

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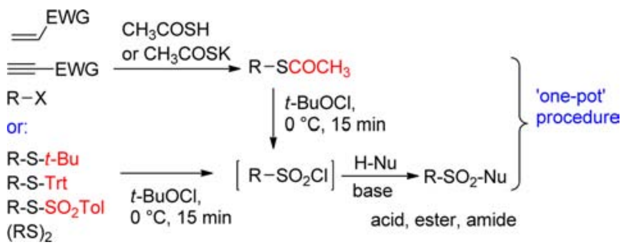
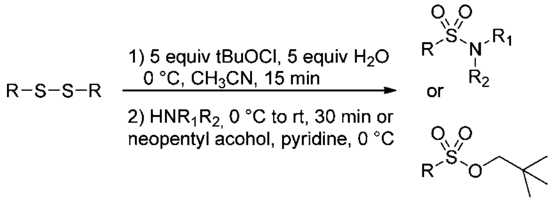
ABSTRACT



Starting from alkyl halides or Michael acceptors, thioacetates were prepared *in situ* and further treated with *t*-BuOCl, affording the corresponding sulfonyl chlorides which were trapped with nucleophiles such as water, alcohol, or amines. The three steps can be achieved in a one-pot procedure. Oxidative deprotection also proved to be efficient with *S*-trityl and *S*-*tert*-butyl groups, making it a convenient route toward cysteic acid derivatives.

Sulfonic acid derivatives have always been the subject of intensive research in organic synthesis. Sulfonamides exhibit numerous biological properties, and they are most well-known as antibacterial compounds.[1] Sulfonic esters are widely used as intermediates for nucleophilic displacement of alcohols, and sulfonic acid salts are among the most efficient solubilizing groups. Therefore, there is still much ongoing research in this area. The common precursor for such compounds generally consists of the sulfonyl chloride, most often obtained via chlorination of the parent sulfonic acids with harsh, HCl-generating reagents such as PCl_5, $SOCl_2$, $POCl_3$, and triphosgene, which are not compatible with sensitive functional groups or require difficult purifications. Milder methods, for instance using cyanuric chloride[2] or $PPh_3{\cdot}Cl_2$,[3] also give good results, however with concomitant formation of stoichiometric amounts of byproducts. On the other hand, oxidative processes, generally starting from thiols or disulfides, are widely used since they afford a better scope of functional groups on the substrates. The most widely used method consists of bubbling gaseous Cl_2 into an aqueous or a biphasic mixture containing thiols.[4]

Scheme 1. Oxidation of Disulfides



Although high yields are generally obtained, this method is not safe and the reaction medium is highly acidic and oxidizing. Thus, other methodologies using milder reagents[5]

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(1) Obreza, A.; Gobec, S. *Curr. Med. Chem.* **2004**, *11*, 3263.
(2) Blotny, G. *Tetrahedron Lett.* **2003**, *44*, 1499.
(3) Kataoka, T.; Iwama, T.; Setta, T.; Takagi, A. *Synthesis* **1998**, 423.

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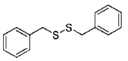
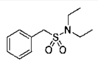
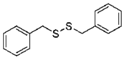
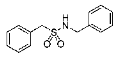
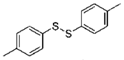
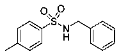
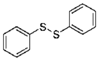
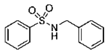
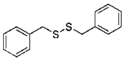
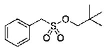
Table 1. Oxidation of Disulfides

entry	disulfide	product	nr	yield %
1			**1**	95
2			**2a**	96
3			**3**	96
4			**4**	88
5			**2b**	78

have been developed during the past decade, such as TMSCl/KNO_3,[5a] $ZrCl_4/H_2O_2$,[5b,c] trichloroisocyanuric acid,[5d] and *N*-chlorosuccinimide.[5]As we needed a traceless, organic solvent-soluble reagent, we turned our attention toward *t*-BuOCl. This reagent is commercially available; however, it can be very easily prepared using bleach and *t*-BuOH in acetic acid and can be stored for months at 4 °C over a 50 g scale. Its handling is safe provided that there is neither contact with rubber or reducing agents nor prolonged exposure to direct sunlight. In addition, one of its advantages relies on its ability to release the basic *tert*-butoxide anion, thus avoiding the use of an additional base to neutralize HCl, as required with Cl_2 oxidations. Moreover, *t*-BuOH, isobutene, or *tert*-butyl chloride are the final byproducts; thus a simple concentration *in vacuo* affords ready-to-use, clean sulfonyl chlorides.

First, we sought the optimal conditions for the oxidation, using dibenzyl disulfide as a model substrate (Scheme 1). For more convenience, we preferred to trap the sulfonyl chloride with benzylamine in order to obtain stable and easy-to-purify sulfonamides. In a preliminary experiment, we observed that treatment of dibenzyl disulfide with the minimum amount of *t*-BuOCl required (5 molar equiv) gave a 60% conversion. We presumed that the oxygen atoms of the sulfonyl chloride arose from the *tert*-butoxide anion with further isobutene elimination. In order to achieve a faster transformation of $S^+{-}Cl$ to S=O bonds, we added a stoichiometric amount of water, i.e. 5 molar equiv (Table 1). The use of water was also proposed with TCCA[5d] and *N*-chlorosuccinimide.[6]

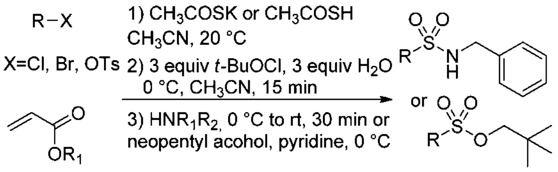
Under those conditions, the oxidation proceeded at 0 °C in a very short reaction time (15 min). Further quenching with excess diethylamine or benzylamine afforded the expected sulfonamides with high yields (88–96%, Table 1, entries 1–4). We also checked the suitability of this method for the formation of the stable neopentyl ester (entry 5); in this case pyridine was added to afford the esterification. Among various solvents that we tried, i.e. chloroform, dichloromethane, toluene, acetonitrile, and 1,4-dioxane, acetonitrile was chosen because of the high yields and good dissociative properties required for further one-pot substitution–oxidation reactions.

Moreover, as most thiols and disulfides are stench reagents, we were even more interested in developing a one-pot methodology for the nucleophilic introduction of the sulfur atom by means of a thioacetate, followed by *t*-BuOCl oxidation and trapping of the sulfonyl chloride with alcohols or amines.

Recently, another group[6a] has published an efficient method for the straight conversion of thioesters into sulfonyl chlorides, using *N*-chlorosuccinimide. We tested this reagent for the oxidation of benzyl thioacetate and observed a good yield of sulfonyl chloride. However, as an excess (4 equiv) of reagent was used, further trapping with benzylamine yielded stoichiometric amounts of the imine $PhCH{=}N{-}CH_2Ph$, as a result of the oxidation of the amine. Surprisingly, with 3 equiv of NCS, the sulfonyl chloride was cleanly obtained, but further trapping with benzylamine only afforded a 20% yield of sulfonamide. When using *t*-BuOCl, 3 equiv also afforded a complete oxidation, and any excess of the reagent and side products could be evaporated from the crude reaction medium. As we needed a reactive and versatile reagent, we kept *tert*-butyl hypochlorite as the oxidizing agent.

Having these conditions in hand, we focused on one-pot reactions, which would include the preliminary formation of thioacetates in the reaction sequence (Scheme 2). As listed in Table 2 (entry 1) a preliminary attempt with preformed benzyl thioacetate gave a 90% yield from oxidation/trapping, using 3 equiv of *t*-BuOCl at 0 °C. Then, we examined the formation of thioesters by means of nucleophilic substitution with potassium thioacetate. The *in situ* formation of this substrate from benzyl bromide and CH_3COSK (1:1 ratio) followed by the same oxidative procedure afforded a slightly lower 80% yield (entry 2).

Scheme 2. One-Pot Reactions



As expected, less reactive, nonbenzylic alkyl substrates gave modest yields (entries 3–6). The nature of the leaving group (bromide vs tosylate) did not have a significant influence on the yields. Interestingly, displacement of halide with potassium thiotosylate, followed by oxidation with 3 equiv of *t*-BuOCl, gave an excellent yield of sulfonyl chloride. However the use of this substrate is limited due to the concomitant formation of tosyl chloride (entry 7).

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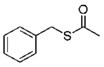
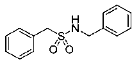
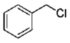
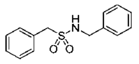
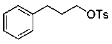
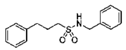
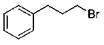
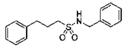
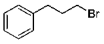
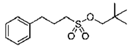
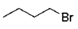
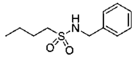
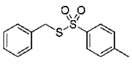
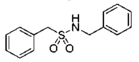
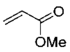
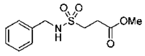
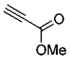
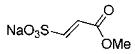
(5) (a) Prakash, G. K. S.; Mathew, T.; Panja, C.; Olah, G. A. *J. Org. Chem.* **2007**, *72*, 5847–5850. (b) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287–9291. (c) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *Synlett* **2009**, 2773–2776. (d) Massah, A. R.; Sayadi, S.; Ebrahimi, S. *RSC Adv.* **2012**, *2*, 6606.

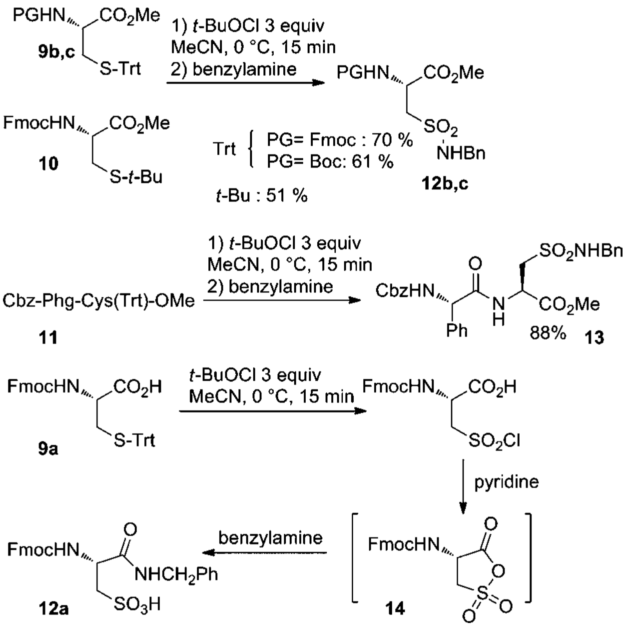
(6) (a) Nishiguchi, A.; Maeda, K.; Miki, S. *Synthesis* **2006**, *24*, 4131. (b) Veisi, H.; Ghorbani-Vagheit, R.; Hemmatia, S.; Mahmoodic, J. *Synlett* **2011**, 2315–2320.

Table 2. One-Pot Formation of Sulfonamides

entry	substrate	product	nr	yield %
1			**2a**	90[a]
2			**2a**	80
3			**5a**	64
4			**5a**	52
5			**5b**	33
6			**6**	46
7			**2a**	95[a]
8			**7**	42
9			**8**	30[b]

[a] Previously prepared thioester as the substrate. [b] Water/NaOAc as nucleophile.

Scheme 3. Cysteic Acid Derivatives



Considering that thioesters may also be readily prepared via Michael addition, we examined the one-pot reaction of thioacetic acid onto ethyl acrylate or methyl propiolate followed by the oxidation in the same solvent (CH_3CN). In this case, there is a need for a 1:1 molar ratio of the initial reagents. Upon completion of the addition (TLC), the reaction medium was cooled to 0 °C and treated under the previous conditions. The expected sulfonamides were obtained, though with modest yields, whereas NMR of the crude reaction mixtures before trapping showed a complete and clean formation of the sulfonyl chlorides. In the case of methyl propiolate, the sodium sulfonate was targeted, in order to avoid the possible Michael addition of the amine on the residual activated double bond. As an accurate amount of sodium hydroxide may be difficult to measure, we used an exact stoichiometric amount of sodium acetate as the source of the sodium cation, in the presence of water.

Eventually, we turned our attention toward the use of this oxidative deprotection method in the field of amino acid derivatives. Cysteine is an important and common amino acid, and its oxidized derivative cysteic acid is well-known. It can be used as a strong solubilizing group or as a nonprotonable, stable isostere of aspartate.[7] When purchased from chemical suppliers for solid-phase synthesis, cysteine is often provided under its *S*-trityl protected form. As *S*-Trt deprotections are performed under strong acidic conditions, we thought that the intermediate chlorosulfonium $-S^+(Cl)$-Trt could easily release the trityl cation. As depicted in Scheme 3, we observed a rapid oxidative deprotection with subsequent amidification using the same protocol, affording protected cysteic acid sulfonamides **12b,c**. Interestingly, even the very stable *tert*-butyl group could be deprotected during the oxidation process. It is worth noting that, when replacing acetonitrile with THF, our method is suitable for *N*-Boc-bearing substrates. Indeed, the electrophilic cleavage of *S*-Trt or *S*-*t*-Bu by *t*-BuOCl is selective of the sulfur atom, making our method compatible with a *N*-Boc protecting group. As expected, the *N*-Fmoc protecting group remained unchanged during the oxidation process, though some deprotection occurred during the reaction with benzylamine. A peptidic substrate is also compatible with this method, for instance the dipeptide Cbz-Phg-Cys(Trt)-OMe gave a good 88% yield of the corresponding cysteic acid derivative **13**. With the aim of finding a clean route toward peptide coupling with the formation of water-soluble cysteic acid containing peptides, we used the sulfonyl chloride as an internal coupling agent for the carboxylic acid. Thus, treating the intermediate acid/sulfonyl chloride with pyridine prior to coupling with the amine would give rise to the cyclic carboxysulfonic anhydride **14** postulated in Scheme 3.

Pleasingly, the formation of the carboxamide, although with a low yield after reversed-phase chromatography, gave support to this proposal. However, as solid-phase peptide syntheses generally use a high excess of the activated acid, we can expect better yields under solid-phase conditions.

In this work, we developed a new, versatile, and easy-to-use oxidation method for the formation of sulfonyl chlorides, using *t*-BuOCl as a cheap and rather safe reagent. As its reactivity is higher than observed with other chlorinating agents, it allowed the in situ *S*-deprotection of thioesters, *S*-trityl and even *S*-*tert*-butyl thioethers, with concomitant oxidation and subsequent reaction with nucleophiles, making the method particularly convenient for amino acid derivatives.

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(7) (a) Zhang, L.; Tam, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 2363. (b) Bischoff, L.; David, C.; Roques, B. P.; Fournie-Zaluski, M.-C. *J. Org. Chem.* **1999**, *64*, 1420.

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Supporting Information Available. Experimental procedures and full analytical, spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.