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Chlorotrimethylsilane−Nitrate Salts as Oxidants: Direct Oxidative Conversion of Thiols and Disulfides to Sulfonyl Chlorides

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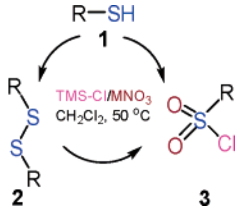
Received May 1, 2007

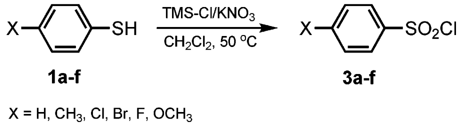


A mixture of nitrate salt and chlorotrimethylsilane is found to be a mild and efficient reagent for the direct oxidative conversion of thiols (**1**) and disulfides (**2**) to the corresponding sulfonyl chlorides (**3**) in excellent yields through oxidative chlorination. Sulfides and sulfoxides were also found to undergo oxidation to sulfones under similar reaction conditions. In most cases these reactions are highly selective, simple, and clean, affording products in high yield and purity.

Recently, we have achieved regioselective nitration of arylboronic acids using chlorotrimethylsilane and nitrate salts.[1] Ipso-substituted nitroaromatics were obtained in high yields and purity in most of these reactions. Since most of the nitrating agents have oxidizing properties, we decided to examine the oxidizing property of this reagent system more closely. One of the important oxidation reactions in synthetic organic chemistry is oxidation of sulfur compounds. Most common methods involve the use of peroxy compounds such as peroxy acids, hydrogen peroxide, etc. Oxidative chlorination of sulfur compounds to sulfonyl chlorides serves as an important step in organic synthesis. Sulfonyl chlorides are used in the production of detergents, ion exchange resins, elastomers, pharmaceuticals, dyes, herbicides, as mild alkylating agents, and as intermediates in the production of sulfonic acid amide and esters.[2] Various methods for the oxidative chlorination of sulfur compounds (thiols, sulfides, thioacetates, thiocarbamates, etc.) to sulfonyl chlorides are known.[3] However, many of these reactions involve stepwise oxidation followed by chlorination giving low yields and are not convenient and safe due to the use of hazardous and noxious reagents.

Use of *N*-chlorosuccinimide with thiol derivatives for the synthesis of sulfonyl chlorides has been reported by Nishiguchi et al.[4] and Kim et al.[5] It also has been found by Sohmiya et al. that alkyl and aryl benzyl sulfides react with iodosobenzene and hydrogen chloride-treated silica gel to give the corresponding alkyl and aryl sulfonyl chlorides.[6] This method of preparation takes longer and the reaction requires the presence of specific functional groups such as benzyl or substituted benzyl groups in the substrate. Use of nitrate salts with SO_2Cl_2 to give the sulfonyl chloride from thiols has been reported.[3f] In most of these methods the separation and purification of the products are very tedious due to undesirable side reactions resulting in lower selectivity and yields.

SCHEME 1. Oxidative Chlorination of Thiols to Sulfonyl Chlorides with TMS-Cl/KNO$_3$



Herein, we report a simple and convenient method for the direct oxidative chlorination of thiols and disulfides to the corresponding sulfonyl chlorides using nitrate salt and chlorotrimethylsilane as a reagent system. It is further found that sulfides and sulfoxides under suitable conditions undergo oxidation to their respective sulfones. In most cases, products obtained need no further purification. Removal of the solvent from the reaction mixture provides analytically pure product.

To utilize the oxidizing property of the "TMS-Cl/KNO$_3$" system, first the thiols (**1a**−**f**) were subjected to oxidation with the TMS-Cl/nitrate salt system. Interestingly, oxidative chlorination of the substrates occurred resulting in the direct formation of the corresponding arene sulfonyl chlorides (**3a**−**f**) in good yields (Scheme 1). In all the cases studied arene sulfonyl chlorides could be obtained in high purity by filtration and evaporation of the solvent without further purification.

Since many arenesulfonyl chlorides are susceptible to hydrolysis during workup resulting in tedious purification proce-

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(1) Prakash, G. K. S.; Panja, C.; Mathew, T.; Surampudi, V.; Olah, G. A. *Org. Lett.* **2004**, *6*, 2205.

(2) (a) Green, T. W.; Wuts, P. G. M. *Protective groups in organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1999. (b) Kociensky, P. J. *Protecting Groups*; Thieme: New York, 1994. (c) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339. (d) Brewster, J. H.; Ciotti, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 6214. (e) Blotny, G.; Biernat, J. F.; Taschner, E. *Liebigs Ann. Chem.* **1963**, *663*, 195. (f) Moore, J. D.; Herpel, R. H.; Lichtsinn, J. R.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 105. (g) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (h) Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 1145. (i) Lassalle, G.; Galtier, D.; Galli, F. European patent 643047, 1995. (j) Lezina, O. M.; Kuchin, A. V.; Rubtsova, S. A. Russian patent 2289574, 2006.

(3) (a) Monnee, M. C.; Marijne, M. F.; Brouwer, A. J.; Liskamp, R. M. *Tetrahedron Lett.* **2000**, *41*, 7991. (b) Piatek, A.; Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **2002**, *85*, 1973. (c) Humljan, J.; Gobec, S. *Tetrahedron Lett.* **2005**, *46*, 4069. (d) Kværnø, L.; Werder, M.; Hauser, H.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 1145. (e) Meinzer, A.; Breckel, A.; Thaher, B. A.; Manicone, N.; Otto, H.-H. *Helv. Chim. Acta* **2004**, *87*, 90. (f) Park, Y. J.; Shin, H. H.; Kim, Y. H. *Chem. Lett.* **1992**, 1483. (g) Schindler, W. *Helv. Chim. Acta* **1957**, *40*, 2148. (h) Sandler, S. R.; Karo, W. In *Organic Functional group Preparations*; Academic Press: New York, 1983; Vol. I, p 630. (i) Langler, R. F. *Can. J. Chem.* **1976**, *54*, 498. (j) Grossert, J. S.; Langler, R. F. *Can. J. Chem.* **1977**, *55*, 407. (k) Langler, R. F.; Marini, Z. A.; Spalding, E. S. *Can. J. Chem.* **1979**, *57*, 3193. (l) Douglass, I. B. *J. Org. Chem.* **1974**, *39*, 563.

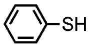
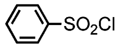
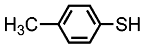
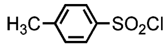
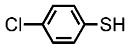
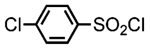
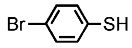
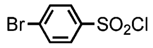
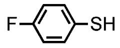
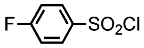
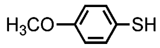
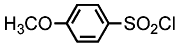
(4) Nishiguchi, A.; Maeda, K.; Miki, S. *Synthesis* **2006**, 4131.

(5) Kim, D. W.; Ko, Y. K.; Kim, S. H. *Synthesis* **1992**, 1203.

(6) Sohmiya, H.; Kimura, T.; Fujita, M.; Ando, T. *Tetrahedron* **1998**, *54*, 13737.

10.1021/jo070907g CCC: $37.00

TABLE 1. Oxidative Chlorination of Aryl Thiols

entry	thiol (**1a-f**)	time (h)	sulfonyl chloride (**3a-f**)	yield (%)
a		1		85
b		2		85
c		2.5		88
d		2		90
e		1		95
f		1		80

dures, the presently developed method appears to be highly useful. Table 1 shows the results of the oxidative chlorination of some arene thiols (**1a**−**f**). Suitable conditions for these reactions were explored and found to be 1−3 h at 50 °C. At room temperature reactions required longer time and often resulted in a mixture of products.

An investigation of the mechanistic aspects of oxidative chlorination of thiols (**1**) showed the main intermediate to be the corresponding disulfide (**2**). When the progress of reactions was monitored at different time intervals by TLC and GCMS, formation of disulfides (**2**) was observed. The reactions were carried out slowly at room temperature and the disulfides (**2**) were separated in some cases. To further confirm the intermediacy of the disulfides in the oxidative chlorination of thiols, reactions were repeated with different symmetric disulfides. When disulfides themselves were reacted under similar reaction conditions, oxidative chlorination took place as expected and we obtained exclusively the corresponding sulfonyl chlorides (Scheme 2). All reactions resulted in the formation of the corresponding sulfonyl chlorides in high yields, in expected stoichiometric amounts (Table 2). This shows that sequential oxidation of the thio function followed by S−S bond cleavage and subsequent chlorination occurs during the direct conversion of thiols to sufonyl chlorides.

Previous studies by Sohmiya et al.[6] showed that the ease of cleavage of the C−S bond with the neighboring function (S and C of the benzyl group) is important in their reactions. However, disulfides gave lower yields and thiols gave unidentified materials showing that the iodosobenzene/HCl reagent system is unusually strong for their conversion. Results of our reactions, in contrast, clearly demonstrate that the "TMS-Cl/nitrate salt" system acts as a very effective selective reagent for the conversion of thiols (**1**) and disulfides (**2**) to their respective sulfonyl chlorides (**3**) in good yields.

SCHEME 2. Oxidative Chlorination of Disulfides to Sulfonyl Chlorides with TMS-Cl/KNO$_3$

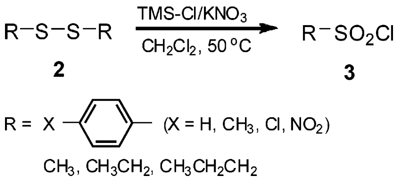
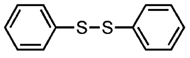
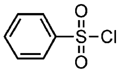
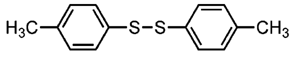
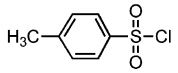
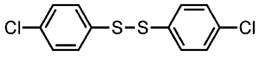
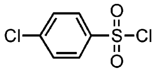
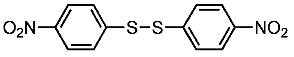
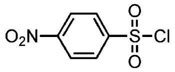
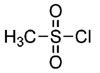
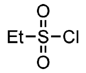
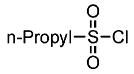


TABLE 2. Oxidative Chlorination of Disulfides to Sulfonyl Chlorides

entry	disulfide (**2**)	time (h)	sulfonyl chloride (**3**)	yield (%)
a		6		85
b		4		88
c		8		95
g[a]		15		85
h	$H_3C{-}S{-}S{-}CH_3$	8	 $H_3C{-}SO_2{-}Cl$	90
i	Et−S−S−Et	6	 Et−SO_2−Cl	90
j	n-Propyl−S−S−n-Propyl	4	 n-Propyl−SO_2−Cl	98

[a] NH_4NO_3 was used.

Scheme 3 shows the suggested mechanistic pathway for the formation of sulfonyl chlorides from the thiols (**1**) and disulfides (**2**). Use of chlorotrimethylsilane in conjunction with inorganic salts as reagents for various organic oxidations and other reactions is well studied.[7] Chlorotrimethylsilane is known to react with nitrate salts to give trimethylsilyl nitrate (**5**), which acts as an efficient oxidizing agent.[8,9] Lee et al. have also studied the formation of trimethylsilyl nitrate (**5**) from the TMS-Cl/nitrate salt system and its role in the conversion of anilines to aryl halides and deoximation of aldoximes and ketoximes.[10]

Chlorination of thiols (**1**) leads to the formation of sulfenyl chloride (**6**), which gives the corresponding symmetric disulfide (**2**), similar to the chlorination of thiols by sulfuryl chloride.[3f] To confirm this route, we have carried out chlorination of benzenethiol (**1a**) using chlorotrimethylsilane at 50 °C (in the absence of nitrate salt). Observation by GCMS showed the formation of the disulfide (**2a**) through the intermediacy of sulfenyl chloride (**6**). After 2 h, most of the thiol (**1a**) was converted to disulfide (**2a**). Disulfide (**2a**) can interact with trimethylsilyl nitrate (**5**) to give rise to an unstable sulfenyl nitrate intermediate (**7**) and trimethylsilyl thiol derivative **8** (Scheme 3, path a). Topping et al. have studied in detail the formation of sulfenyl nitrate intermediate (**7**) and its behavior under thermal conditions.[11] A mechanism involving the decomp-

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(7) Vankar, P. S.; Reddy, M. V. R.; Vankar, Y. D. *Org. Prep. Proced. Int.* **1998**, *30*, 373 and references therein.

(8) Schmidt, M.; Schmidbauer, H. *Angew. Chem.* **1959**, *71*, 220.

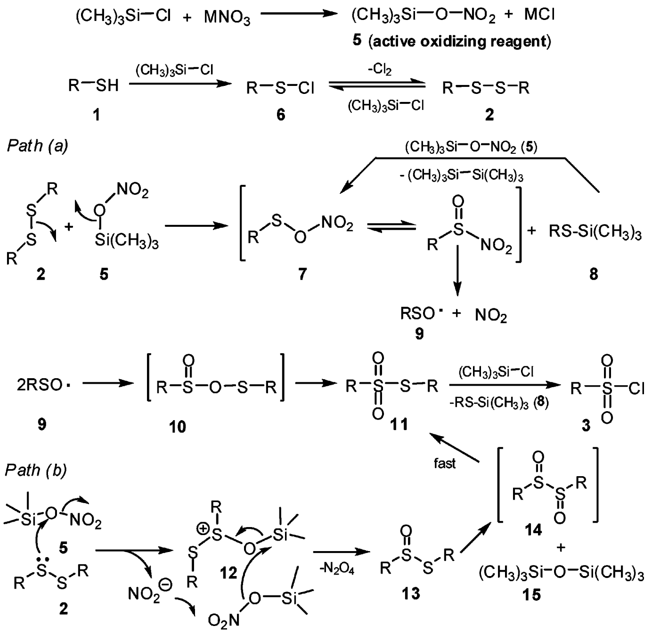
(9) (a) Olah, G. A.; Ramaiah, P.; Sandford, G.; Orlinkov, A.; Prakash, G. K. S. *Synthesis* **1994**, 468. (b) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration*; Wiley-Interscience: New York, 1989; p 42.

(10) (a) Lee, J. G.; Kwak, K. H.; Hwang, J. P. *Tetrahedron Lett.* **1990**, *31*, 6677. (b) Lee, J. G.; Cha, H. T. *Tetrahedron Lett.* **1992**, *33*, 3167.

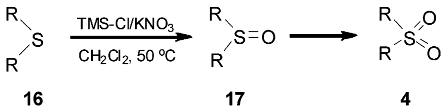
(11) Topping, R. M.; Kharasch, M. M. *J. Org. Chem.* **1962**, *27*, 4353.

(12) (a) Chau, M. M.; Kice, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 7711. (b) Oae, S.; Kim, Y. H.; Takata, T.; Fukushima, D. *Tetrahedron Lett.* **1977**, 1195. (c) Oae, S.; Takata, T.; Kim, Y. H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2484. (d) Oae, S.; Shinhama, K.; Fujimori, K.; Kim, Y. H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 775.

SCHEME 3. Mechanism of Oxidative Chlorination with TMS-Cl/Metal Nitrates



SCHEME 4. Oxidation of Sulfides and Sulfoxides to Sulfones



osition of sulfenyl nitrate (**7**) by a primary homolytic cleavage is proposed. This leads to the formation of the arylsulfinyl radical **9** followed by its coupling to form the intermediate **10**, which undergoes subsequent rearrangement to the thiosulfonate ester **11**.[10,11]

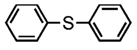
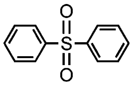
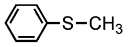
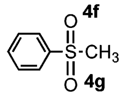
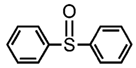
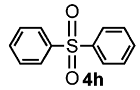
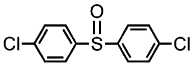
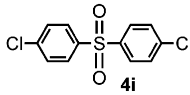
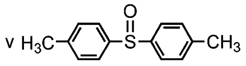
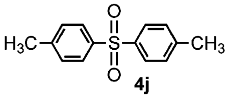
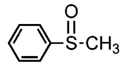
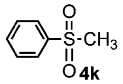
Thiosulfonate ester **11** can react with another molecule of TMS-Cl to give the product sulfonyl chloride (**3**) and the trimethylsilylated thiol (**8**), which reacts further with trimethylsilyl nitrate (**5**) to regenerate sulfenyl nitrate (**7**) followed by subsequent formation of **9** until all the disulfide is consumed. This explains the complete conversion of disulfides to 2 equiv of the sulfonyl chlorides. Another possible route (Scheme 3, path b) is the successive oxidation of both thio groups of the same disulfide molecule by trimethylsilyl nitrate to the intermediate **14** (symmetrical α-disulfoxide) that is known[11a] to undergo rapid isomerization to the thiosulfonate **11**, which can easily furnish sulfonyl chloride (**3**) as described earlier.

Since the formation of sulfonyl chlorides proved the potential of the present system as an effective and mild oxidizing agent, oxidation of sulfides (**16**) and sulfoxides (**17**) to the corresponding sulfones (**4**) was studied. Diphenyl sulfoxide (**17a**) with 2.2 equiv of the reagent, at room temperature, were quantitatively converted to diphenylsulfone (**4h**) in 24 h. This reaction can be achieved with 1 equiv of the reagent but it took 72 h for the completion of the reaction.

After optimizing the reaction conditions, we found that the best results were obtained with much shorter reaction times, with the reactions performed in a pressure tube at 50 °C. The results are summarized in Table 3. When KNO_3 was used as the metal nitrate, the reaction of substrates with α-H such as methyl phenyl sulfide and sulfoxide yielded a mixture with substantial amounts of chlorine substituted products. However, when NH_4NO_3 was used, α-chlorination is lowered and the yield of sulfone increased. With KNO_3 as the nitrate salt, formation of a silyl−enol ether type of intermediate may be preferred from sulfide and sulfoxide having α-H followed by further successive chlorination to give rise to different chlorinated products. Reactions of dialkyl sulfides and sulfoxides were also not clean due to the competing α-chlorination. The mechanistic explanation discussed for the oxidation of the thio group by pathway b (Scheme 3) in the case of disulfides (**2**) can explain the formation of sulfones (**4**) from the corresponding sulfides **16** and sulfoxides **17**. Therefore, the mechanism for the oxidation of sulfides and sulfoxides can be detailed as shown in Scheme 5.

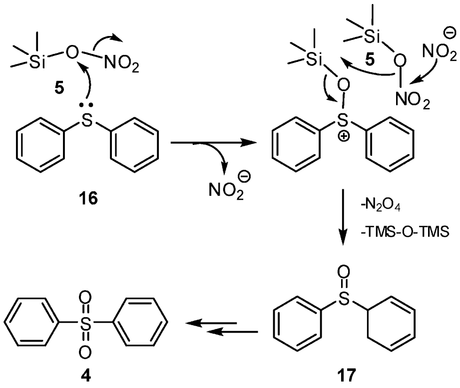
In conclusion, a specific selective oxidative protocol using the "TMS-Cl/nitrate salt" reagent system is found to be very useful for the direct conversion of mercaptans and disulfides to their corresponding sulfonyl chlorides in high yields. This reagent system is also found to be a mild and efficient oxidizing agent for the oxidation of sulfides and sulfoxides to the

TABLE 3. Oxidation of Sulfides and Sulfoxides to Sulfones[a]

entry	sulfide or sulfoxide (**16a,b & 17a-d**)	MNO_3	time (h)	sulfone (**4f-k**)	yield (%)
i	 **16a**	KNO_3	3.5	 **4f**	90
ii	 **16b**	NH_4NO_3	2	 **4g**	Mixture
iii	 **17a**	KNO_3	1.5	 **4h**	85
iv	 **17b**	KNO_3	2	 **4i**	82
v	 **17c**	KNO_3	1	 **4j**	90
vi	 **17d**	NH_4NO_3	2	 **4k**	Mixture

[a] TMS-Cl/MNO_3: 2.2 equiv for sulfoxides and 5 equiv for sulfides.

SCHEME 5. Mechanism of Oxidation of Sulfides and Sulfoxides to Sulfones



corresponding sulfones in good to excellent yields. The reaction is highly selective, simple, and clean in most cases.

Experimental Section

General Procedure for the Oxidation and Oxidative Chlorination Reaction. A mixture of thiols/sulfoxides (1 mmol) in dichloromethane (5 mL), nitrate salt (2.2 mmol), and TMSCl (2.2 mmol) was placed in a sealed glass tube (5 mmol of nitrate salt and TMSCl were used in the case of disulfides/sulfides). The heterogeneous mixture was stirred vigorously at 50 °C until the reaction went to completion (Monitored by TLC). After completion, the reaction mixture was cooled to room temperature and filtered and the filtrate was washed with water (2 × 10 mL) and brine solution (10 mL) and then dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure to obtain the products, in almost NMR grade purity. The products are well-known and are characterized by comparing their spectroscopic data with those of the authentic samples.

Acknowledgment. Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

Supporting Information Available: General experimental procedure and copies of $^{1}H/^{13}C/^{19}F$ NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070907G