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Poly(*N,N′*-Dichloro-*N*-ethyl-benzene-1,3-disulfonamide) and *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide as Efficient Reagents to Direct Oxidative Conversion of Thiols and Disulfide to Sulfonyl Chlorides

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Poly(*N,N′*-Dichloro-*N*-ethyl-benzene-1,3-disulfonamide) (PCBS) and *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide (TCBDA) were found to be a mild and efficient reagent 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, 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.

Key Words : Oxidative chlorination, Sulfonyl chloride, Thiol, Disulfide, *N*-Chloro sulfonamides

Introduction

Aryl and heteroarylsulfonyl chlorides were 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] β_3 receptor agonists,[3] and HCV polymerase inhibitors.[4]

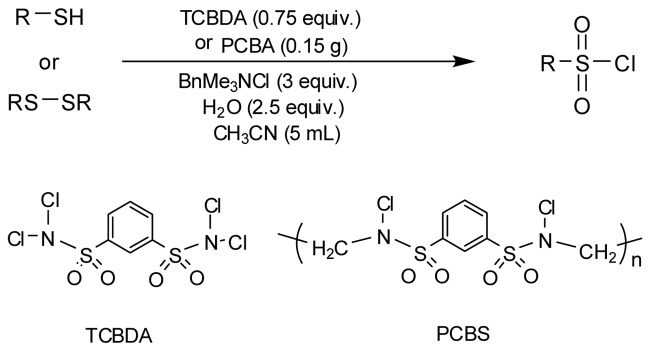
The development of simple, versatile, and environmentally friendly processes or methodologies for widely used organic compounds from readily available reagents is one of the major challenges for chemists in organic synthesis. Organic sulfur compounds are widespread in numerous natural products and widely 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] or 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.

Result and Discussions

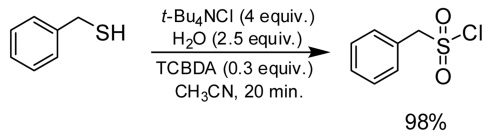
Therefore, the discovery of milder and practical routes for the synthesis of sulfonyl chlorides is highly desirable. As part of our continuing studies on the use of *N*-halo reagents in organic synthesis,[16,17] herein, we introduce for the first time TCBDA/$BnMe_3NCl/H_2O$ or PCBA/$BnMe_3NCl/H_2O$ as valuable reagents system for the direct oxidative chlorination of thiol and disulfide derivatives to the corresponding sulfonyl chlorides (Scheme 1).

Initially, we surmised that it might be possible to generate controlled amounts of Cl_2 in nonprotic organic solvents by mixing a *tetra*-alkylammonium chloride salt with *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide (TCBDA). We were pleased to find that treatment of *tetra*-butylammonium chloride (4 equiv), H_2O (2.5 equiv) with TCBDA (0.3 equiv) in CH_3CN (20 min, rt) provided a light yellow solution as a good oxidize chlorinating system to synthesis of benzylsolfunyl chlorides from benzyl thiol (1 equiv) under mild conditions (Scheme 2).

Using the above optimized reaction conditions; the reactions of various thiols were investigated. As shown in Table 1, aromatic thiols carrying either electron-donating or electron-

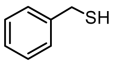
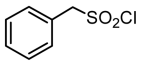
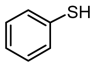
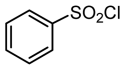
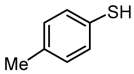
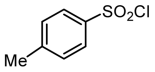
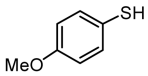
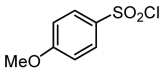
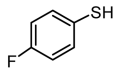
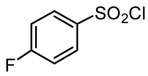
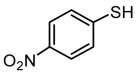
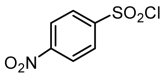
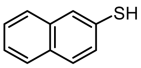
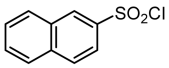
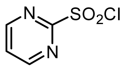
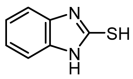
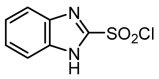
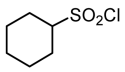
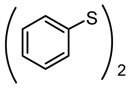
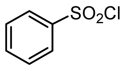
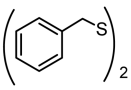
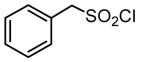
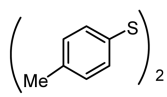
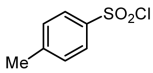
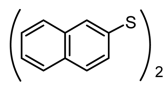
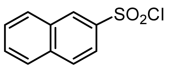
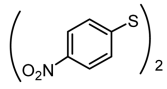
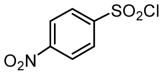
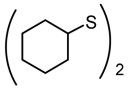
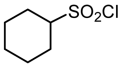


Scheme 1. Direct oxidative chlorination of thiol and disulfide derivatives.



Scheme 2. Synthesis of benzylsolfunyl chlorides from benzyl thiol.

Table 1. Oxidative Chlorination of Thiol and Disulfide Derivatives with TCBDA and PCBS

Entry	Thiol	Sulfonyl chloride[a]	TCBDA	PCBS
			Yield (%)	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 from their physical properties, comparison with authentic samples and by spectroscopic methods.

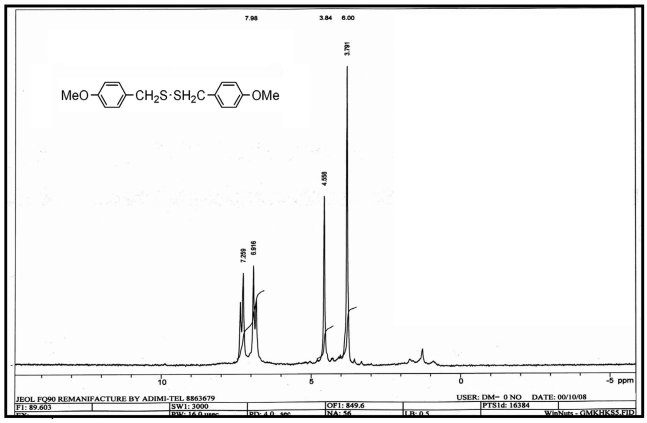


Figure 1. ^{1}H NMR spectrum (FT-90 MHz) of 4-methoxybenzyl disulfide in $CDCl_3$.

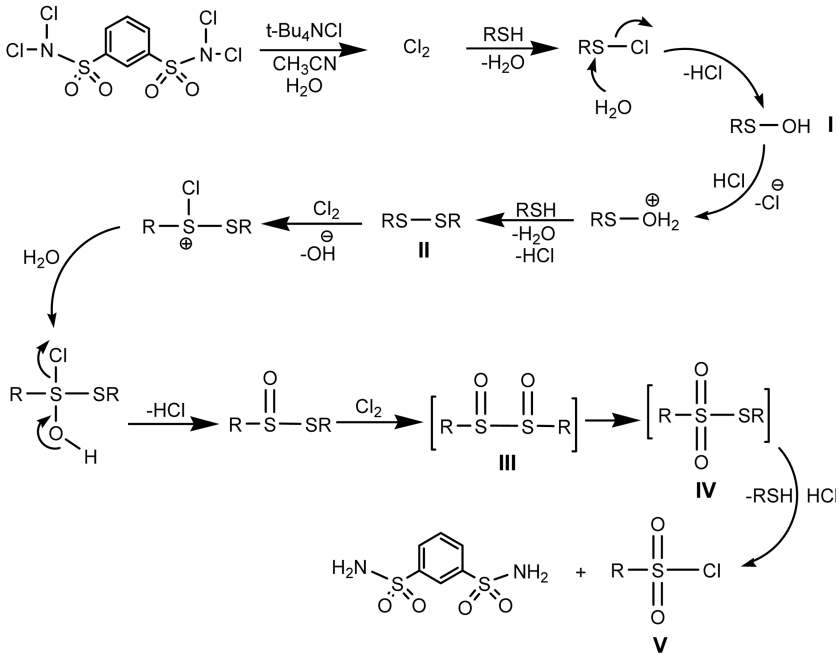
withdrawing substituents afforded excellent yields of products with high purity (monitored by ^{1}H NMR). Heterocyclic thiols, such as 2-mercaptopyrimidine and 2-mercaptobenzimidazole, were also investigated. Under the same conditions, the desired products were obtained in excellent yields (Table 1, entries 8 and 9). Furthermore, aliphatic compound such as cyclohexanethiol, also afforded the Sulfonyl chloride in excellent yield (Table 1, entries 10).

An investigation into the mechanistic aspects of oxidative chlorination of thiols showed the corresponding disulfide is 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 TCBDA in the presence of *tetra*-butylammonium chloride (1.5 equiv), H_2O (1.5 equiv) for 5 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 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 TCBDA (0.15 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 (Entry 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, and occurs during the direct conversion of thiols into the corresponding sulfonyl chlorides.

Also, we found that poly(*N,N'*-Dichloro-*N*-ethyl-benzene-1,3-disulfonamide) (PCBS) was suitable reagent for the conversion of thiols and disulfides to the corresponding sulfonyl chlorides in excellent yields under same conditions. The results were shown in Table 1 (entries, 1-16).

The possible mechanism for this transformation is shown in Scheme 3.[12] Molecular chlorine generated from TCBDA



Scheme 3. The possible mechanism for this transformation.

or PCBS and *t*-Bu$_4$NCl effects the oxidative chlorination. It is acceptable to assume that the thiol can chlorinate in the presence of chlorine. Therefore, the mechanism proceeds through hydroxylation of thiol leads to the formation of 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) that undergoes rapid isomerization to the thiosulfonate (IV), which can easily furnish sulfonyl chloride (V).

Conclusion

In conclusion, we have developed a simple & effective oxidative chlorination procedure for the synthesis of aryl or heteroaryl sulfonyl chlorides with poly(*N,N′*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) (PCBS) and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide (TCBDA) as a safe and inexpensive equivalent to chlorine gas. Many aromatic sulfur substrates (thiols and disulfides) can be converted to the corresponding arylsulfonyl chlorides in good to excellent yields, making it a superior to those described previously.

Experimental Section

All commercially available chemicals were obtained from Merck and Fluka companies, 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 are in δ (ppm). Infrared (IR) was conducted on a Perkin Elmer GX FT-IR spectrometer. All yields refer to isolated products.

(i) Procedure for the Preparation of Poly(*N,N′*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide [TCBDA]. A sample of white finely powdered poly(*N*-ethyl-benzene-1,3-disulfonamide) (1 g) or benzene-1,3-disulfonamide (1 g) was dissolved in a solution of NaOCl (50 mL, 14%), at 25 °C for 30 min. The color of the solution did not change. After this time, acetic acid (20 mL, 50%) was added to the solution. The insoluble chlorinated reagent was removed by filtration and washed with water (5 mL).

Analytical data for *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide: white solid, mp 145-147 °C, IR (KBr): 3050, 2950, 2900, 1570, 1462, 1417, 1377, 1304, 1167, 1082, 807, 776, 675 cm^{-1}, ^{1}H NMR ($CDCl_3$, FT-250 MHz): δ 7.95-8.09 (m, CH aromatic, 1H), 8.11-8.58 (m, CH aromatic, 2H), 8.79 (s, CH aromatic, 1H), m/e ($[M+H]^+$): 374, 339, 337, 321, 319, 305, 303, 272, 269, 267, 156, 154, 139, 125, 120, 104, 91, 77, 63. Anal. Calcd for $C_6H_4N_2S_2O_4Cl_4$: C, 19.25; H, 1.06; N, 7.48; S, 17.11. Found: C, 19.05; H, 1.16; N, 6.94; S, 16.28.

Analytical data for poly(*N,N′*-dichloro-*N*-ethyl-benzene-1,3-disulfonamide): white solid, mp 175-178 °C, IR (KBr): 3050, 2950, 2900, 1578, 1462, 1418, 1377, 1303, 1168, 1081, 809, 779, 674, 603, 570 cm^{-1}, ^{1}H NMR ($CDCl_3$, FT-250 MHz): δ 7.56-8.48 (b, CH aromatic).

(ii) General Procedures for the Conversion of Disulfide to Sulfony Chloride. To a stirred mixture of disulfide compound (1 mmol), *t*-Bu$_4$NCl (2 mmol), and water (1.5 mmol) in CH_3CN (5 mL) at 0 °C, *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide (0.3 mmol) or poly(*N,N′*-Dichloro-*N*-ethyl-benzene-1,3-disulfonamide) (0.25 g) was added as a solid in portions over 1-2 min. After the addition, the mixture was stirred for 20 min. until completion in room temperature. The mixture was filtered and filtrate was

evaporated under vacuum. Then, CH_2Cl_2 (10 mL) was added, and insoluble reagent was removed by filtration. The filtrate was evaporated under vacuum to afford the analytically pure product. All of the products are known compounds and characterized easily by comparison with authentic samples (^{1}H NMR, ^{13}C NMR, and mp).

(iii) General Procedures for the Conversion of Thiols to Sulfony Chloride. To a stirred mixture of Thiol compound (1 mmol), *t*-Bu_4NCl (4 mmol), and water (2.5 mmol) in CH_3CN (5 mL) at 0 °C, *N,N,N′,N′*-Tetrachlorobenzene-1,3-disulfonamide (0.3 mmol) or poly(*N,N′*-Dichloro-*N*-ethylbenzene-1,3-disulfonamide) (0.5 g) was added as a solid at portions over 1-2 min. After the addition, the mixture was stirred for 20 min. until completion in room temperature. The mixture was filtered and filtrate was evaporated under vacuum. Then, CH_2Cl_2 (10 mL) was added, and insoluble reagent was removed by filtration. The filtrate was evaporated under vacuum to afford the analytically pure product. All of the products are known compounds and characterized easily by comparison with authentic samples (^{1}H NMR, ^{13}C NMR, mp).

Analytical Data for Selected Compounds.

Phenylmethanesulfonyl Chloride (1): White crystals; mp 91-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.85 (s, 2H), 7.45-7.50 (m, 5H). Anal. Calcd for $C_7H_7ClO_2S$: C, 44.10; H, 3.70; Cl, 18.60; S, 16.82. Found: C, 44.20; H, 3.59; Cl, 18.25; S, 16.90; Mass (*m/z*): 190.0352.

4-Nitrobenzenesulfonyl Chloride (6): White crystals; mp 72-74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J = 8.8 Hz, 2H), 8.45 (d, J = 8.9 Hz, 2H). Anal. Calcd for $C_6H_4ClNO_4S$: C, 32.52; H, 1.82; Cl, 16.00; N, 6.32; S, 14.47. Found: C, 32.65; H, 1.89; Cl, 15.67; N, 6.37; S, 14.57. Mass (*m/z*): 221.1202.

Cyclohexanesulfonyl Chloride (10): Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22-1.42 (m, 3H), 1.60-1.93 (m, 3H), 1.99-2.08 (m, 2H), 2.41-2.46 (m, 2H), 3.55 (tt, J = 3.5, 11.9 Hz, 1H). Mass (*m/z*): 183.0223.

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