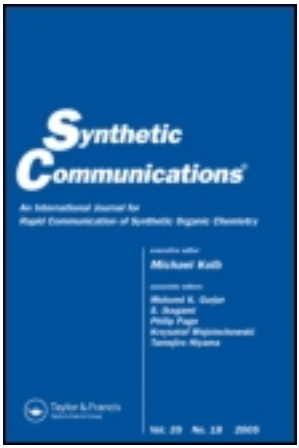

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 10 Jan 2011

To cite this article: Schuyler Antane, Ronald Bernotas, Yanfang Li, Robert McDevitt & Yinfa Yan (2004): Chloromethyl Sulfones from Sulfonyl Chlorides via a One-Pot Procedure, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:13, 2443-2449

To link to this article: http://dx.doi.org/10.1081/SCC-120039498

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 13, pp. 2443–2449, 2004

Chloromethyl Sulfones from Sulfonyl Chlorides via a One-Pot Procedure

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ABSTRACT

A simplified one-pot transformation of a diverse set of aryl- and heteroaryl-sulfonyl chlorides into the corresponding chloromethyl sulfones is described.

Key Words: Chloromethyl sulfones; One-pot procedure; Sulfinate salts; Sulfonyl chlorides.

INTRODUCTION

Chloromethyl sulfones have found use in the preparation of alkenes,[1] aziridines,[2] and epoxides.[3] Makosza[4a–d] has utilized chloromethyl phenyl

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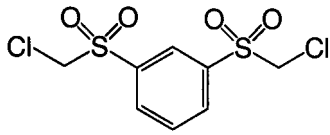
DOI: 10.1081/SCC-120039498 0039-7911 (Print); 1532-2432 (Online)

sulfone (**1**, A = Ph) and chloromethyl-*p*-tolyl sulfone (**1**, A = *p*-CH_3Ph) in vicarious nucleophilic substitution (VNS) reactions with nitroarenes (**2**) to afford VNS adducts (**3**). These adducts have been elaborated into both 3-sulfonyl-substituted indole derivatives (**4**: Z = CH)[4c,d] and the analogous indazoles (**4**: Z = N)[4e] (Sch. 1). Our interest in preparing a diverse set of 3-aryl/heteroarylsulfonyl-indoles and -indazoles **4** via VNS chemistry led us to investigate simplified methods of preparing a variety of aryl and heteroaryl chloromethyl sulfones (**1**).

Haloalkyl sulfones (e.g., **1**) are useful for preventing aquatic organisms from attaching to fishing nets and ship hulls,[5] in herbicide compositions,[6] and as bactericidals,[7] antifungals,[7] algaecides,[8] and insecticides.[9]

Chloromethyl sulfones (**1**) have been prepared by alkylation of sulfinate salts (**6**) with chloroform,[10] with bromochloromethane in the presence of aliquat[11] or, alternatively, in the presence of tetra-alkylammonium or phosphonium halides.[12] While there are relatively few commercially available sulfinate salts, such salts may readily be obtained from a sodium sulfite-mediated reduction of the corresponding sulfonyl chlorides under aqueous conditions.[13] In practice, this two-step procedure proved somewhat cumbersome due to the sulfinate salts' water solubility and hygroscopic nature, which made their isolation difficult. In exploring possible improvements to this two-step procedure, we have found that it was neither necessary nor desirable to isolate intermediate sulfinate salts (**6**). The aqueous reaction mixture containing the reduced sulfonyl chlorides could simply be treated with a phase transfer catalyst (PTC) and an excess of bromochloromethane to afford the desired chloromethylsulfones (Sch. 2). This PTC approach proved to be operationally convenient while generally maintaining good yields (60–80%). We have applied this method to a wide variety of sulfonyl chlorides summarized in Table 1.

In addition, we have found that more than one sulfonyl group can be present in the reactant. For example, 1,3-benzenedisulfonyl chloride was treated with two times the usual reagents to afford 1,3-*bis*-chloromethanesulfonylbenzene (**7**), albeit in a modest 20% yield.



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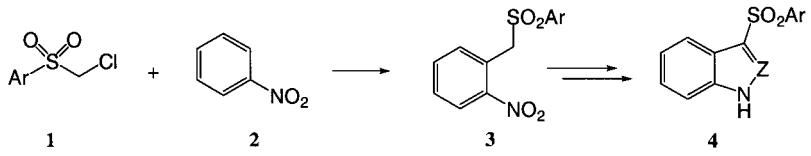
In summary, we have found a one-pot approach to the synthesis of a diverse group of chloromethyl sulfones from commercially available sulfonyl chlorides. Beyond the numerous preventative uses mentioned above, we have



1 2 3 4

Scheme 1.

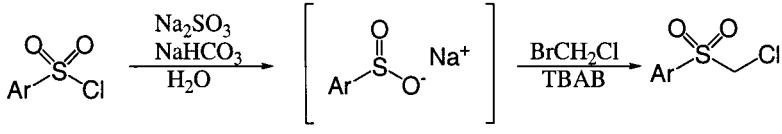
used these intermediates to produce a variety 3-arylsulfonyl- and 3-heteroarylsulfonyl indoles and -indazoles as intermediates for potential therapeutic agents, which we will describe in due course.

EXPERIMENTAL

^{1}H NMR spectra (400 MHz) were recorded in d_6-DMSO using a Varian Unity plus spectrometer. Mass spectra were recorded on a Finnigan Trace MS or a Micromass LCT. Bromochloromethane, sodium sulfite, tetra-butylammonium bromide, and most aryl/heteroaryl sulfonyl chlorides (**5**) were available from Aldrich. Other sulfonyl chlorides were obtained from Fluka (**5d**), Maybridge (**5f**, **5g**), Acros (**5j**), and Lancaster (**5k**).

General Procedure

A stirred mixture of sulfonyl chloride **5** (4.4 mmol), sodium sulfite (1.03 g, 8.2 mmol), and sodium bicarbonate (0.726 g, 8.06 mol) in water (5 mL) is heated at ca. 100°C for 1 hr. The crude sodium sulfinate solution is allowed to cool for 30 min, and then treated with bromochloromethane (5 mL, 76.9 mmol) and tetra-*N*-butyl ammonium bromide (0.140 g, 0.4 mmol). The resultant mixture is heated at 75°C overnight. All solvents are removed in vacuo at 50°C. The residue is diluted with dichloromethane (or ethyl acetate) and filtered through a plug of silica gel to give the desired chloromethyl



5a-m **6** **1a-m**

Scheme 2.

Table 1. Preparation of chloromethyl sulfones **1**.

$ArSO_2Cl$	Ar	Yield of **1** (%)
5a	1-Naphthalene	63
5b	2-Fluorobenzene	77
5c	2-(Trifluoromethyl)-benzene	31
5d	1-(8-Quinoline)	64
5e	2-[5-Chloro-thiophene]	76
5f	2-[5-Chloro-3-methyl-benzothiophene]	18
5g	4-[2,1,3-benzothiadiazole]	72
5h	4-Iodobenzene	75
5i	3,4-Dimethoxybenzene	63
5j	4-Methanesulfonylbenzene	71
5k	4-Bromo-2,5-difluoro-benzene	75
5l	3-Trifluoromethylbenzene	83
5m	2,4,6-Trimethylbenzene	29

sulfone of sufficient purity. In some cases, further purification by crystallization (**1j**: methanol; **1m**: hexanes) or by column chromatography (**1f**: hexanes/ethyl acetate) was required.

Examples

1-[(Chloromethyl)sulfonyl]naphthalene (1a). M.p. 94–96°C. ^{1}H NMR (d_6-DMSO): 8.66 (1H, d, $J = 7.9$ Hz), 8.43 (1H, d, $J = 8.2$ Hz), 8.30 (1H, d, $J = 7.3$ Hz), 8.19 (1H, d, $J = 8.1$ Hz), 7.73–7.83 (3H, m), 5.42 (2H, s). MS (EI) m/z: 240/242 ($M^{+\cdot}$). Anal. calcd for $C_{11}H_9ClO_2$: C, 54.89; H, 3.77. Found: C, 54.48; H, 3.74.

Chloromethyl-2-fluorophenyl sulfone (1b). Oil. ^{1}H NMR (d_6-DMSO): 7.88–7.94 (2H, m), 7.52–7.60 (2H, m), 5.37 (2H, s). MS (EI) m/z: 208/210 ($M^{+\cdot}$). Anal. calcd for $C_7H_6ClFO_2S$: C, 40.30; H, 2.90. Found: C, 40.24; H, 2.79.

Chloromethyl 2-(trifluoromethyl)phenyl sulfone (1c). M.p. 60–62°C. ^{1}H NMR (d_6-DMSO): 8.25–8.28 (1H, m), 8.12–8.14 (1H, m), 8.03–8.06 (2H, m), 5.33 (2H, s). MS (EI) m/z: 258/260 (M+.). Anal. calcd for $C_8H_6ClF_3O_2S$: C, 37.15; H, 2.34. Found: C, 37.28; H, 2.11.

8-[(Chloromethyl)sulfonyl]quinoline (1d). M.p. 140–142°C. ^{1}H NMR (d_6-DMSO): 9.13–9.14 (1H, m), 8.64 (1H, d, $J = 8.4$ Hz), 8.47–8.50 (2H, m), 7.89 (1H, t, $J = 7.58$ Hz), 7.78–7.81 (1H, m), 5.74 (2H, s). MS (EI) m/z: 242/244 (M + H). Anal. calcd for $C_{10}H_8ClNO_2S$: C, 49.69; H, 3.34; N, 5.80. Found: C, 49.32; H, 3.32; N, 5.69.

2-Chloro-5-[(chloromethyl)sulfonyl]thiophene (1e). M.p. 83–85°C. ^{1}H NMR (d_6-DMSO): 7.80 (1H, d, $J = 4.3$ Hz), 7.46 (1H, d, $J = 4.1$ Hz), 5.45 (2H, s). MS (EI) m/z: 230/232/234 ($M^{+\cdot}$). Anal. calcd for $C_5H_4Cl_2OS_2$: C, 25.98; H, 1.74. Found: C, 26.33; H, 1.74.

5-Chloro-2-[(chloromethyl)sulfonyl]-3-methyl-l-benzothiophene (1f). M.p. 159–161°C. ^{1}H NMR (d_6-DMSO): 8.14–8.17 (2H, m), 7.62–7.65 (1H, m), 5.41 (2H, s), 2.68 (3H, s). MS (EI) m/z: 294/296/298 ($M^{+\cdot}$). Anal. calcd for $C_{10}H_8Cl_2O_2S_2$: C, 40.69; H, 2.73. Found: C, 40.76; H, 2.56.

4-[(Chloromethyl)sulfonyl]-2,1,3-benzothiadiazole (1g). M.p. 142–144°C. ^{1}H NMR (d_6-DMSO): 8.58 (1H, d, $J = 8.8$ Hz), 8.42 (1H, d, $J = 7.2$ Hz), 7.98–8.01 (1H, m), 5.56 (2H, s). MS (EI) m/z: 248/250 ($M^{+\cdot}$). Anal. calcd for $C_7H_5ClN_2O_2S_2$: C, 33.81; H, 2.03; N, 11.26. Found: C, 33.66; H, 1.94; N, 11.08.

1-Chloromethanesulfonyl-4-iodo-benzene (1h). M.p. 170–172°C. ^{1}H NMR (d_6-DMSO): 8.07 (2H, d, $J = 8.5$ Hz), 7.65 (2H, d, $J = 8.7$ Hz), 5.29 (2H, s). MS (EI) m/z: 316 ($M^{+\cdot}$). Anal. calcd for $C_7H_6ClIO_2S$: C, 26.56; H, 1.91. Found: C, 26.55; H, 1.68.

4-Chloromethanesulfonyl-1,2-dimethoxy-benzene (1i). M.p. 96–98°C. ^{1}H NMR (d_6-DMSO): 7.48 (1H, d, $J = 8.5$ Hz), 7.36 (1H, s), 7.19 (1H, d, $J = 8.7$ Hz), 5.20 (2H, s), 3.84 (3H, s), 3.82 (3H, s). MS (EI) m/z: 250 ($M^{+\cdot}$). Anal. calcd for $C_9H_{11}ClO_4S_2$: C, 43.12; H, 4.42. Found: C, 43.22; H, 4.52.

1-Chloromethanesulfonyl-4-methanesulfonyl-benzene (1j). M.p. 177–179°C. ^{1}H NMR (d_6-DMSO): 8.17–8.24 (4H, dd, $J = 8.8$, 17.4 Hz), 5.43 (2H, s), 3.32 (3H, s). MS (ES) m/z: 266.9 ([M − H]−). Anal. calcd for $C_8H_9ClO_4S_2$: C, 35.75; H, 3.38. Found: C, 35.83; H, 2.97.

1-Bromo-4-chloromethanesulfonyl-2,5-difluoro-benzene (1k). M.p. 50–52°C. ^{1}H NMR (d_6-DMSO): 8.16–8.20 (1H, m), 7.81–7.84 (1H, m), 5.40 (2H, s). MS (EI) m/z: 304 ($M^{+\cdot}$). Anal. calcd for $C_7H_4BrClF_2O_2S$: C, 27.52; H, 1.32. Found: C, 27.86; H, 1.56.

1-Chloromethanesulfonyl-3-trifluoromethyl-benzene (1l). M.p. 66–68°C. ^{1}H NMR (d_6-DMSO): 8.25 (1H, s), 8.20 (2H, t, $J = 7.8$ Hz), 8.03 (1H, t, $J = 7.7$ Hz), 5.45 (2H, s). MS (EI) m/z: 258 ($M^{+\cdot}$). Anal. calcd for $C_8H_6ClF_3O_2S$: C, 37.15; H, 2.34. Found: C, 37.31; H, 2.24.

2-Chloromethanesulfonyl-1,3,5-trimethyl-benzene (1m). M.p. 89–91°C. ^{1}H NMR (d_6-DMSO): 7.09 (2H, s), 5.12 (2H, s), 2.57 (6H, s), 2.26 (3H, s). MS (EI) m/z: 232 ($M^{+\cdot}$). Anal. calcd for $C_{10}H_{13}ClO_2S$: C, 51.61; H, 5.63. Found: C, 51.63; H, 5.28.

1,3-*bis*-Chloromethanesulfonyl-benzene (7). M.p. 149–151°C. ^{1}H NMR (d_6-DMSO): 8.38 (1H, s), 8.34 (2H, d, $J = 7.8$ Hz), 8.03 (1H, t, $J = 7.9$ Hz), 5.45 (4H, s). MS (ES) m/z: 300.9 ([M − H]−). Anal. calcd for $C_8H_8BrCl_2O_4S_2$: C, 31.69; H, 2.66. Found: C, 32.07; H, 2.41.

ACKNOWLEDGMENT

Physical analysis was provided by Discovery Analytical Chemistry.

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Received in the USA March 3, 2004