The Use of *N,N*-Dimethylformamide-Sulfonyl Chloride Complex for the Preparation of Thiophenesulfonyl Chlorides

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Synopsis. A 1:1 *N,N*-dimethylformamide-SO_2Cl_2 complex was found to be a useful agent for the one-step preparation of thiophenesulfonyl chlorides.

Thiophenesufonyl chlorides, key intermediates of the syntheses of sulfur derivatives of thiophene, have been mostly prepared by the chlorosulfonation of thiophenes with chlorosulfuric acid.[1] In the reaction of acid-sensitive thiophenes, however, polymerization and the rearrangement and/or elimination of the substituent such as halogen on the thiophene ring disturb the formation of the desired sulfonyl chlorides. In addition, the thiophenesulfonic acids are formed as the main products in some cases, and further tedious procedures are needed for converting the sulfonic acids to the sulfonyl chlorides. It is also the case with an alternative method *via* sulfonation using SO_3-organic compound adducts.[2]

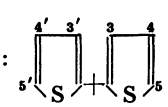
It has been briefly reported by Kojtcheff *et al.* that a 1:1 *N,N*-dimethylformamide (DMF)-SO_2Cl_2 complex serves as a chlorosulfonating agent depending on the substrate.[3] Despite the potential utility, little systematic study of the direct chlorosulfonation using DMF-SO_2Cl_2 complex seems to have been made. On searching for a simple and convenient procedure for the preparation of thiophenesulfonyl chlorides, we studied the reactions of some thiophene derivatives with the complex.

The reaction procedure simply consits of heating a mixture of the thiophene derivatives and the complex at an appropriate temperature for 1—3 h.

The results are summarized in Table 1.

By this procedure, all thiophene derivatives examined, except 2-methoxy- (**1d**), 2-(1-cyclohexenyl)- (**1j**), and 2-acetylthiophenes, gave the corresponding sulfonyl chlorides as the main products. It is noteworthy

TABLE 1. REACTION OF THIOPHENE DERIVATIVES WITH DMF-SO_2Cl_2 COMPLEX

Substituent R	Reaction Conditions[a]	Product	Yield/%[b]	Bp, °C/mmHg or Mp, °C(lit,)
1a: H	A	**2a**: 2-SO_2Cl	79	bp 88—93/2.5(123—124/14[1a]), 82—84/2[1b]) amide mp 141—142(146—147[2a]), 141—142[1a])
1b: 2-CH_3	A	**2b**: 2-CH_3, 5-SO_2Cl	56	bp 105—110/4(96—98/3[1d]) amide mp 117—118(119—119.5[1d])
1c: 3-CH_3	A	**2c**: 3-CH_3, 2-SO_2Cl } c) **2'c**: 4-CH_3, 2-SO_2Cl }	78	bp 100—108/5(98—99/0.5 for **2c**[1e]) amide mp 120—143(146 for **2c**[1e])
1d: 2-CH_3O	B	**3d**: 2-CH_3O, 5-CHO	47	bp 97—99/4(79—81/0.9[7]) acid mp 161.5—162.5(162—163[7])
1e: 2-Cl	A	**2e**: 2-Cl, 5-SO_2Cl	60	bp 101—102/3(mp 28[1g]) amide mp 113—114(116[1c])
1f: 2-Br	A	**2f**: 2-Br, 5-SO_2Cl	60	bp 105—110/4(mp 44—46[1h]) amide mp 138—139(144[1g]), 141[2b])
1g: 2-I	A	**2g**: 2-I, 5-SO_2Cl	43	mp 49—50(51—52[1h]) amide mp 162—163 (165[1h]), 163—164[2a])
		2a: 2-SO_2Cl	8	
1h: 2-$C_6H_5CH_2$	C	**2h**: 2-$C_6H_5CH_2$, 5-SO_2Cl	54	oil; amide mp 98—99
		3h: 2-$C_6H_5CH_2$, 5-CHO	10	mp 25—26(27.5—28[8]) acid mp 128.5—129.5 (129[8])
1i: 2-C_6H_5	A	**2i**: 2-C_6H_5, 5-SO_2Cl	41	mp 86—86.5; amide mp 221—222
		3i: 2-C_6H_5, 5-CHO	21	mp 93.5—94(93—93.5[9])
1j: 2-C_6H_9[d]	B	**3j**: 2-C_6H_9, 5-CHO	7	mp 65.5—66
1k: 2-$COOCH_3$	D	**2k**: 2-$COOCH_3$, 5-SO_2Cl } e) **2'k**: 2-$COOCH_3$, 4-SO_2Cl }	9	oil; amide mp 149—151
1l: 2,5-$(CH_3)_2$	A	**2l**: 2,5-$(CH_3)_2$, 3-SO_2Cl	66	bp 106—108/3(115—130/2.5[1f]) amide mp 138—139(138.5—140.5[1f])
7: 	E	**8**: 5-SO_2Cl	23	mp 69—70; amide mp 61.5—62.5
		9: 5,5'-$(SO_2Cl)_2$	30	mp 118—119; amide mp 164—165
		10: 5,5'-$(CHO)_2$	4	mp 86.5—87.5
		11: 5-CHO, 5'-SO_2Cl	12	mp 52.5—53.5; anilide mp 125—126

a) Unless otherwise noted, substrate/DMF-SO_2Cl_2 = 1/1.3(mole ratio). A: 95—98 °C, 1 h. B: 50—60 °C, 1h. C: 80—85 °C, 1 h. D: 115—120 °C, 3 h. E: 65—70 °C, 1.5 h, substrate/DMF-SO_2Cl_2 = 1/2.6. b) Isolated yield based on the substrate used. c) 2c/2'c = 90/10 (NMR). Amide, Anal. ($C_5H_7O_2NS_2$) C, H. d) 1-cyclohexenyl. e) Amide, Anal. ($C_6H_7NO_4S_2$) C, H.

that methylthiophenes (**1b** and **1c**), which were expected to be much more reactive than anisole[4] and to yield the aldehydes,[3] afforded the sulfonyl chlorides. With 2-iodothiophene (**1g**), a replacement of the iodine atom by a chlorosulfonyl group was observed, but to a lesser extent than by the chlorosulfuric acid procedure.[1h] In some cases, the corresponding aldehydes were produced as the by-products in yields of up to *ca.* 20%, which could be easily separated from the sulfonyl chlorides by usual methods. The reaction of methyl 2-thiophenecarboxylate (**1k**) was attained only with difficulty, affording a mixture of the two isomeric sulfonyl chlorides (**2k** and **2'k**) in low yield.

Repeated attempts to chlorosulfonate **1d** and **1j** with the complex gave only tars, and when the reactions were carried out under mild conditions, only the aldehydes (**3d** and **3j**) were isolated from the reaction products. The results offer a sharp contrast with those of anisole[3] and styrene,[5] which were chlorosulfonated with the complex in the ring and in the side chain, respectively. 2-Acetylthiophene reacted easily with the complex to give unidentified materials. In this case DMF-SO_2Cl_2 complex probably functioned as a chloroformylating agent, and 2-acetylthiophene underwent the reaction in the side chain as in the Vilsmeier reaction.[6,10] Actually, the reaction of cyclohexanone with the complex was found to afford 2-chlorocyclohex-1-enecarbaldehyde in *ca* 40% yield.

In conclusion, the DMF-SO_2Cl_2 procedure is particularly useful for the preparation of several thiophenesulfonyl chlorides. The yields are approximately equal or superior to the previously reported ones. The principal advantages of this procedure over the conventional ones are the operational simplicity, one-step procedure, and the use of easy-to-handle reagents.

Experimental

All melting and boiling points are uncorrected. The IR spectra were obtained on a Hitachi EPI-S2 spectrometer, and the NMR spectra on Hitachi R-22 spectrometer at 90 MHz using TMS as an internal reference.

*Reaction of Thiophene (**1a**) with DMF-SO_2Cl_2 Complex (Typical Procedure).* Freshly distilled SO_2Cl_2 (17.6 g, 0.13 mol) was added dropwise with shaking to ice-cooled DMF (9.5 g, 0.13 mol); the temperature was kept below 25 °C during the addition. The hygroscopic solid complex, thus formed within 10 min, was held at the same temperature for additional 30 min. Thiophene (**1a**; 8.4 g, 0.1 mol) was added to the complex and the mixture was heated on a water-bath at 95—98 °C for 1 h with occasional shaking. The viscous brown mixture was cooled, poured into ice-water, and then extracted with $CHCl_3$. The $CHCl_3$ solution was washed successively with water, 5% $NaHCO_3$ solution, and water and dried. Evaporation of the solvent left a liquid, which was distilled *in vacuo* to give 2-thiophenesulfonyl chloride (**2a**; 13.5 g, bp 88—93 °C/2.5 mmHg (1 mmHg≈133.322 Pa)).

*Reaction of 2-Phenylthiophene (**1i**) with DMF-SO_2Cl_2 Complex (Typical Procedure).* 2-Phenylthiophene (**1i**; 3.2 g, 0.02 mol) was heated with 1.3 molar equivalent of DMF-SO_2Cl_2 complex at 95—98 °C on a water-bath for 1 h. Water was added to the cooled reaction mixture. The products were extracted with $CHCl_3$. The combined extracts were washed with water and dried. After evaporating the solvent, the residue was chromatographed (silica gel/hexane-$CHCl_3$ (1:3)) to give 5-phenyl-2-thiophenesulfonyl chloride (**2i**; 2.1 g, mp 86—87 °C) and 5-phenyl-2-thiophenecarbaldehyde (**3i**; 0.3 g, mp 93—94 °C). The aqueous layers were concentrated under reduced pressure to *ca* 10 ml and extracted with ether. Evaporation of the solvent from the extracts gave another crop of **3i** (0.5 g, mp 91—93 °C) **2i**: IR (CCl_4) 1175, 1385 cm^{-1} (ν_{SO_2}). NMR (CCl_4) δ=7.23 and 7.75 (1H, d each, $J_{3,4}$=4.0 Hz, 3-H and 4-H), 7.3—7.7 (5H, m, phenyl). Anal. ($C_{10}H_7ClO_2S_2$) C, H. Sulfonamide: Anal. ($C_{10}H_9NO_2S_2$) C, H.

*5-Benzyl-2-thiophenesulfonyl Chloride (**2h**)*: IR ($CHCl_3$) 1175, 1385 cm^{-1} (ν_{SO_2}). NMR (CCl_4) δ=6.86 and 7.70 (1H, d each, $J_{3,4}$=3.9 Hz, 3-H and 4-H), 7.1—7.5 (5H, m, phenyl), 4.20 (2H, s, CH_2). Sulfonamide: Anal. ($C_{11}H_{11}NO_2S_2$) C, H.

*5-(1-Cyclohexenyl)-2-thiophenecarbaldehyde (**3j**)*: IR (CCl_4) 1680 cm^{-1} (ν_{CO}). NMR ($CDCl_3$) δ=9.75 (1H, s, CHO), 7.02 and 7.60 (1H, d each, $J_{3,4}$=4.1 Hz, 3-H and 4-H), 6.42 (1H, m, cyclohexenyl CH), 1.5—2.6 (8H, m, cyclohexenyl CH_2). Anal. ($C_{11}H_{12}OS$) C, H.

*2-(5-Chlorosulfonyl-2-thienyl)-2-(2-thienyl)propane (**8**)*: IR (KBr) 1175, 1380 cm^{-1} (ν_{SO_2}). NMR ($CDCl_3$) δ=7.76 (1H, d, $J_{3,4}$=4.0 Hz, 4-H), 7.92 (1H, ABXq, 5'-H), 6.9—7.1 (3H, m, 3-H, 3'-H and 4'-H), 1.88 (6H, s, $C(CH_3)_2$). Anal. ($C_{11}H_{11}ClO_2S_3$) C, H. Sulfonamide: Anal. ($C_{11}H_{13}NO_2S_3$) C, H.

*2,2-Bis(5-chlorosulfonyl-2-thienyl)propane (**9**)*: IR (KBr) 1170, 1380 cm^{-1} (ν_{SO_2}). NMR ($CDCl_3$) δ=7.76 and 7.00 (2H, d each, $J_{3,4}$=4.0 Hz, 4-H and 4'-H, and 3-H and 3'-H), 1.93 (6H, s, $C(CH_3)_2$). Anal. ($C_{11}H_{10}Cl_2O_4S_4$) C, H. Sulfonamide: Anal. ($C_{11}H_{14}N_2O_4S_4$) C, H.

*2,2-Bis(5-formyl-2-thienyl)propane (**10**)*: IR (KBr) 1660 cm^{-1} (ν_{CO}). NMR ($CDCl_3$) δ=9.86 (2H, s, CHO), 7.71 and 7.08 (2H, d each, $J_{3,4}$=4.2 Hz, 4-H and 4'-H, and 3-H and 3'-H), 1.89 (6H, s, $C(CH_3)_2$). Anal. ($C_{13}H_{12}O_2S_2$) C, H.

*2-(5-Formyl-2-thienyl)-2-(5-chlorosulfonyl-2-thienyl)-propane (**11**)*: IR (KBr) 1180, 1385 cm^{-1} (ν_{SO_2}), 1670 cm^{-1} (ν_{CO}). NMR ($CDCl_3$) δ=9.91 (1H, s, CHO), 7.82 and 7.74 (1H, d each, $J_{3,4}$=4.0 Hz, 4-H and 4'-H), 7.11 and 7.03 (1H, d, $J_{3,4}$=4.0 Hz, 3-H and 3'-H), 1.91 (6H, s, $C(CH_3)_2$). Anal. ($C_{12}H_{11}ClO_3S_3$) C, H. Sulfonanilide: Anal. ($C_{18}H_{17}NO_3S_3$) C, H.

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