

The reaction of the *N,N*-dichloroamide of 5-chloro-2-thienylsulfonic acid with trichloroethylene as a convenient synthetic route to a series of trichloroethylamides of 5-chloro-2-thienylsulfonic acid

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**Dedicated to academician Oleg N. Chupakhin on his 70th birthday, with heartiest wishes
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Abstract

N-(2,2,2-Trichloroethylidene)-5-chloro-2-thienylsulfonamide, the first representative of the polyhaloalkylidenamides of heterylsulfonic acids, has been synthesized by the reaction of *N,N*-dichloro-5-chloro-2-thienylsulfonamide with trichloroethylene and used as a regioselective C-amidoalkylating agent of aromatic compounds and in reactions with nucleophiles, forming a series of *N*-(2,2,2-trichloroethyl) amides of 5-chloro-2-thienylsulfonic acid.

Keywords: Chloralimines, *N,N*-dichloroamides, heterylsulfonamides, C-amidoalkylation, trichloroethylene

Introduction

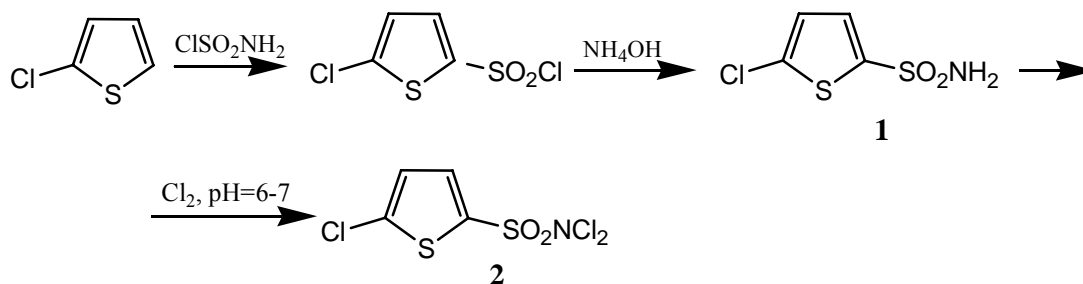
The presence of strongly electron-withdrawing substituents in the structure of the *N*-sulfonylimines of polyhaloaldehydes is responsible for the high activity of these compounds in their reactions with O-, N-, S-, and P- nucleophiles in the processes of C-amidoalkylation with aromatics and heteroaromatics, and permit their use as active heterodienophiles. Owing to their reactivity, the polychloroethylideneamides of sulfonic acids serve as basic intermediates in the preparation of a wide range of polyfunctional chlorine-containing sulfonamide derivatives, including those of cyclic structure.¹ Therefore, the development of convenient synthetic routes to these valuable compounds is an urgent problem. The synthesis of previously unknown representatives of heterylsulfonylimines containing electron-deficient azomethine groups also ranks among the most important tasks in our current research.

It was shown earlier that the most convenient, and sometimes the only possible approach to the N-sulfonylimines of chloral and of dichloroacetaldehyde, involves radical reaction of N,N-dichloroamides of sulfonic acids with trichloroethylene and 1,2-dichloroethylene, respectively.¹⁻³

Results and Discussion

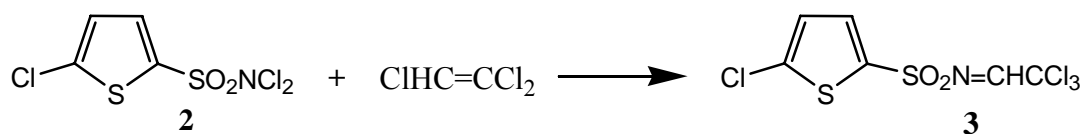
As a continuation of our systematic development of synthetic routes to polyhaloethylamides, based on the interaction of N,N-dihaloamides with polyhaloethenes, we have carried out the chlorination of 5-chloro-2-thienylsulfonamide **1** to the N,N-dichloroamide **2** in order to investigate the behavior of the latter in its reaction with polychloroethenes.

The dichloroamide **2** was prepared according to Scheme 1, without isolation of the intermediate 5-chloro-2-thienylsulfonyl chloride in pure form, which simplified the procedure and increased the yield.



Scheme 1

With the goal of elaborating the synthetic routes to trichloroethylideneamides of thienylsulfonic acids we have examined the reaction of the dichloroamide **2** with trichloroethylene. The results show that *N*-(2,2,2-trichloroethylidene)-5-chlorothien-2-ylsulfonamide **3** is obtained in good yield on boiling the reaction mixture for 10–12 h.



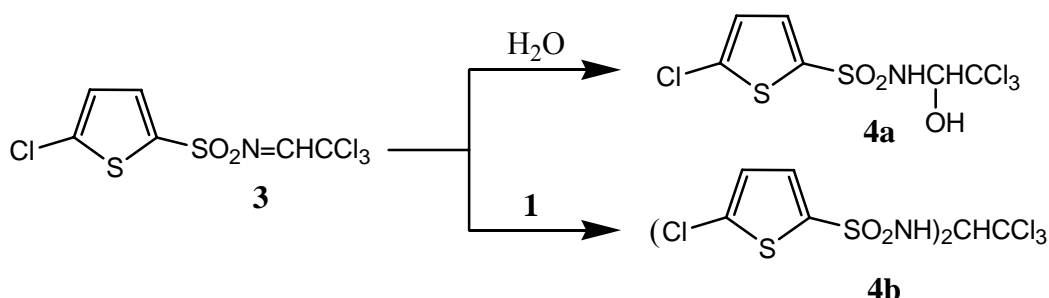
Scheme 2

Previously, a similar interaction of trichloroethylene with the N,N-dichloroamide of 2-thienylsulfonic acid had been studied, but the latter turned out to be poorly stable, and this did not allow the synthesis of thienylsulfonylchloralimine.⁴

It is established that the trichloroethylidene amide **3** readily forms, in quantitative yield, the *N*-(1-hydroxy-2,2,2-trichloroethyl)amide of 5-chlorothien-2-ylsulfonic acid, **4a**, either during its exothermic reaction with water or when kept in moist air. We have also carried out an

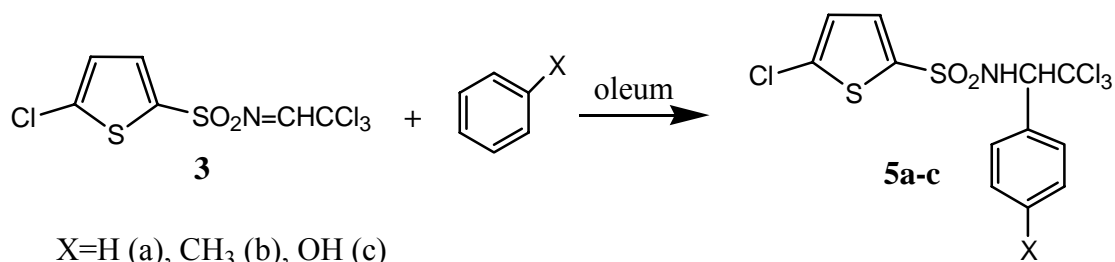
independent synthesis of the hydroxyethyl amide **4a** by the interaction of the sulfonamide **1** with chloral.

The imine **3** reacts actively with N-nucleophiles, for example with the thienylsulfonamide **1**, to give 1,1-bis-(5-chlorothien-2-ylsulfonamido)-2,2,2-trichloroethane, **4b**.



Scheme 3

A study of the amidoalkylating activity of the azomethine **3** has been undertaken. It was found that, analogously to the trifluoromethylsulfonyl-⁵ and arenesulfonyl-chloralimines,⁶ compound **3** reacts with benzene, toluene and phenol, in the presence of oleum, to give the amidotrichloroethyl- substituted arenes **5a–c** in high yield. The process does not need additional



Scheme 4

initiation, and the optimal reaction time is 3–5 h. There are no noticeable processes leading to destruction of the thienyl ring of the amidoalkylating agent, whereas the substitution occurs specifically in position 4 in the aromatic ring.

Conclusions

We have synthesized the first representatives of the polyhaloethylideneamides of heterosulfonic acids, *i.e.*, *N*-(2,2,2-trichloroethylidene)-5-chlorothien-2-ylsulfonamide, **3**, and have found a new example confirming the general character of the reaction of *N,N*-dichloroamides with 1,2-polyhaloethenes leading to compounds having an azomethyne group. Therefore, a new promising approach in organic synthesis, that of designing potential biologically active compounds combining in their structure the sulfonamide, polyhaloalkyl, and thienyl

pharmacophoric groups, is in progress, based on the highly reactive heterosulfonylimine of chloral.

Experimental Section

General Procedures. IR spectra were recorded on a SPECORD IR 75 spectrometer in KBr, with resolution of 1 cm^{-1} from $1700\text{--}500\text{ cm}^{-1}$ and 2 cm^{-1} in the νNH region. ^1H - and ^{13}C - NMR spectra were recorded on a Bruker DPX-400 instrument (400 and 100.6 MHz, respectively) in organic solvents with HMDS as internal standard, at concentrations 5–10%.

5-Chloro-2-thienylsulfonamide (1). 2-Chlorothiophene (10 ml, 0.1 mol) was added dropwise to a refluxed mixture of chlorosulfonic acid (40 ml, 0.6 mole) and CCl_4 (40 ml) for 1 h at -15°C . Then CCl_4 (20 ml) was added and refluxing was continued during 30 min. Thereafter the mixture was poured onto ice, the organic layer was separated, and the aqueous portion extracted with CCl_4 (3x10 ml), and the combined organic phases concentrated under reduced pressure. The residue was mixed with aqueous ammonia (50 ml, 20%) and allowed to stand for 24 h. The precipitate of amide **1** was filtered off, dried, and recrystallized from ethanol– CHCl_3 (1:3). Yield 19.21g (97 %), m.p. 107°C . IR (KBr, ν , cm^{-1}): 1170, 1320 (SO_2), 3270, 3360 (NH_2); δH , ppm [$(\text{CD}_3)_2\text{CO}$]: 6.90 br. s. (2H, NH_2), 7.04, 7.41 AB (2H, 2,5-thienyl). Anal. Calcd. for $\text{C}_4\text{H}_4\text{ClNO}_2\text{S}_2$: C 24.31; H 2.04; Cl 17.94; N 7.09; S 32.44. Found: C 24.93; H 2.15; Cl 17.41; N 7.17; S 32.63%.

***N,N*-Dichloroamide of 5-chloro-2-thienylsulfonic acid (2).** The sulfonamide **1** (1.63 g, 0.01 mol) was added to an acetate buffer solution (20 ml, pH 6–7), the mixture stirred for 20 min, and then filtered. Chlorine was bubbled through the filtrate at 10°C until precipitation was complete. The precipitate was filtered off, washed with water, and dried over P_2O_5 under vacuum to give **2** (2.00 g, 75 %), m.p. 127°C (CCl_4). IR (KBr, ν , cm^{-1}): 1180, 1320 (SO_2); δH , ppm (CDCl_3): 7.03, 7.44 AB (2H, 2,5-thienyl). Anal. Calcd. for $\text{C}_4\text{H}_2\text{Cl}_3\text{NO}_2\text{S}_2$: C 18.02; H 0.86; Cl 39.90; N 5.25; S 24.06. Found: C 18.12; H 0.95; Cl 40.15; N 5.61; S 24.48%.

***N*-(2,2,2-Trichloroethylidene)amide of 5-chloro-2-thienylsulfonic acid (3).** A solution of dichloroamide **2** (2.36 g, 0.01 mol) in trichloroethylene (10 ml, 0.1 mol) was boiled ($90\text{--}92^\circ\text{C}$) under argon as long as chlorine was obtained (10–12 h). The solvent was evaporated in vacuum, and the residue recrystallized from CCl_4 . Yield 2.92g (83 %), m.p. 137°C . IR (KBr, ν , cm^{-1}): 1150, 1330 (SO_2), 1610 ($\text{CH}=\text{N}$); δH , ppm (CDCl_3): 7.11, 7.68 AB (2H, 2,5-thienyl), 8.51 s (1H, $\text{CH}=\text{N}$). Anal. Calcd. for $\text{C}_6\text{H}_3\text{Cl}_4\text{NO}_2\text{S}_2$: C 22.04; H 0.92, Cl 43.36; N 4.28, S 19.61. Found: C 22.98; H 1.01; Cl 44.21; N 5.02; S 20.43%.

***N*-(1-Hydroxy-2,2,2-trichloroethyl)amide of 5-chloro-2-thienylsulfonic acid (4a).**

(A) Imine **3** (3.24 g, 0.01 mol) was allowed to stand in air for 24 h to give **4a** (3.30 g, 100%).

(B) Chloral (2.94 g, 0.02 mol), the sulfonamide **1** (1.95 g, 0.01 mol), CHCl_3 (10–15 ml), and conc. sulfuric acid (0.05–0.10 ml) were stirred vigorously at $60\text{--}70^\circ\text{C}$ for 20 min. Then the

chloroform was evaporated in vacuum, and the residue washed with water and dried to give **4a** (3.21 g, 97 %). M.p. 124–126°C. IR (KBr, ν , cm^{-1}): 1160, 1340 (SO_2), 3210 (NH), 3480 (OH); δ_{H} , ppm (CDCl_3): 5.42 (1H, CH-N, $J_{\text{CH-NH}}$ 9.5 Hz), 6.92, 7.48 AB (2H, 2,5-thienyl), 8.15 d (1H, NH, $J_{\text{CH-NH}}$ 9.5 Hz). Anal. Calcd. for $\text{C}_6\text{H}_5\text{Cl}_4\text{NO}_3\text{S}_2$: C 20.89; H 1.46; Cl 41.10; N 4.06; S 18.58. Found: C 20.48; H 1.28; Cl 41.31; N 4.18; S 18.33%.

1,1-Bis-(5-chloro-2-thienylsulfonamido)-2,2,2-trichloroethane (4b). The dichloroamide **2** (2.36 g, 0.01 mol) and trichloroethylene (10 ml, 0.1 mol) were boiled under argon for 12 h. Then sulfonamide **1** (1.65 g, 0.01 mol) was added and the mixture stirred at 70–80°C for 5 h. The precipitate produced was filtered off and dried. Yield 3.95 g (86 %), m.p. 192–194°C. IR (KBr, ν , cm^{-1}): 1150, 1340 (SO_2), 3200–3280 (NH); δ_{H} , ppm (CDCl_3): 5.80 t (1H, CH-N, $J_{\text{CH-NH}}$ 9.3 Hz), 7.08, 7.51 AB (4H, 2,5-thienyl), 8.42 d (2H, NH, $J_{\text{CH-NH}}$ 9.3 Hz). Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{Cl}_5\text{N}_2\text{O}_4\text{S}_4$: C 22.89; H 1.34; Cl 33.79; N 5.34; S 24.44. Found: C 23.08; H 1.43; Cl 34.29; N 5.58; S 23.92 %.

N-(1-Phenyl-2,2,2-trichloroethyl)amide of 5-chloro-2-thienylsulfonic acid (5a). Benzene (10–12 ml), imine **3** (3.24 g, 0.01 mol) and oleum (0.1 mol, 3–20% SO_3) were stirred vigorously for 5h, then the benzene was evaporated in vacuum. The residue was washed with aq. ammonia (5% NH_3) then with water, dried and recrystallized from chloroform to give **5a** (3.21 g, 81 %), m.p. 181–183°C. IR (KBr, ν , cm^{-1}): 1150, 1330 (SO_2), 3260 (NH); δ_{H} , ppm (CDCl_3): 5.21 d (1H, CH-N, $J_{\text{CH-NH}}$ 10.0 Hz), 7.22–7.37 m (7H, Ph and thienyl), 8.17 d (1H, NH, $J_{\text{CH-NH}}$ 10.0 Hz). Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{Cl}_4\text{NO}_2\text{S}_2$: C 35.58; H 2.24; Cl 35.00; N 3.46; S 15.83. Found: C 35.78; H 2.37; Cl 35.21; N 3.32; S 15.23 %.

N-[1-(4-Methylphenyl)-2,2,2-trichloroethyl]amide of 5-chloro-2-thienylsulfonic acid (5b). The amide was obtained in a similar manner from imine **3** (3.24 g, 0.01 mol) and toluene (10–12 ml); yield 3.41 g (83 %), m.p. 122–123°C. IR (KBr, ν , cm^{-1}): 1160, 1340 (SO_2), 3250 (NH); δ_{H} , ppm [$(\text{CD}_3)_2\text{CO}$]: 2.29 s (3H, CH_3), 5.23 d (1H, CH-N, $J_{\text{CH-NH}}$ 10.1 Hz), 6.79, 7.20 AB (2H, 2,5-thienyl), 7.08, 7.47 AA'BB' (4H, C_6H_4), 8.01 d (1H, NH, $J_{\text{CH-NH}}$ 10.01 Hz); Anal. Calcd. for $\text{C}_4\text{H}_2\text{Cl}_3\text{NO}_2\text{S}_2$: C 37.25; H 2.65; Cl 33.83; N 3.34; S 15.30. Found: C 37.38; H 2.70; Cl 34.21; N 3.42; S 15.53%.

N-[1-(4-Hydroxyphenyl)-2,2,2-trichloroethyl]amide of 5-chloro-2-thienylsulfonic acid (5c). Amide **5c** was obtained in a similar manner from imine **3** (3.24 g, 0.01 mol) and phenol (1.88 g, 0.02 mol) in CCl_4 as solvent. Yield 3.28 g (78%), m.p. 157–158°C. IR (KBr, ν , cm^{-1}): 1140, 1330 (SO_2), 3190 (NH), 3330 (OH); δ_{H} , ppm [$(\text{CD}_3)_2\text{CO}$]: 5.19 d (1H, CH-N, $J_{\text{CH-NH}}$ 10.0 Hz), 6.80, 7.43 AB (2H, 2,5-thienyl), 6.84, 7.51 AA'BB' (4H, C_6H_4), 8.37 d (1H, NH, $J_{\text{CH-NH}}$ 10.0 Hz). Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{Cl}_4\text{NO}_3\text{S}_2$: C 34.22; H 2.15; Cl 33.67; N 3.33; S 15.23. Found: C 34.33; H 2.25; Cl 34.01; N 3.72; S 15.03 %.

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