Russian Journal of Organic Chemistry, Vol. 41, No. 1, 2005, pp. 91–94. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 1, 2005, pp. 93–96.

Synthesis of *N*-Arylsulfonyl-α-thienylglycines from *N*-(2,2,2-Trichloro-1-thienylethyl)arenesulfonamides

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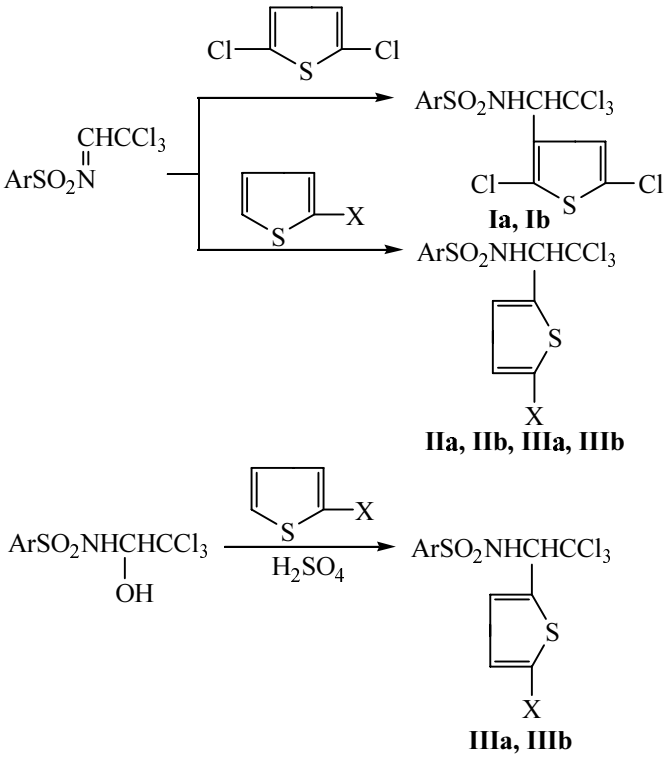
Received March 30, 2004

Abstract—Reactions of *N*-(2,2,2-trichloroethylidene)arenesulfonamides with thiophene, 2-chlorothiophene, and 2,5-dichlorothiophene, as well as of *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides with 2-chlorothiophene, lead to formation of the corresponding *N*-(2,2,2-trichloro-1-thienylethyl)arenesulfonamides. Alkaline hydrolysis of the latter occurs selectively at the trichloromethyl group to give *N*-arylsulfonyl-α-thienylglycines.

We previously found that *N*-(2,2,2-trichloroethylidene)arenesulfonamides and *N*-(1-X-2,2,2-trichloroethyl)arenesulfonamides (where X is a readily departing group, such as OH, OAlk, OAc, or $NHSO_2R$) are capable of acting as C-amidoalkylating agents toward aromatic and heteroaromatic compounds [1–3]. The products of these reactions, 1-arylsulfonylamino-2,2,2-trichloroethyl-substituted arenes, undergo alkaline hydrolysis to afford *N*-arylsulfonyl(aryl)glycines [4, 5]. *N*-Arylsulfonyl-(3-indolyl)-glycines were also synthesized in this way [5]. In continuation of our systematic studies on the amidoalkyl-ating ability of *N*-(2,2,2-trichloroethylidene)- and *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides with a view to develop synthetic approaches to N-substituted heterylglycines, in the present work we examined conditions of synthesis of *N*-(2,2,2-trichloro-1-thienylethyl)arenesulfonamides and their alkaline hydrolysis.

Thiophene and chlorothiophenes were brought into reactions with *N*-(2,2,2-trichloroethylidene)- and *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides which were prepared as described in [6, 7]. *N*-(2,2,2-Trichloroethylidene)arenesulfonamides reacted with chlorothiophenes in the presence of oleum (method *a*) to give substituted thiophenes **Ia**, **Ib**, **IIIa**, and **IIIb** in 82–93% yield. In the reactions with 2,5-dichlorothiophene, the substitution occurred at position *3* of the heteroring with formation of products **Ia** and **Ib**, while from 2-chlorothiophene 5-(1-arylsulfonylamino-2,2,2-trichloroethyl)-thiophenes **IIa** and **IIb** were obtained (Scheme 1).

Scheme 1.



I–III, Ar = Ph (**a**), 4-ClC_6H_4 (**b**); **II**, X = H; **III**, X = Cl.

Compounds **IIa** and **IIb** were also prepared by reaction of *N*-(2,2,2-trichloroethylidene)arenesulfonamides with thiophene in the presence of boron trifluoride–ether complex, following a procedure analogous to that reported in [8].

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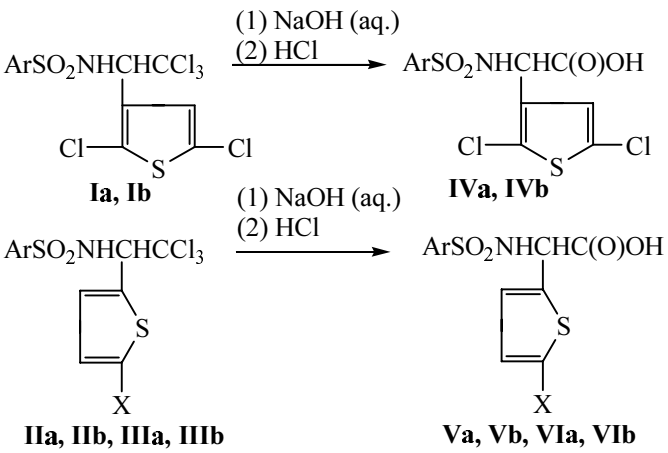
Scheme 2.



IV–**VI**, Ar = Ph (**a**), 4-ClC_6H_4 (**b**); **V**, X = H; **VI**, X = Cl.

Compounds **IIIa** and **IIIb** were also synthesized in 72–75% yield by reaction of 2-chlorothiophene with *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides in the presence of concentrated sulfuric acid (method *b*). It is seen that the yield of compounds **IIIa** and **IIIb** according to method *a* is greater than in method *b*, while the optimal reaction time is the same in both cases. It should be noted that variation of the concentration of free sulfuric anhydride from 3 to 20% in method *a* has no appreciable effect on the reaction outcome and that amidoalkylation of chlorothiophene according to method *b* does not occur in sulfuric acid with a concentration lower than 96%. Moreover, method *b* turned out to be unsuitable for the synthesis of *N*-[2,2,2-trichloro-1-(2,5-dichloro-3-thienyl)ethyl]arenesulfonamides **I** and *N*-[2,2,2-trichloro-1-(2-thienyl)ethyl]arenesulfonamides **II** from 2,5-dichlorothiophene and thiophene, respectively. Likewise, *N*-(2,2,2-trichloroethylidene)arenesulfonamides failed to react with thiophene derivatives in sulfuric acid instead of oleum. When the amount of oleum or sulfuric acid was greater than that specified in Experimental, the yield of compounds **I**–**III** decreased; probable reasons are acidophobic properties of the thiophene system and side sulfonation of the heteroring.

Presumably, the mechanism of amidoalkylation involves formation of $ArSO_2NHC^+HCCl_3$ ion via protonation of the nitrogen atom in Schiff bases (method *a*) or successive protonation of the oxygen atom in the hydroxy group of hydroxyethyl amides and elimination of water (method *b*). The rate of formation of the above cation and its stability in method *b* are likely to be lower than in method *a*. Therefore, the yields of compounds **IIIa** and **IIIb** in method *b* were lower, and the reactions of 2,5-dichlorothiophene with *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides under the same conditions gave no detectable amounts of products **Ia** and **Ib**.

Compounds **I**–**III** were brought into hydrolysis in aqueous alkali. The reaction occurred at the trichloromethyl group with high selectivity, and the products were the corresponding *N*-arylsulfonyl-α-thienylglycine salts. The hydrolysis at 70–80°C was complete within 3 h. The subsequent acidification of the reaction mixture gave *N*-arylsulfonyl-α-thienylglycines **IV**–**VI** in up to 50% yield (Scheme 2). Like *N*-arylsulfonyl-α-arylglycines, amino acids **IV**–**VI** attract interest as potential biologically active compounds [5].

The hydrolysis of compounds **I**–**III** was not accompanied by dehydrochlorination. On the other hand, partial hydrolysis of the C–N bond was observed: the reaction mixtures contained a small amount of the corresponding arenesulfonamides whose fraction increased on raising the concentration of alkali, reaction time, and temperature (above 80°C).

Compounds **I**–**VI** are colorless or slightly colored crystalline substances which are insoluble in water and aliphatic hydrocarbons and soluble in polar organic solvents. The structure of previously unknown compounds **Ia**, **Ib**, **IIIa**, **IVa**, **IVb**, **Va**, **Vb**, **VIa**, and **VIb** was determined by spectral methods (see Experimental). The properties of compounds **IIa**, **IIb**, and **IIIb** were in agreement with published data [3, 8].

The IR spectra of **I**–**III** contained strong absorption bands due to vibrations of the SO_2 and NH groups, while absorption bands typical of O–H and C=N bonds in the initial sulfonamides were absent. Glycine derivatives **IV**–**VI** showed in the IR spectra absorption bands corresponding to vibrations of the carboxy group. In the ^{1}H NMR spectra of **I**–**III**, protons of the NH–CH fragment give rise to two doublets with a coupling constant of 9–10 Hz. In addition, multiplet signals from aromatic protons were present. The ^{1}H NMR spectra of compounds **IIIa** and **IIIb** contained an *AB* system typical of protons in the heterocyclic fragments. Protons in position *4* of the thiophene ring in **Ia** and **Ib** appeared as singlets. These data are consistent with formation of 2,5-di- and 2,3,5-trisubstituted thiophene derivatives, respectively. In the ^{1}H NMR spectra of substituted glycines **IV**–**VI** we observed no spin–spin coupling in the NH–CH fragment, and protons therein appeared as two singlets. Under conditions of fast deuterium exchange, only one singlet remains in the spectrum. The carboxy proton gives

a broadened singlet in a weak field. The elemental compositions of compounds **I**–**VI** do not contradict the assumed structures.

Thus, reactions of *N*-(2,2,2-trichloroethylidene)-arenesulfonamides with thiophene, 2-chlorothiophene, and 2,5-dichlorothiophene and of *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamides with 2-chlorothiophene result in formation of *N*-(2,2,2-trichloro-1-thienylethyl)arenesulfonamides; alkaline hydrolysis of the latter provides a convenient method of synthesis of *N*-arylsulfonyl-α-thienyl)glycines. Our results confirm the general character of the synthetic approach to N-substituted α-aryl-(heteryl)glycines on the basis of hydrolytic transformation of the corresponding *N*-trichloroethyl amides.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz) from 5–10% solutions in acetone-d_6 containing HMDS as internal reference. The IR spectra were obtained on a Specord IR75 instrument from samples prepared as KBr pellets.

N-[2,2,2-Trichloro-1-(2-thienyl)ethyl]benzenesulfonamide (**IIa**) and *N*-[2,2,2-trichloro-1-(2-thienyl)ethyl]-4-chlorobenzenesulfonamide (**IIb**) were synthesized by reaction of the corresponding *N*-(2,2,2-trichloroethylidene)arenesulfonamides with thiophene in the presence of boron trifluoride–ether complex according to the procedure reported in [8]. *N*-[2,2,2-Trichloro-1-(5-chloro-2-thienyl)ethyl]-4-chlorobenzenesulfonamide (**IIIb**) was prepared by reaction of *N*-(2,2,2-trichloroethylidene)-4-chlorobenzenesulfonamide with 2-chlorothiophene in the presence of oleum [3].

Gnereal procedure for amidoalkylation of thiophene and chlorothiophenes. *a.* Halothiophene, 0.01–0.02 mol, and oleum containing 3 to 20% of SO_3, 0.5–1 ml, were added to a solution of 0.01 mol of *N*-(2,2,2-trichloroethylidene)arenesulfonamide [6] in 10–15 ml of anhydrous trichloroethylene, chloroform, or carbon tetrachloride. The mixture was vigorously stirred for 4–5 h, the solvent was distilled off under reduced pressure, and the residue was washed with 50 ml of 10% aqueous ammonia and water (until neutral reaction), dried in air, and recrystallized from acetone–carbon tetrachloride (1 : 1).

b. A mixture of 0.01 mol of *N*-(2,2,2-trichloro-1-hydroxyethyl)arenesulfonamide [6, 7], 2.38 g (0.02 mol) of 2-chlorothiophene, 15 ml of chloroform or carbon tetrachloride, and 1–3 ml of 98–100% sulfuric acid was vigorously stirred for 5 h. The mixture was then treated as described above in *a*.

***N*-[2,2,2-Trichloro-1-(2,5-dichlorothiophen-3-yl)ethyl]benzenesulfonamide (Ia)** was synthesized according to method *a* from 2.86 g (0.01mol) of *N*-(2,2,2-trichloroethylidene)benzenesulfonamide and 1.53 g (0.01 mol) of 2,5-dichlorothiophene in trichloroethylene in the presence of 1 ml of oleum. Yield 3.82g (87%), mp 141°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1160, 1330 (SO_2); 1530–1540 (C=C_{arom}); 3040–3060 (C–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.29 s (1H, CH), 7.47–7.70 m (5H, C_6H_5), 7.20 s (1H, 4-H, thienyl). Found, %: C 32.40; Cl 42.90; N 3.20; S 15.29. $C_{12}H_8Cl_5NO_2S_2$. Calculated, %: C 32.79; Cl 40.33; N 3.19; S 14.59.

***N*-[2,2,2-Trichloro-1-(2,5-dichlorothiophen-3-yl)ethyl]-4-chlorobenzenesulfonamide (Ib)** was synthesized according to method *a* from 3.21 g (0.01mol) of *N*-(2,2,2-trichloroethylidene)-4-chlorobenzenesulfonamide and 1.53 g (0.01 mol) of 2,5-dichlorothiophene. Yield 4.41 g (93%), mp 154°C. IR spectrum, ν, cm^{-1}: 3230 (NH); 1150, 1310 (SO_2); 1520 (C=C_{arom}); 3050–3060 (C–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.27 s (1H, CH), 7.47 d and 7.67 d (4-H, C_6H_4), 7.16 s (1H, 4-H, thienyl). Found, %: C 30.29; Cl 43.98; N 2.61; S 12.70. $C_{12}H_7Cl_6NO_2S_2$. Calculated, %: C 30.41; Cl 44.87; N 2.95; S 13.53.

***N*-[2,2,2-Trichloro-1-(5-chlorothiophen-2-yl)-ethyl]benzenesulfonamide (IIIa).** *a*. From 2.86 g (0.01 mol) of *N*-(2,2,2-trichloroethylidene)benzenesulfonamide and 2.38 g (0.02 mol) of 2-chlorothiophene in trichloroethylene we obtained 3.32 g (82%) of compound **IIIa**.

b. From 3.04 g (0.01 mol) of *N*-(2,2,2-trichloro-1-hydroxyethyl)benzenesulfonamide and 2.38 g (0.02 mol) of 2-chlorothiophene we obtained 3.04 g (75%) of compound **IIIa**. mp 135–136°C. IR spectrum, ν, cm^{-1}: 3220 (NH); 1180, 1340 (SO_2); 2940 (C–H_{aliph}); 3060–3090 (C–H_{arom}). ^{1}H NMR spectrum, δ, ppm: 5.20 s (1H, CH); 6.85 t, 7.33 d, and 7.65 d (5H, C_6H_5); 7.02 d and 7.40 d (2H, 3-H, 4-H, thienyl). Found, %: C 37.40; Cl 34.18; N 3.32; S 15.30. $C_{12}H_9Cl_4NO_2S_2$. Calculated, %: C 37.52; Cl 34.08; N 3.37; S 15.41.

2,5-Dichlorothiophen-3-yl(phenylsulfonylamino)-acetic acid (IVa). A mixture of 2.20 g (0.005 mol) of *N*-[2,2,2-trichloro-1-(2,5-dichlorothiophen-3-yl)ethyl]-benzenesulfonamide and 50 ml of an aqueous solution of 0.60 g (0.015 mol) of sodium hydroxide was stirred for 3 h at 90°C. The mixture was filtered while hot, the filtrate

was cooled to room temperature, and 10% hydrochloric acid was added to the filtrate until a solid material no longer precipitated. The mixture was kept for 2 h, the precipitate was filtered off, washed with water until neutral washings, dried, and recrystallized from acetone–chloroform (1 : 5). Yield 0.68 g (37%), mp 60°C. IR spectrum, ν, cm^{-1}: 3260 (NH); 1140, 1350 (SO_2); 1700–1710 (C=O); 3420 (OH). ^1H NMR spectrum, δ, ppm: 5.25 s (1H, CH), 10.62 br.s (1H, OH), 7.63–8.02 m (5H, C_6H_5), 6.80 s (1H, 4-H, thienyl). Found, %: C 38.95; Cl 18.74; N 3.60; S 17.00. $C_{12}H_9Cl_2NO_4S_2$. Calculated, %: C 39.36; Cl 19.36; N 3.82; S 17.51.

4-Chlorophenylsulfonylamino(2,5-dichlorothiophen-3-yl)acetic acid (IVb) was synthesized as described above for compound **IVa** from 2.38 g (0.005 mol) of *N*-[2,2,2-trichloro-1-(2,5-dichlorothiophen-3-yl)ethyl]-4-chlorobenzenesulfonamide. Yield 0.95 g (47%), mp 115°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1160, 1340 (SO_2); 1710 (C=O); 3430 (OH). ^1H NMR spectrum, δ, ppm: 5.23 s (1H, CH), 13.88 br.s (1H, OH), 7.63 d and 7.98 d (4H, C_6H_4), 6.78 s (1H, 4-H, thienyl). Found, %: C 35.30; Cl 25.86; N 3.45; S 15.30. $C_{12}H_8Cl_3NO_4S_2$. Calculated, %: C 35.97; Cl 26.50; N 3.50; S 16.00.

Phenylsulfonylamino(2-thienyl)acetic acid (Va) was synthesized in a similar way from 2.85 g (0.005 mol) of compound **IIa**. Yield 0.63 g (53%), mp 98–100°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1160, 1350 (SO_2); 1690–1710 (C=O); 3430–3480 (OH). ^1H NMR spectrum, δ, ppm: 5.41 s (1H, CH); 10.54 br.s (1H, OH); 7.58–8.01 (5H, C_6H_5); 7.35 d, 7.71 d, and 7.88 d (1H each, thienyl). Found, %: C 46.45; N 4.82; S 21.61. $C_{12}H_{11}NO_4S_2$. Calculated, %: C 48.47; N 4.71; S 21.36.

4-Chlorophenylsulfonylamino(2-thienyl)acetic acid (Vb) was synthesized in a similar way from 2.25 g (0.005 mol) of compound **IIb**. Yield 0.64 g (43%), mp 197°C. IR spectrum, ν, cm^{-1}: 3250 (NH); 1170, 1340 (SO_2); 1690–1710 (C=O); 3440 (1H, OH). ^1H NMR spectrum, δ, ppm: 5.33 s (1H, CH); 9.00 br.s (1H, OH); 7.68 d, 7.90 d (4H, C_6H_4); 6.98 t, 7.46 d, and 7.65 d (1H each, thienyl). Found, %: C 42.73; Cl 13.45; N 4.13; S 16.70. $C_{12}H_{10}ClNO_4S_2$. Calculated, %: C 43.44; Cl 10.69; N 4.22; S 19.33.

5-Chlorothiophen-2-yl(phenylsulfonylamino)-acetic acid (VIa) was synthesized in a similar way from 3.73 g (0.01 mol) of compound **IIIa**. Yield 1.16 g (35%), mp 105°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1180, 1350 (SO_2); 1700–1710 (C=O); 3370 (OH). ^1H NMR spectrum, δ, ppm: 5.35 s (1H, CH), 10.62 br.s (1H, OH), 7.59–8.01 (5H, C_6H_5), 6.84 (2H, thienyl). Found, %: C 39.87; Cl 10.69; N 4.34; S 20.47. $C_{12}H_{10}ClNO_4S_2$. Calculated, %: C 43.44; Cl 10.85; N 4.22; S 19.33.

4-Chlorophenylsulfonylamino(5-chlorothiophen-2-yl)acetic acid (VIb) was synthesized in a similar way from 2.14 g (0.005 mol) of compound **IIIb**. Yield 0.74 g (40%), mp 80°C. IR spectrum, ν, cm^{-1}: 3230 (NH); 1160, 1330 (SO_2); 1720 (C=O); 3320–3410 (OH). ^1H NMR spectrum, δ, ppm: 5.38 s (1H, CH), 7.57 d and 7.83 d (4H, C_6H_4), 7.01 d and 7.40 d (2H, thienyl). Found, %: C 41.09; Cl 21.25, N 3.13; S 14.76. $C_{12}H_9Cl_2NO_4S_2$. Calculated, %: C 39.36; Cl 19.36; N 3.82; S 17.51.

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