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2,5-Dihalothiophenes in the Reaction with Chlorosulfonic Acid

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Abstract — The mixtures of mono- and dihalothiophenesulfonyl chlorides, formed in the sulfochlorination reaction of 2,5-dichlorothiophene and 2,5-dibromothiophene, were treated with aqueous ammonia and thus converted into mixtures of the corresponding stable thiophenesulfonamides. The structure and composition of the latter were studied by physicochemical methods: GC–MS and ^{1}H, ^{13}C, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, and NOESY NMR spectroscopy. As a result of the above chemical transformations, 2,5-dichlorothiophene afforded a mixture of 5-chlorothiophene-2-sulfonamide and 4,5-dichlorothiophene-3-sulfonamide in a roughly 70 : 30 ratio. In the case of 2,5-dibromothiophene, a mixture of 5-bromothiophene-2-sulfonamide, 4,5-dibromothiophene-3-sulfonamide, and 3,5-dibromothiophene-2-sulfonamide (3 : 54 : 43) was formed.
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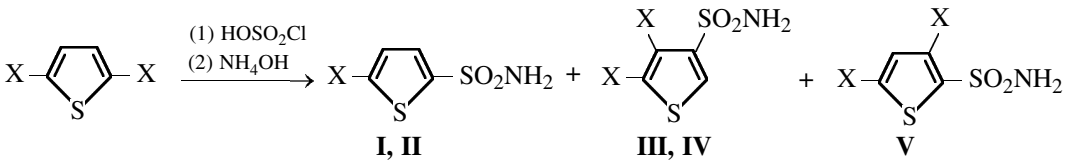
Developing expedient synthetic approaches to prospective biologically active thiophene derivatives and proceeding with systematic development of the methods of synthesis of polyhaloethylidene- and ethylamides of thiophenesulfonic acids [1, 2], based on the reaction of *N,N*-dihaloamides with polyhaloethenes and acetylenes [3], we attempted to prepare dihalothiophenesulfonamides. We planned to perform sulfochlorination of 2,5-dichloro(bromo)thiophene, to convert the resulting sulfonyl chlorides into the corresponding sulfonamides and then to *N,N*-dichloroamides, and, finally, to react the latter with polyhaloethenes. Earlier we successfully used this route to synthesize the first representative of chloral heterylsulfonylimines, *N*-(2,2,2-trichloroethylidene)-5-chlorothiophene-2-sulfonamide [1, 2].

In the present work, when studying the reaction of 2,5-dichloro- and 2,5-dibromothiophenes with a 4–6-fold molar excess of chlorosulfonic acid at –25 to –30°C and in the reaction mixture diluted with CCl_4, we found that sulfochlorination involves both halogen substitution in position 2 and halogen migration from position 2 to 3 or 4.

Since the mixtures of thiophenesulfonyl chlorides, formed in the sulfochlorination reaction, proved unstable on treatment and storage, we treated them with aqueous ammonia, thus converting them into mixtures of the corresponding stable thiophenesulfonamides whose structure and composition were further studied by physicochemical methods.



X = Cl (**I, III**), Br (**II, IV, V**).

Analysis of the amination products showed that the sulfochlorination reaction affords 5-halothiophene-2-sulfonyl chlorides, as well as 4,5-dihalothiophene-3-sulfonyl chlorides. The formation of 3,5-dihalothiophene-2-sulfonyl chloride was observed only in the reaction with 2,5-dibromothiophene.

It should be added that under the above conditions 2-chlorothiophene is sulfochlorinated without substitution of chlorine, affording 5-chlorothiophene-2-sulfonyl chloride exclusively [1, 2].

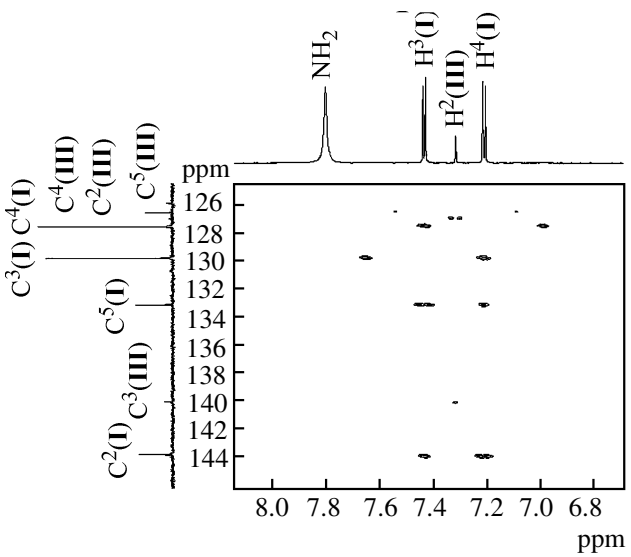
Apparently, the presence of such a strong acid as chlorosulfonic is sufficient for generation of stable halo-substituted thiophenium cations, cationic σ complexes, from both the starting dihalothiophenes and their sulfochlorinated derivatives. Subsequent transformations of these thiophenium cations might form the corresponding sulfochlorinated halo- and dihalo-substituted thiophene derivatives.

The disproportionation of 2,5-dichloro(dibromo)-thiophenium ions, leading eventually to 2-chloro-(bromo)- and 2,4-dichloro(dibromo)thiophenes in the presence of strong Brønsted or Lewis acids in organochlorine solvents has been described and discussed in the literature [4–7]. However, there is no information on similar transformations of dihalothiophenes under the action of chlorosulfonic acid.

The composition of the mixtures of thiophenesulfonamides was determined by NMR spectroscopy and GC–MS. Compound **I** was prepared by us earlier [1, 2].

The ^{1}H NMR spectrum of the mixture of chloro-substituted thiophenesulfonamides contain two doublets at 7.20 and 7.43 ppm [^3J(H, H) 4.0 Hz], belonging to compound **I**, a singlet at 7.31 ppm corresponding to compound **III**, and a broadened signal of the amino group at 7.79 ppm, belonging to both these compounds. In the ^{13}C NMR spectrum, eight signals are observed, three of which correspond to the methine carbon atoms and five to quaternary carbon atoms, which were assigned on the basis of the ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra.

The 2D ^{1}H–^{13}C HSQC NMR spectrum shows cross peaks between protons at 7.20, 7.43, and 7.31 ppm and carbons at 127.51, 129.78 and 126.48 ppm, respectively. To assign the quaternary carbon atoms, the ^{1}H–^{13}C HMBC method optimized for ^nJ(C, H) of 10 Hz was employed (see figure). In the HMBC spectrum, the proton at 7.20 ppm gives three cross peaks: C^2(**I**): 144.0 ppm, ^3J(C, H) 11.1 Hz; C^5(**I**): 133.15 ppm, ^2J(C, H) 2.2 Hz; and C^3(**I**): 129.78 ppm, ^2J(C, H) 5.5 Hz, which unequivocally proves structure **I**. The proton at 7.31 ppm gives three cross peaks: C^3(**III**): 140.17 ppm, ^2J(C, H) 3.2 Hz; C^4(**III**): 126.94 ppm, ^3J(C, H) 13.5 Hz; and C^5(**III**): 125.81 ppm, ^4J(C, H) < 1 Hz, which confirms structure **III**. The assignment was made with due regard that vicinal ^{13}C–^{1}H coupling constants are substantially larger than geminal ones, that is, ^3J(C, H) > ^2J(C, H). Further evidence for suggested structures **I** and **III** is provided by the observation in the NOESY spectrum of cross peaks between H^4(**I**) (7.43 ppm) and H^5(**III**) (7.31 ppm) and the amino group (7.79 ppm).



^{1}H–^{13}C HMBC NMR spectrum of the mixture of thiophenesulfonamide chloro derivatives **I** and **III**.

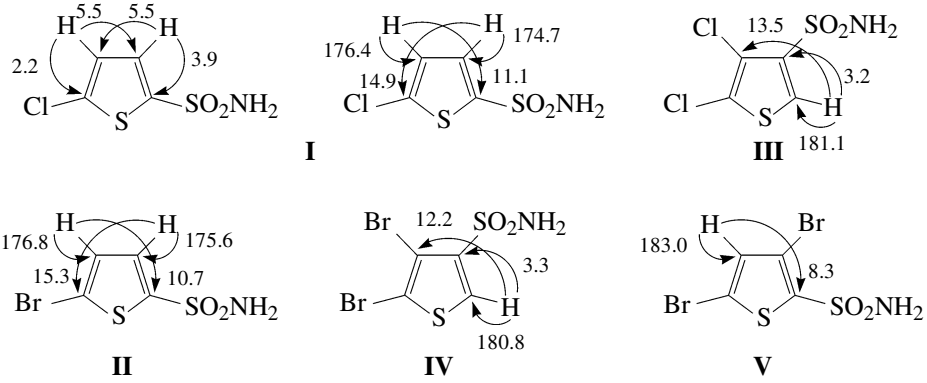
In the ^{1}H NMR spectrum of the mixture of bromo-substituted thiophenesulfonamides, there are two doublets at 7.29 and 7.38 ppm [^3J(H, H) 3.8 Hz], belonging to compound **II**, a singlet at 7.40 ppm from compound **IV**, a singlet at 7.49 ppm from compound **V**, and a broadened signal of the amino group at 7.82 ppm from all the three compounds **II**, **IV**, and **V**.

The assignment of the methine carbon signals was made on the basis of the 2D HSQC NMR spectrum which shows cross peaks between the protons at 7.29 and 7.38 ppm of compound **II** and carbon atoms at 130.87 and 130.58 ppm, respectively, H^2 at 7.40 ppm with carbon at 130.50 ppm of compound **IV**, and H^4 at 7.49 ppm with carbon at 135.08 ppm of compound **V**. The quaternary carbon signals were assigned by the ^{1}H–^{13}C HMBC NMR. In the HMBC spectrum, the H^4 signal of compound **II** at 7.29 ppm gives a cross peak with the more downfield C^2 signal at 146.72 ppm [^3J(C, H) 10.7 Hz]. The H^3 signal of compound **II** at 7.38 ppm gives a cross peak with the more upfield C^5 signal with ^3J(C, H) 15.3 Hz, which unambiguously proves structure **II**. The H^2 signal of compound **IV** at 7.40 ppm shows three cross peaks: with C^3 [143.37 ppm, ^2J(C, H) 3.3 Hz], C^4 [112.93 ppm, ^3J(C, H) 12.2 Hz], and C^5 [111.63 ppm, ^4J(C, H) < 1 Hz], which proves structure **IV**. The H^4 signal of compound **V** at 7.49 ppm shows three cross peaks: one with C^2 [141.26 ppm, ^3J(C, H) 8.3 Hz] and two

with C^5 (116.80 ppm) and C^3 [111.27 ppm, ^2J(C, H) ~ 2–3 Hz], which corresponds to structure **V**. The final assignment of the C^5 and C^3 signals of compound **V** was made by means of B3LYP/cc-pVDZ quantum-chemical computation of the shielding constants in this compound.

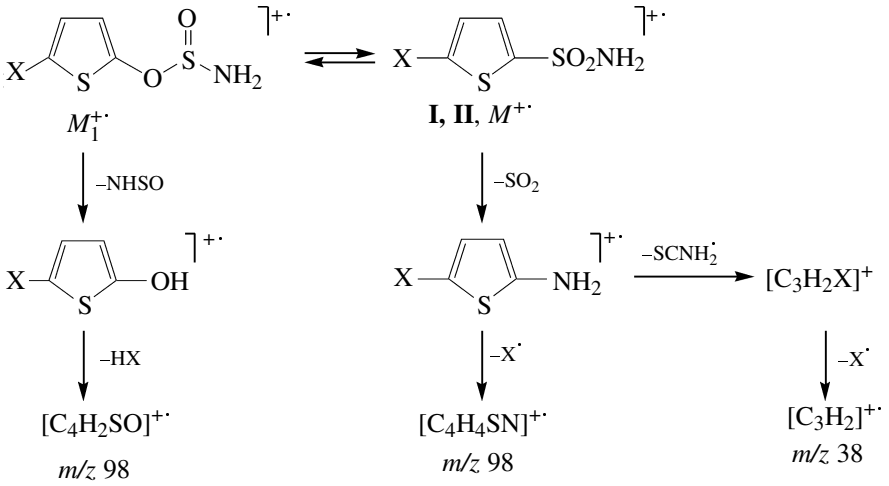
The direct and long-range coupling constants were measured by means of 2D ^1H–^{13}C HMBC and ^1H–^{13}C HSQC techniques, as well as by analysis of the decoupled ^{13}C NMR spectrum. The resulting ^1H–^{13}C coupling constants (Hz) for compounds **I**–**V** are shown in Scheme 1.

Scheme 1.



The mass-spectra of halogenated thiophenesulfonamides **I**–**V** are characterized by a stable molecular ion $[M]^{+\cdot}$ (W· 16–20%, see table) whose fragmentation is typical of arenesulfonamides [8–10]. Actually, the fragmentation of **I**–**V** involves the isomerization of $[M]^{+\cdot}$ prior to its dissociation, leading to skeletal rearrangement ions arising from C–O and C–N bond formation [8–10]. The main fragmentation pathway of the molecular ion of 5-halo-substituted thiophenesulfonamides **I**, **II** involves formation of an odd-electron $[M - SO_2]^{+\cdot}$ ion which further expels $X^{\cdot}$ and $H_2NCS^{\cdot}$ radicals (Scheme 2). A similar fragmentation pathway is also characteristic of compounds **III**–**V** (see table).

Scheme 2.



The rearranged radical ion $[M - NHSO]^{+\cdot}$ characteristic of sulfonamides [11] is more probably formed from dihalothiophene-3-sulfonamides **III**–**V** (Scheme 2). No elimination of CO from the molecular ions of sulfonamides **I**–**IV** was observed.

The third explicitly pronounced fragmentation pathway of the molecular ions of compounds **I**–**V** involves rupture of the S–N bond and expulsion of an $NH_2^{\cdot}$ radical. The probability of this fragmentation pathway practically halves with increasing number

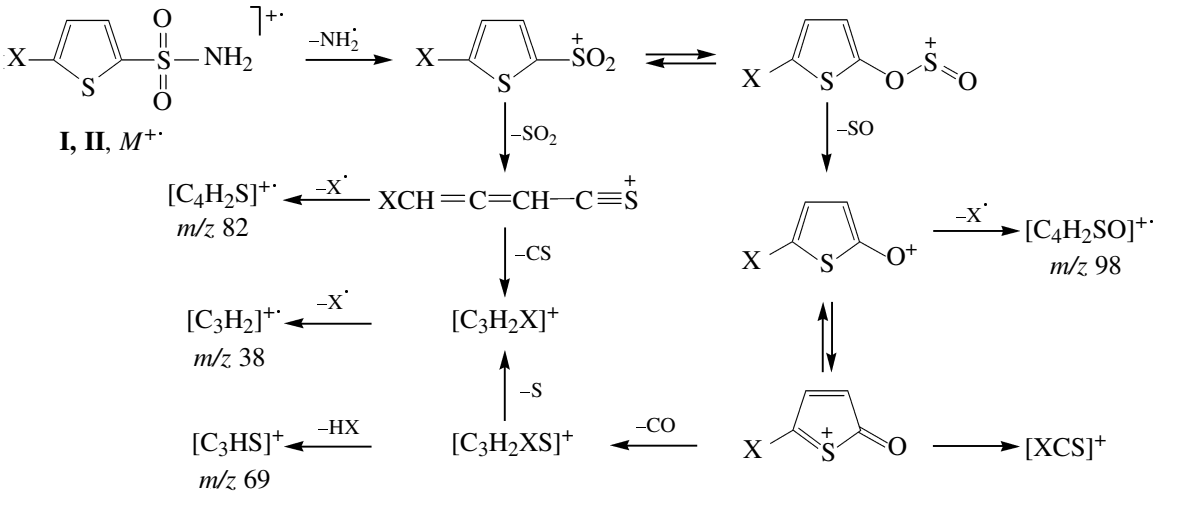
Principal characteristic ions in the mass-spectra of thiophenesulfonamide halo derivatives **I**–**V**, *m/z* (*I*, % of total ion current, mass numbers are given for ^{35}Cl and ^{79}Br)

Ion	Compound				
	I	**II**	**III**	**IV**	**V**
$M^{+\cdot}$	197 (16)	241 (18)	231 (16)	319 (18)	319 (20)
$[M - NH_2]^+$	181 (16)	225 (14)	215 (7)	303 (9)	303 (9)
$[M - SO_2]^+$	133 (10)	177 (8)	167 (6)	255 (8)	255 (6)
$[M - NHSO]^{+\cdot}$	134 (13)	178 (3)	168 (5)	256 (4)	256 (3)
$[(M - NH_2) - SO_2]^+$	117 (3)	161 (5)	151 (8)	239 (4)	239 (3)
$[(M - H_2NSO) - CO]^+$	105 (6)	149 (5)	139 (1)	227 (3)	227 (4)
$[(M - H_2NSO) - X]^{+\cdot}$ [a]	98 (1)	98 (1)	132 (11)	176 (2)	176 (1)
$[(M - H_2NSO_2) - X]^{+\cdot}$	82 (4)	82 (13)	116 (6)	160 (10)	160 (10)
$[(M - H_2NSO_2) - CS]^+$	73 (18)	117 (3)	107 (13)	195 (1)	195 (3)
$[CSX]^+$	79 (1)	123 (–)	79 (4)	123 (1)	123 (1)
$[(M - H_2NSO_2) - CSX]^{+\cdot}$	38 (4)	38 (7)	72 (2)	116 (1)	116 (3)
$[HOS(O)NH_2]^{+\cdot}$, *m/z* 81	(3)	(5)	(6)	(11)	(11)
$[C_3HS]^+$, *m/z* 69	(2)	(2)	(3)	(3)	(4)
$[H_2N{=}S{=}O]^+$, *m/z* 64	(6)	(6)	(6)	(9)	(7)
m/z 57	(4)	(3)	(1)	(1)	(1)
$[CHS]^+$, *m/z* 45	(3)	(4)	(2)	(4)	(4)
m/z 38 $[C_3H_2]^+$	(4)	(7)	(1)	(1)	(1)
m/z 37 $[C_3H]^+$	(2)	(3)	(3)	(5)	(6)

[a] The $[(M - NHSO) - HX]^{+\cdot}$ peak overlaps with the $[(M - H_2NSO) - X]^+$ peak.

of halogen atoms in the molecule. Scheme 3 exemplifies this fragmentation pathway by 5-halothiophene-2-sulfonamide and illustrates formation of the most abundant ions in the spectrum.

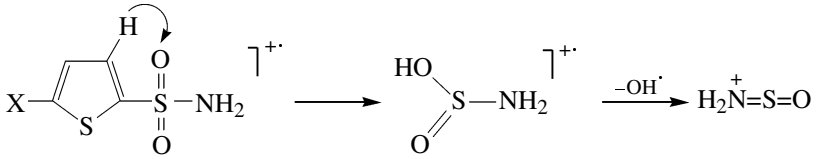
Scheme 3.



It is noteworthy that all spectra contain an intense odd-electron sulfinic acid ion peak at *m/z* 81, formed by rupture of the C–S bond and hydrogen migration (Scheme 4). Subsequent expulsion of the hydroxyl radical leads to an *m/z* 64 ion peak.

Therefore, the main fragmentation pathways of the molecular ions of compounds **I**–**V** are associated with C–S bond rupture and formation of skeletal rearrangement ions arising due to C–O and C–N bond formation. As the number of halogen atoms increases, the

Scheme 4.



I, II, $M^{+\cdot}$ *m/z* 81 *m/z* 64

contribution of this pathway increases. The nature and number of halogen atoms in the molecule do not affect the fragmentation pathway. The processes of halogen and CO expulsion from the molecular ion are also not observed.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered on a Bruker DPX-400 spectrometer at 400.6 (^{1}H) and 100.61 MHz (^{13}C) in 5-mm tubes for 5–10% DMSO-d_6 solutions against internal HMDS. The ^{13}C–^{1}H coupling constants were measured by 2D HSQC and HMBC techniques with the following parameters: spectrum width 800 Hz (^{1}H) and 5 kHz (^{13}C), pulse duration 6 (^{1}H) and 14 μs (^{13}C), relaxation delay 2.5 s, time of reading of the free induction decay signal 2 s, digital resolution 0.1 (^{1}H) and 0.5 Hz/point (^{13}C).

The mass spectra were recorded on a QP5050A GC–MS instrument (Shimadzu) at 70 eV. Chromatographic separation was performed on an SPBTM–5MS capillary column (60 m × 0.25 mm × 0.25 μm). Injector temperature 250°C, ion source temperature 220°C. The oven temperature was programmed from 60 to 250°C at a rate of 10 deg min^{-1}.

Reaction of 2,5-dihalothiophenes with chlorosulfonic acid. To a solution of 2.67–4.01 ml (40–60 mmol) of a freshly distilled chlorosulfonic acid in 5 ml of CCl_4, 10 mmol of 2,5-dichloro- or 2,5-dibromothiophene was added dropwise with vigorous stirring and cooling to –30°C. The reaction mixture was stirred for another 30 min at –25°C and 30 min at room temperature, and then poured on ice. The organic layer was separated, the solvent was removed under reduced pressure, the residue was mixed with 50 ml of 25% aqueous ammonia with intermittent shaking, kept for 3 h, and then neutralized with 10% HCl. The precipitate of thiophenesulfonamide formed was filtered off, dried, and investigated by physicochemical methods.

Under the above conditions, 2,5-dichlorothiophene formed 1.21 g of a mixture containing, according to ^{1}H NMR data, 70% of 5-chlorothiophene-2-sulfonamide (**I**) (yield 43%) and 30% of 4,5-dichlorothiophene3-sulfonamide (**III**) (yield 15%).

Similarly, from 2,5-dibromothiophene, 1.83 g of a mixture was obtained containing, according to ^{1}H NMR data, 3% of 5-bromothiophene-2-sulfonamide (**II**) (yield <2%), 54% of 4,5-dibromothiophene-3-sulfonamide (**IV**) (yield 30%), and 43% of 3,5-dibromothiopene-2-sulfonamide (**V**) (yield 25%).

5-Chlorothiophene-2-sulfonamide (I). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.20 d (1H, H^4), 7.43 d (1H, H^3), 7.79 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 127.51 (C^4), 129.78 (C^3), 133.15 (C^5), 144 (C^2).

5-Bromothiophene-2-sulfonamide (II). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.29 d (1H, H^4), 7.38 d (1H, H^3), 7.82 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 116.81 (C^5), 130.58 (C^3), 130.87 (C^4), 146.72 (C^2).

4,5-Dichlorothiophene-3-sulfonamide (III). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.31 s (1H, H^2), 7.79 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 125.81 (C^5), 126.48 (C^2), 126.94 (C^4), 140.17 (C^3).

4,5-Dibromothiopene-3-sulfonamide (IV). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.40 s (1H, H^2), 7.82 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 111.63 (C^5), 112.93 (C^4), 130.50 (C^2), 143.37 (C^3).

3,5-Dibromothiophene-2-sulfonamide (V). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.49 s (1H^4, H), 7.82 s (2H, NH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 116.80 (C^5), 111.27 (C^3), 135.08 (C^4), 141.26 (C^2).

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