

5-(2-Thienylsulfanyl)thiophene-2-carbaldehyde: Thioacetalization, Chloromethylation, and Oxidation

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Abstract—5-(2-Thienylsulfanyl)thiophene-2-carbaldehyde reacted with propane-1-thiol and propane-1,3-dithiol in the presence of chloro(trimethyl)silane to give previously unknown 5-[bis(propylsulfanyl)methyl]-2-(2-thienylsulfanyl)thiophene and 2-[5-(2-thienylsulfanyl)thiophen-2-yl]-1,3-dithiane. Chloromethylation of 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde with formaldehyde in a stream of hydrogen chloride in the presence of zinc chloride resulted in the formation of an oligomeric product consisting of thiophene rings connected alternately by sulfur and methylene bridges. The oligomer is formed via fast polycondensation of the primary chloromethylation product with the initial aldehyde. 5-(2-Thienylsulfanyl)thiophene-2-carbaldehyde was oxidized at the sulfide and aldehyde groups with 30% hydrogen peroxide in glacial acetic to produce 5-(2-thienylsulfonyl)thiophene-2-carboxylic acid.

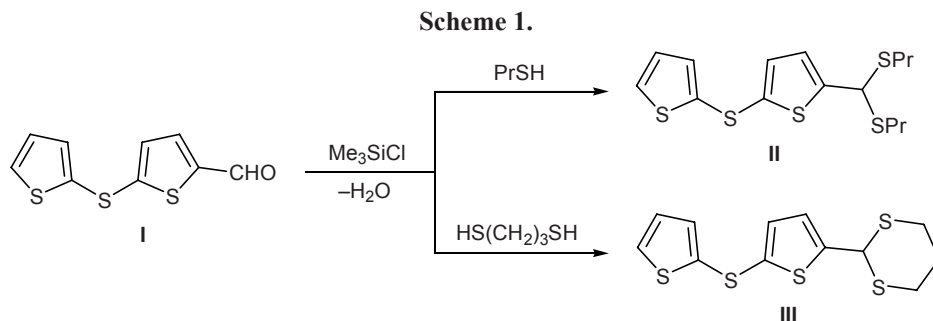
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The reactivity of thiophene and its derivatives makes them interesting as potential starting compounds for the preparation of many important products, including medical agents, biostimulators, pesticides, complexing agents, luminophores, heat-resistant and conducting polymeric materials, and polymeric monolayers [1–8]. Therefore, structures containing a thiophene fragment may be considered to be a promising heterocyclic system for the design of materials of new generation.

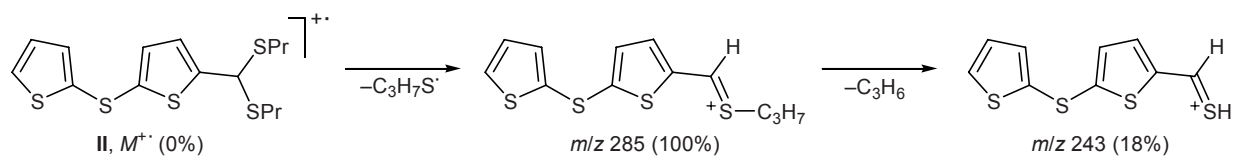
5-(2-Thienylsulfanyl)thiophene-2-carbaldehyde (**I**) has become accessible due to development of a simple procedure for the preparation of bis(2-thienyl) sulfide [9, 10]. Apart from thiophene fragments, molecule **I** contains aldehyde and sulfide moieties, so that its chemical transformations could underlie synthetic ap-

proaches to compounds possessing practically important properties. On the basis of 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde (**I**) we previously synthesized Schiff bases [11] and aldehyde azines [12] that attract interest as potential biologically active substances.

With a view to obtain new functionalized derivatives, in the present work we tried to perform further functionalization of aldehyde **I** at the carbaldehyde group, thiophene rings, and exocyclic sulfur atom. We recently showed that chloro(trimethyl)silane Me_3SiCl successfully catalyzes thioacetalization of thiophene-2-carbaldehyde and its derivatives [13]. In these reactions Me_3SiCl acts as source of protons and effective dehydrating agent via hydrolysis with formation of hexamethyldisiloxane.



Scheme 2.



In continuation of these studies we examined the reactions of 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde (**I**) with propane-1-thiol and propane-1,3-dithiol at reduced temperature using 4–5-fold excess of chloro-(trimethyl)silane. These reactions led to the formation of previously unknown compounds, 2-[bis(propylsulfanyl)methyl]-5-(2-thienylsulfanyl)thiophene (**II**) and 2-[5-(2-thienylsulfanyl)thiophen-2-yl]-1,3-dithiane (**III**), respectively (Scheme 1). The structure of compounds **II** and **III** was confirmed by the ^1H and ^{13}C NMR and mass spectra and elemental analyses. According to the ^1H NMR data, the 1,3-dithiane fragment in molecule **III** has a *chair* conformation.

Sulfide **II** under electron impact gives rise to unstable molecular ion $M^{+\bullet}$ which is not observed in the mass spectrum (Scheme 2). The main fragmentation patterns are those involving cleavage of the S–S bond and elimination of sulfur-containing radical SC_3H_7 , in keeping with the mass spectra of open-chain thiophenecarbaldehyde dithioacetals [13]. The $[M - \text{C}_3\text{H}_7\text{S}]^+$ ion (m/z 285) is the most abundant, and its further decomposition is accompanied by elimination of C_3H_6 molecule. Sulfide **III** under electron impact gives stable molecular ion $M^{+\bullet}$, m/z 316 (54%), and the subsequent dissociative ionization pattern is similar to that reported for 2-aryl-1,3-dithianes [14]. Odd-electron ion $[M - \text{C}_3\text{H}_6\text{S}]^+$ with m/z 242 (100%) is characterized by the maximal intensity in the spectrum. Further decomposition of structures **II** and **III** includes elimination of H_2S and CS molecules and HS and S species.

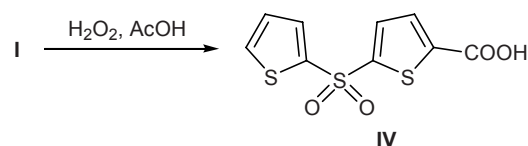
It is known that chloromethylation of thiophene-2-carbaldehyde with chloromethyl methyl ether in the presence of anhydrous aluminum chloride gives the corresponding 4-chloromethyl derivative and that the aldehyde group in the initial compound remains intact [15, 16]. We examined the behavior of 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde (**I**) in the reaction with formaldehyde and dry hydrogen chloride in the presence of ZnCl_2 . Unlike published data [15, 16], this reaction at 10–18°C resulted in the formation of an oligomeric product with a composition of $\text{C}_{28}\text{H}_{19}\text{ClS}_9\text{O}_2$. Presumably, both formaldehyde and aldehyde group in aldehyde **I** are involved in the

condensation process. The oligomeric product was isolated as a dark brown powder with mp 78–103°C. It is insoluble in alcohol and acetone but readily soluble in chloroform, which suggests that its molecular weight is not high. Its composition is determined by the number of units consisting of thienyl fragments. The molecular weight of the oligomer was estimated at ~700 a.m.u. on the basis of the concentration of residual chlorine and concentrations of the other elements. In the IR spectrum we observed absorption bands typical of stretching (3085 , $1525\ \text{cm}^{-1}$) and bending vibrations (1213 – $1080\ \text{cm}^{-1}$) of C–H and C=C bonds in thiophene ring, indicating that the polymer chain was formed without decomposition of thiophene rings.

Under analogous conditions, but in the absence of formaldehyde, we isolated a dark grey oligomeric product having a similar elemental composition but higher molecular weight (~1200 a.m.u.). These findings suggest that not only formaldehyde but also the aldehyde group at the thiophene ring is involved in the condensation process. However, in no case we succeeded in obtaining the desired chloromethyl derivative. Presumably, as in the chloromethylation of bis(2-thienyl) sulfide examined by us previously [17], the reaction of aldehyde **I** with formaldehyde and HCl is accompanied by fast polycondensation of the primary chloromethylation product with the initial aldehyde, which is facilitated by activation of position 2 in the thiophene ring.

Taking into account that sulfonyl-containing intermediates and precursors are important in the design of analogs of biologically active natural compounds [18], 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde (**I**) was oxidized with 30% hydrogen peroxide in glacial acetic acid at 50–55°C. The oxidation occurred at both sulfide and aldehyde groups with formation of previously unknown 5-(2-thienylsulfonyl)thiophene-2-carboxylic acid (**IV**) which was isolated in 47% yield (Scheme 3).

Scheme 3.



The IR spectrum of **IV** contained strong absorption bands at 1140 and 1330 cm^{-1} due to stretching vibrations of the sulfonyl group; in addition, absorption bands belonging to stretching vibrations of the C=O and OH groups were present at 1680 and 3430 cm^{-1} , respectively. The ^1H NMR spectrum of sulfone **IV** lacked aldehyde proton signal (δ 9.7 ppm in the spectrum of initial aldehyde **I**), indicating that oxidation of the aldehyde group occurred.

Thus we have proposed new methods for the synthesis of previously unknown sulfides **II** and **III** and sulfone **IV** which attract interest as potential biologically active compounds, practically important materials, and intermediate products for organic synthesis.

EXPERIMENTAL

The reaction mixtures and products were analyzed by GLC on an LKhM-8MD-2 chromatograph (2000 \times 3-mm column packed with 5% of XE-60 on Chromaton N-AW-HMDS; carrier gas helium; linear oven temperature programming from 30 to 230°C at a rate of 12 deg/min). The IR spectra were recorded in KBr on Specord 75IR and Bruker IFS-25 instruments. The ^1H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400.13 and 101.61 MHz, respectively, using CDCl_3 and $(\text{CD}_3)_2\text{CO}$ as solvents and hexamethyldisiloxane as internal reference. The mass spectra were obtained on a Shimadzu GCMS-QP5050A instrument (SPB-5 capillary column, 60 m \times 0.25 mm, film thickness 0.25 μm ; carrier gas helium, flow rate 0.7 ml/min; oven temperature programming from 60 to 260°C at a rate of 15 deg/min; detector temperature 250°C; ion source temperature 200°C, quadrupole mass analyzer; electron impact, 70 eV; a.m.u. range 34–650).

2-[Bis(propylsulfanyl)methyl]-5-(2-thienylsulfanyl)thiophene (II). Propane-1-thiol, 0.69 g (9 mmol), was added dropwise to a mixture of 0.9 g (4 mmol) of aldehyde **I** and 1.73 g (1.6 mmol) of Me_3SiCl , cooled to -5°C . The reaction started even after addition of a few drops of propane-1-thiol and was accompanied by heat evolution. The mixture was vigorously stirred for 0.5 h at -5 to 0°C and was then allowed to warm up to room temperature. The progress of the reaction was monitored by GLC. Excess chloro(trimethyl)silane and its hydrolysis product (HMDS) were removed under slightly reduced pressure, the dark brown residue, 1.22 g (85%), was dissolved in hexane, and the solution was cooled. Drops of a tarry material separat-

ed from the solution onto the bottom of the flask were collected, and treatment with hexane was repeated three times more. The extracts were combined and evaporated. Yield 1.11 g (78%), dark red oily substance, $n_D^{22} = 1.6130\text{--}1.6125$. ^1H NMR spectrum, δ , ppm: 0.95 t (3H, CH_3), 1.59 sext (2H, CH_2CH_3 , $^3J = 7.34$ Hz), 2.52 d.t (2H, SCH_2 , *AB* system, $^2J_{AB} = 12.59$, $^3J = 7.21$ Hz), 2.61 d.t (2H, SCH_2 , *AB* system), 5.03 s (1H, CH), 6.90 d.d (1H, 3-H, $^3J_{3,4} = 3.67$, $^4J_{4,2\text{-CH}} = 0.86$ Hz), 6.92 d.d (1H, 4'-H, $^3J_{4',3'} = 3.67$, $^3J_{4',5'} = 5.38$ Hz), 6.98 d (1H, 4-H, $^3J_{3,4} = 3.67$ Hz), 7.16 d.d (1H, 3'-H, $^3J_{3',4'} = 3.67$, $^4J_{3',5'} = 1.22$ Hz), 7.30 d.d (1H, 5'-H). ^{13}C NMR spectrum, δ_C ppm: 13.64 (CH_3), 22.1 (CH_2), 34.14 (CH_2S), 48.49 (CH), 125.90 (C^4), 127.44 ($\text{C}^{4'}$), 129.80 ($\text{C}^{5'}$), 131.84 (C^3), 132.94 ($\text{C}^{3'}$). Mass spectrum, m/z (I_{rel} , %): 285 (100) [$M - \text{SC}_3\text{H}_7$] $^+$, 243 (18) [$285 - \text{C}_3\text{H}_6$] $^+$, 211 (6), 210 (3), 209 (5), 127 (6), 115 (12), 70 (9), 69 (8), 45 (17), 43 (17), 41 (20), 39 (11). Found, %: C 50.55; H 5.49; S 42.98. $\text{C}_{15}\text{H}_{20}\text{S}_5$. Calculated, %: C 50.0; H 5.55; S 44.44.

2-[5-(2-Thienylsulfanyl)thiophen-2-yl]-1,3-dithiane (III) was synthesized in a similar way from 1.1 g (0.01 mol) of aldehyde **I** and 1.19 g (0.011 mol) of propane-1,3-dithiol in 5.4 g (0.05 mol) of Me_3SiCl . Yield of crude oily product 3.02 g (89%). By washing with diethyl ether and subsequent treatment according to the procedure described above for compound **II** we isolated 1.71 g (54%) of sulfide **III** as light brown crystals. ^1H NMR spectrum, δ , ppm: 1.93 d.t.t (1H, 5- H_{ax} , $^2J = 13.98$, $^3J = 10.23$, 3.65 Hz), 2.23 d.t.t (1H, 5- H_{eq} , $^3J = 2.79$, 5.64 Hz), 2.88 d.d.d (2H, 4- H_{eq} , 6- H_{eq} , $^2J = 14.32$ Hz), 2.92 d.d.d (2H, 4- H_{ax} , 6- H_{ax}), 5.22 s (1H, 2-H), 6.92 d.d (1H, 3'-H, $^3J = 3.71$ Hz), 6.94 d.d (1H, 4''-H, $^3J_{4'',3''} = 3.69$, $^3J_{4'',5''} = 5.39$ Hz), 6.98 d (1H, 4'-H, $^3J = 3.71$ Hz), 7.18 d.d (1H, 3''-H, $^3J_{4'',3''} = 3.69$, $^4J_{3'',5''} = 1.22$ Hz), 7.29 d.d (1H, 5''-H). ^{13}C NMR spectrum, δ_C , ppm: 25.22 (C^5), 30.98 (C^4 , C^6), 44.24 (C^2), 126.98 ($\text{C}^{3'}$), 127.92 ($\text{C}^{4''}$), 130.13 ($\text{C}^{5''}$), 132.60 ($\text{C}^{4'}$), 133.89 ($\text{C}^{3''}$). Mass spectrum, m/z (I_{rel} , %): 316 (54) [M] $^+$, 242 (100) [$M - \text{SC}_3\text{H}_6$] $^+$, 211 (14), 210 (4), 209 (14), 198 (12), 197 (6), 153 (11), 135 (6), 127 (11), 122 (9), 115 (9), 95 (26), 73 (4), 71 (22), 69 (21), 57 (11), 51 (7), 47 (6), 45 (47), 44 (4), 43 (9), 41 (16), 39 (23). Found, %: C 44.84; H 3.26; S 51.80. $\text{C}_{12}\text{H}_{12}\text{S}_5$. Calculated, %: C 45.57; H 3.80; S 50.63. M 316.55.

5-(2-Thienylsulfonyl)thiophene-2-carboxylic acid (IV). Aldehyde **I**, 1 g (4.4 mmol), was dissolved in 3.25 g (54 mmol) of glacial acetic acid, 2.64 ml of 30% hydrogen peroxide was added, and the mixture was stirred for 6 h at $50\text{--}55^\circ\text{C}$. The mixture was dilut-

ed with cold water (for more complete precipitation), and the precipitate was filtered off, washed with water, and dried. Yield 0.57 g (47%), light brown crystals, mp 211–213°C (decomp.; from ethanol–water, 1:1). IR spectrum, ν , cm^{-1} : 3430 (OH), 3110, 3095, 3030 (C–H), 1680 (C=O), 1525, 1500, 1445, 1390 (C=C, thiophene), 1330, 1140 (S=O), 1110, 1090, 1020, 920, 850, 830, 760, 720, 680, 670 (CH), 600, 570, 540, 520 (C–S). ^1H NMR spectrum (acetone- d_6), δ , ppm: 8.04 d.d (5'-H), 7.87 d.d (3'-H, $^4J = 1.3$ Hz), 7.24 d.d (4'-H, $^3J_{5'4'} = 5.0$ Hz, $^3J_{3'4'} = 3.84$ Hz), 7.78 d.d (4-H), 7.75 d.d (3-H), 5.13 br.s (OH). Mass spectrum: m/z 274 $[M]^+$. Found, %: C 39.69; H 2.00; S 34.87. $\text{C}_9\text{H}_6\text{O}_4\text{S}_3$. Calculated, %: C 39.42; H 2.19; S 35.04. M 274.32.

Reaction of 5-(2-thienylsulfanyl)thiophene-2-carbaldehyde (I) with formaldehyde and hydrogen chloride. Dry gaseous hydrogen chloride was bubbled at a high rate through a mixture of 5.6 g (0.025 mol) of aldehyde I, 2.7 ml of concentrated hydrochloric acid, 2 ml of 40% formaldehyde, and 0.2 g of zinc(II) chloride, maintaining the temperature at 16–18°C. The mixture turned dark blue. After vigorous stirring for 3 h, oligomeric product separated from the reaction mixture as a dark dense material. It was washed with hot methanol, treated with three portions of boiling water under reflux to remove formaldehyde and ZnCl_2 , and washed on a filter with ethanol and diethyl ether. The product was dried under reduced pressure and ground in a mortar. Yield 5.1 g, dark brown material which turned almost black in 2 weeks. IR spectrum, ν , cm^{-1} : 3085 (C–H, thiophene), 2961, 2870 (CH_2), 1656 w (C=O), 1516, 891, 800, 749 (C=C), 1421, 1373, 1342, 1284 (δCH_2), 1213, 1133, 1079 (δCH , thiophene), 666, 636, (C–S), 611 (C–Cl). Found, %: C 47.39; H 2.90; Cl 5.13; S 40.42.

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