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Synthesis of Open-Chain Dithioacetals from Thiophene-2-carbaldehyde and Its Analogs

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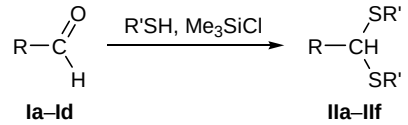
Abstract—A procedure for the synthesis of dithioacetals containing various thiophene fragments was developed on the basis of the reaction of thiophene-2-carbaldehyde and its analogs with thiols in chlorotrimethylsilane.

Interest in thiophene derivatives originates from the fact that many compounds of this series exhibit pharmacological activity [1, 2]. Therefore, structures containing a thiophene fragment may be regarded as a quite promising type of heterocycles for design of new medicines and biologically active substances. Available information on the synthesis of open-chain dithioacetals of the thiophene series is limited to our first publication [3] where we showed that alkanethiols react with thiophene-2-carbaldehyde and its chloro derivative in chlorotrimethylsilane (Me_3SiCl) in a different way than with aliphatic aldehydes [4, 5]; as a result, previously unknown dithioacetals were obtained. Known methods for the preparation of dithioacetals by reactions of carbonyl compounds with thiols require the presence of various protic acids, dry hydrogen chloride [6], sulfur dioxide [7], or Lewis acids (BF_3, $TiCl_4$, $InCl_3$, etc.) as catalyst [8–10]. However, in these cases additional treatment of the reaction mixtures is necessary to isolate the target products, which strongly complicates the experimental procedure.

Taking into account the above stated, we continued studies on reactions of aldehydes of the thiophene series in the system thiol–Me_3SiCl. The reactions were performed with a large number of aldehydes and thiols under various conditions (see table), and competing reaction of thiophene-2-carbaldehyde and paraformaldehyde with 1-propanethiol was examined. In addition, the reaction of thiophene-2-carbaldehyde with ethanethiol was monitored by NMR spectroscopy.

We found that alkanethiols readily react with aldehydes **Ia**–**Id** at reduced temperature in a 4–8-fold excess of chlorotrimethylsilane to give dithioacetals **IIa**–**IIf** in high yields (Scheme 1). Due to high volatility of Me_3SiCl, it can readily be removed from the reaction mixture at room temperature (without exerting side effects on the process), and the products are isolated by vacuum distillation of the residue.

Scheme 1.



Ia, **IIa**, **IIb**, R = 2-thienyl; **Ib**, **IIc**, **IId**, R = 5-chloro-2-thienyl; **Ic**, **IIe**, R = 5-methyl-2-thienyl; **Id**, **IIf**, R = thieno-[2,3-*b*]thienyl; **IIa**, **IIc**, R' = Et; **IIb**, **IId**–**IIf**, R' = Pr.

In the absence of chlorotrimethylsilane, reactions of aldehydes **Ia**–**Id** with alkanethiols give dithioacetals **IIa**–**IIf** in a poor yield (8–23%). The use of 4–8 equiv of Me_3SiCl raises the yield of **IIa**–**IIf** to 40–50% at an aldehyde-to-thiol ratio of 1:1, while in the presence of 2 or 3 equiv of thiol the yield increases to 70–98%. In the latter case, the reaction is complete in 0.5 h (see table, run nos. 10–12). However, in most cases the reaction time was 1.5 h with a view to compare the results with those obtained in the absence of Me_3SiCl.

According to the data of NMR monitoring (the reaction was performed in an NMR ampule), thiophene-2-carbaldehyde reacts with ethanethiol in Me_3SiCl at a high rate at room temperature immediately after mixing the reactants. Therefore, reactions of aldehydes **Ia**–**Id** with alkanethiols R'SH were carried out at –8 to –5°C to avoid oxidation of thiols

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Reactions of thiophene-2-carbaldehydes RCHO (**Ia**–**Id**) with alkanethioles R'SH

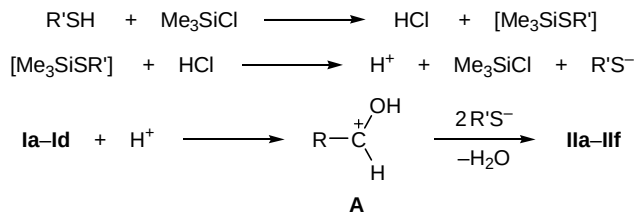
Run no.	Aldehyde (mol)	Alkanethiol (mol)	Me_3SiCl (mol)	Temperature, °C	Reaction time, h	Yield of **IIa**–**IIf**,[a] %
1	**Ia** (0.02)	EtSH (0.04)	–	–5 to 0	1.5	9
2	**Ia** (0.02)	EtSH (0.02)	(0.155)	–8 to –5	1.5	38
3	**Ia** (0.02)	EtSH (0.04)	(0.156)	–8 to –5	1.5	68
4	**Ia** (0.02)	PrSH (0.04)	–	–5 to 0	1.5	9
5	**Ia** (0.02)	PrSH (0.02)	(0.155)	–5 to 0	1.5	44
6	**Ia** (0.02)	PrSH (0.04)	(0.156)	–5 to 0	1.5	70
7	**Ib** (0.02)	EtSH (0.04)	–	–5 to 0	1.5	24
8	**Ib** (0.02)	PrSH (0.02)	(0.08)	–6 to 0	1.5	48
9	**Ib** (0.02)	PrSH (0.04)	(0.08)	–5 to 0	1.5	86
10	**Ib** (0.0064)	EtSH (0.013)	(0.03)	–8 to –2	0.5	91
11	**Ic** (0.01)	PrSH (0.02)	(0.08)	–5 to 0	0.5	73
12	**Id** (0.01)	PrSH (0.03)	(0.05)	–5 to 0	0.5	98

[a] Calculated on the initial aldehyde.

and polymerization of aldehydes. Under these conditions, the contribution of oxidation of alkanethiols to the corresponding dialkyl disulfides was insignificant (1–5%); the oxidation products were identified by GLC and mass spectrometry. In addition, small amounts (2–10%) of polymeric compounds were obtained. Thus the proposed procedure may be recommended for use on a preparative scale.

Competing reactions of aliphatic aldehydes and aldehydes **Ia**–**Id** were studied using thiophene-2-carbaldehyde (**Ia**) and paraform as model compounds. Their reaction with the system 1-propanethiol–Me_3SiCl gave bis(propylsulfanyl)methane and a polymeric product whose structure was not identified. According to the GLC data, the reaction mixture also contained unchanged aldehyde **Ia**. These data indicate that aliphatic aldehydes are more reactive than aldehydes **Ia**–**Id** toward thiols under the given conditions. Here, aldehyde **Ia** underwent only polymerization. Presumably, the mechanism of the process is as follows. Chlorotrimethylsilane reacts with alkanethiol to give hydrogen chloride which facilitates protonation of the carbonyl oxygen atom (Scheme 2). This stage occurs more readily with aliphatic aldehydes, for the carbonyl group in aromatic and heteroaromatic aldehydes is deactivated due to conjugation with the aromatic system. Carbocation **A** derived from aliphatic aldehydes reacts with one thiolate ion and one chloride ion to produce chloroalkyl sulfides [4], while the corresponding cation derived from thiophenecarbaldehydes always takes up two thiolate ions. The least aromatic aldehyde **Id** reacts with 1-propanethiol most effectively: the yield of the corresponding dithioacetal reaches 98% in 0.5 h in the presence of 5 equiv of Me_3SiCl (no side processes occur at –5 to 0°C).

Scheme 2.



The formation of a small amount of disulfides in reactions of aldehydes with thiols in Me_3SiCl indicates that thiols are partially oxidized with aldehydes. Aliphatic thiols are oxidized more difficultly than aromatic; therefore, the corresponding disulfides are formed in small or trace amounts. A different pattern was observed with benzenethiol. Neither aldehyde **Ia** nor benzenethiol reacted with Me_3SiCl in 24 h. Aldehyde **Ia** also failed to react with benzenethiol in the absence of Me_3SiCl. On the other hand, the reaction of thiophene-2-carbaldehyde (**Ia**) with benzenethiol in Me_3SiCl at –5 to 0°C afforded diphenyl disulfide as the major product (63% calculated on the initial benzenethiol). Thus benzenethiol is readily oxidized to diphenyl disulfide with thiophene-2-carbaldehyde in the presence of Me_3SiCl. Here, the formation of benzenethiolate ions is suppressed, and the yield of the corresponding dithioacetal, 2-[bis(phenylsulfanyl)-methyl]thiophene, sharply falls down. Arenethiols are known to undergo oxidation on exposure to air, and

even in basic medium their reactions are often accompanied by formation of sulfanyl radicals whose combination yields disulfides.

The structure of compounds **IIa–IIf** was proved by their elemental compositions and ^{1}H and ^{13}C NMR and mass spectra. The mass spectra of dithioacetals **IIa–IIf** lack molecular ion peaks, and the most abundant ions are those formed by elimination of R'S radical from the molecular ion ($[M - SR']^+$, 100%)

Thus reactions of aldehydes of the thiophene series with thiols in chlorotrimethylsilane open new prospects in the purposeful synthesis of dithioacetals containing thiophene fragments. The proposed approach may be extended to other aromatic and heteroaromatic aldehydes.

EXPERIMENTAL

The reaction mixtures and products were analyzed by GLC using an LKhM 8MD-2 chromatograph (2000 × 3-mm column packed with 5% XE-60 on Chromaton N-AW-HMDS; carrier gas helium; linear oven temperature programming). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.1 and 100.6 MHz, respectively, using $CDCl_3$ as solvent and HMDS as internal reference. The IR spectra of the polymeric product were recorded on a Bruker JFS-25 instrument in KBr and mineral oil. The mass spectra (electron impact, 60 eV) were obtained on a Shimadzu GCMS-QP5050A GC–MS system (60-m SE-54 capillary column; injector temperature 250°C; oven temperature programming from 70 to 260°C at a rate of 10 deg/min).

Ditihoacetals IIa–IIf (*general procedure*). Ethanethiol or 1-propanethiol was added dropwise to a solution of aldehyde **Ia–Id** in Me_3SiCl, cooled to –5°C. The mixture was vigorously stirred for 0.5–1.5 h at –8 to 0°C and was allowed to warm up to room temperature (for detailed conditions, see table). The progress of the reaction was monitored by GLC. After removal of Me_3SiCl, the products (except for compound **IIf**) were isolated by vacuum distillation. Compound **IIf** was extracted into hexane at room temperature, the extract was cooled, the solution was separated from a small amount of tars, the solvent was evaporated, and the residue was evacuated; 2-[bis(propylsulfanyl)-methyl]thieno[2,3-*b*]thiophene (**IIf**) was isolated as a red mobile oily substance.

2-[Bis(ethylsulfanyl)methyl]thiophene (IIa). Yield 68%, lemon yellow oily substance, bp 132–135°C (1–2 mm). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3), 2.59 d.q (2H, SCH_2, part *A* of *AB* quartet, $^2J_{AB}$ = 12.72, ^3J = 7.46 Hz), 2.66 d.q (2H, SCH_2, part *B* of *AB* quartet), 5.21 s (1H, CH), 6.88 d.d (1H, 4-H, $^3J_{4,3}$ = 3.55, $^3J_{4,5}$ = 5.14 Hz), 7.06 d.d.d (1H, 3-H, ^4J = 0.74 Hz), 7.20 d.d (1H, 5-H, $^4J_{5,3}$ = 1.34 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.02 (CH_3), 25.91 (SCH_2), 47.43 (CH), 125.19 (C^3), 125.51 (C^4), 126.19 (C^5), 144.31 (C^2). Found, %: C 49.88; H 6.48; S 43.33. $[M - SC_2H_5]^+$ 157. $C_9H_{14}S_3$. Calculated, %: C 49.54; H 6.42; S 44.03. *M* 218.

2-[Bis(propylsulfanyl)methyl]thiophene (IIb). Yield 70.4%, light yellow oily substance, bp 135–136°C (1–2 mm), n_D^{20} = 1.5625. ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, CH_3), 1.59 sext (2H, CH_2, ^3J = 7.4 Hz), 2.54 d.t (2H, SCH_2, part *A* of *AB* quartet, $^2J_{AB}$ = 12.72, ^3J = 7.46 Hz), 2.63 d.t (2H, SCH_2, part *B* of *AB* quartet), 5.16 s (1H, CH), 6.88 d.d (1H, 4-H, $^3J_{4,3}$ = 3.55, $^3J_{4,5}$ = 4.89 Hz), 7.06 d.d.d (1H, 3-H, ^4J = 0.74 Hz), 7.19 d.d (1H, 5-H, $^4J_{5,3}$ = 1.34 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.54 (CH_3), 22.48 (CH_2), 34.13 (CH_2S), 48.30 (CH), 125.29 (C^3), 125.65 (C^4), 126.33 (C^5), 145.31 (C^2). Found, %: C 54.33; H 7.00; S 38.93. $[M - SC_3H_7]^+$ 171. $C_{11}H_{18}S_3$. Calculated, %: C 53.65; H 7.31; S 39.02. *M* 246.

2-[Bis(ethylsulfanyl)methyl]-5-chlorothiophene (IIc). Yield 91.4%, light yellow oily substance, bp 125°C (1 mm), n_D^{22} = 1.5870. ^{1}H NMR spectrum, δ, ppm: 1.26 t (3H, CH_3), 2.62 d.q (2H, SCH_2, part *A* of *AB* quartet, $^2J_{AB}$ = 12.59, ^3J = 7.46 Hz), 2.68 d.q (2H, SCH_2, part *B* of *AB* quartet), 5.09 s (1H, CH), 6.73 d (1H, 4-H, $^3J_{4,3}$ = 3.79 Hz), 6.87 d.d (1H, 3-H, ^4J = 0.86 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.18 (CH_3), 26.13 (SCH_2), 47.92 (CH), 125.04 (C^3), 125.45 (C^4), 129.93 (C^5), 144.16 (C^2). Found, %: C 42.68; H 5.35; Cl 14.70; S 37.64. $[M - SC_2H_5]^+$ 191. $C_9H_{13}ClS_3$. Calculated, %: C 42.77; H 5.15; Cl 14.06; S 38.02. *M* 252.5.

2-[Bis(propylsulfanyl)methyl]-5-chlorothiophene (IId). Yield 86.2%, yellow oily substance, bp 165–170°C (2–3 mm), n_D^{20} = 1.5748. ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3), 1.58 sext (2H, CH_2, ^3J = 7.21 Hz), 2.54 d.t (2H, SCH_2, part *A* of *AB* quartet, $^2J_{AB}$ = 12.6 Hz), 2.63 d.t (2H, SCH_2, part *B* of *AB* quartet), 5.02 s (1H, CH), 6.68 d (1H, 4-H, $^3J_{4,3}$ = 3.67 Hz), 6.83 d (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 13.50 (CH_3), 22.42 (CH_2), 34.11 (CH_2S), 48.60 (CH), 125.01 (C^3), 125.45 (C^4), 129.85 (C^5), 144.37 (C^2). Found, %: Cl 13.00; S 34.85. $[M - SC_3H_7]^+$ 205. $C_{11}H_{17}ClS_3$. Calculated, %: Cl 12.65; S 34.29. *M* 280.5.

2-[Bis(propylsulfanyl)methyl]-5-methylthiophene (IIe). Yield 73.4%, light yellow oily substance, bp 152–154°C (3–4 mm), n_D^{20} = 1.5572. ^{1}H NMR spectrum, δ, ppm: 0.99 t (3H, C**H**$_3$CH$_2$), 1.62 sext (2H, CH$_2$, ^3J = 7.32 Hz), 2.57 d.t (2H, SCH$_2$, part *A* of *AB* quartet, $^2J_{AB}$ = 12.69, ^3J = 7.48 Hz), 2.66 d.t (2H, SCH$_2$, part *B* of *AB* quartet), 5.11 s (1H, CH), 2.44 br.s (3H, 5-CH$_3$), 6.54 d.q (1H, 4-H, $^3J_{4,3}$ = 3.45, $^4J \approx$ 1.0 Hz), 6.86 d (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 13.32 (**C**H$_3$CH$_2$), 22.28 (CH$_2$), 33.87 (CH$_2$S), 48.31 (CH), 15.17 (5-CH$_3$), 124.05 (C^4), 125.29 (C^3), 139.52 (C^5), 142.36 (C^2). Found, %: C 55.91; H 8.07; S 36.00. $[M - SC_3H_7]^+$ 185. $C_{12}H_{20}S_3$. Calculated, %: C 55.38; H 7.69; S 36.92. *M* 260.

2-[Bis(propylsulfanyl)methyl]thieno[2,3-*b*]thiophene (IIf). Yield 98%, red oily substance, n_D^{24} = 1.6250. ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH$_3$), 1.61 sext (2H, CH$_2$, ^3J = 7.39 Hz), 2.57 d.t (2H, SCH$_2$, part *A* of *AB* quartet, $^2J_{AB}$ = 12.49 Hz), 2.68 d.t (2H, SCH$_2$, part *B* of *AB* quartet), 5.16 s (1H, CH), 7.13 d (1H, 4-H, $^3J_{4,5}$ = 5.10 Hz), 7.26 s (1H, 3-H), 7.29 d (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 13.59 (CH$_3$), 22.40 (CH$_2$), 34.23 (SCH$_2$), 49.13 (CH), 118.34 (C^3), 119.81 (C^4), 127.17 (C^5), 137.12 (C^8), 145.43 (C^2), 148.59 (C^7). Found, %: C 51.15; H 5.80; S 42.40. $[M - SC_3H_7]^+$ 227. $C_{13}H_{18}S_4$. Calculated, %: C 51.65; H 5.96; S 42.38. *M* 302.

Competing reaction of thiophene-2-carbaldehyde (Ia) and paraformaldehyde with 1-propanethiol in chlorotrimethylsilane. A mixture of 2.24 g (0.02 mol) of aldehyde **Ia**, 0.6 g (0.02 mol) of paraformaldehyde, and 8.64 g (0.08 mol) of Me$_3$SiCl was cooled to –5°C, and 3.04 g (0.04 mol) of 1-propanethiol was slowly added under stirring. After 0.5 h, the precipitate was filtered off, washed with water, acetone, and diethyl ether, and dried. We thus obtained 1.4 g of a black high-melting polymeric powder with the following elemental composition, %: C 56.92; H 3.72; Cl 1.94; S 32.64. IR spectrum, ν, cm^{-1} (mineral oil): 3070 (C–H, thiophene); 2953, 2880 (CH$_2$); 1662 (C=O); 1605, 1556 (C=C, thiophene); 1514, 1411, 1352, 1255, 1201, 1090 (δCH, δCH$_2$); 1047 (δCH, thiophene); 787, 724, 698 (C–S); 419 (C–Cl). The residue was distilled under reduced pressure to isolate 1.66 g (50%) of bis(propylsulfanyl)methane, bp 93–96°C (9 mm), n_D^{20} = 1.4912; published data [4]: bp 94°C (8 mm), n_D^{20} = 1.4895.

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