EFFECT OF THE REACTION CONDITIONS ON THE CHARACTER OF THE PRODUCTS OF ACETYLATION OF 2-METHYLMERCAPTO-, 2-METHOXY-, AND 2-DIMETHYLAMINOTHIOPHENE

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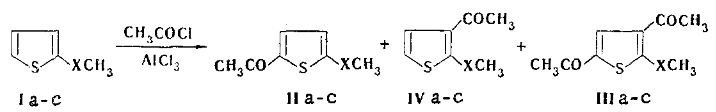
Acetylation of 2-methylmercaptothiophene by the action of acetyl chloride in methylene chloride at − 70°C in the presence of excess $AlCl_3$ gives a mixture of 5-methylmercapto-2-acetylthiophene, 5-methylmercapto-2,4-diacetylthiophene, and a small amount of 3-acetyl-substituted derivative. The acetylation of 2-methoxythiophene gives similar results. 5-Dimethylamino-2-acetylthiophene was obtained from 2-dimethylaminothiophene under similar conditions.

In a study of the directed character of electrophilic substitution in dimethyl(2-thienyl)sulfonium salts [1], we found it necessary to ascertain the ratio of the isomers formed in the reactions of 2-methylmercaptothiophene (Ia) and its analogs (Ib, c), since we detected serious errors in the literature data available on this problem. Moreover, in the light of data recently obtained [2, 3], it was of interest to compare the composition of the products formed under different conditions.

According to the available data [4], the acetylation of 2-methylmercaptothiophene with acetyl chloride in the presence of $SnCl_4$ gives 5-methylmercapto-2-acetylthiophene (IIa) in a yield of ~40%, but ketone IIa is obtained in somewhat better yield with acetic anhydride in the presence of H_3PO_4, and, in addition to the monoacetyl derivative, a very small amount of 5-methylmercapto-2,4-diacetylthiophene (IIIa) can be isolated. By carrying out the acylation of 2-methylmercaptothiophene with acetyl chloride at − 70° in the presence of excess $AlCl_3$, we detected 5-methylmercapto-2,4-diacetylthiophene (~15%), 5-methylmercapto-2-acetylthiophene (25%), and 2-methylmercapto-3-acetylthiophene (IVa, ~3%) in the reaction mixture. Thus, in agreement with the data in [5], the 5 position of 2-methylmercaptothiophene is more active than the 3 position; the formation of a considerable amount of the disubstituted derivative (IIIa) under the above-stated conditions occurs regardless of the presence or absence of excess acetyl chloride. If the reaction mixture is not worked up immediately after mixing of the reagents but is allowed to stand at −70° for a few hours, 5-methylmercapto-2,4-diacetylthiophene (IIIa) becomes the major acylation product (56%). The structures of the products of acetylation of sulfide Ia were confirmed by their PMR spectra (see Table 1). The signals were assigned in accordance with the data in [6], while the assignment for the ring protons of 2-methylmercapto-3-acetylthiophene was made with allowance for the chemical shifts of the ring protons of 3-nitro-2-methylmercaptothiophene that we found earlier in [1]. The spin-spin coupling constants of the ring protons (J ≈ 4 Hz) are characteristic for 2,5-disubstituted thiophenes (J ≈ 5.5 Hz is characteristic for 2,3-disubstituted thiophenes [6]).



I–IV a X=S; b X=O; c X=NCH_3

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TABLE 1. PMR Spectra of the Products of Acetylation of 2-Methylmercapto-, 2-Methoxy-, and 2-Dimethylaminothiophene

Compound	Chemical shifts of the protons, δ, ppm*					J_{34}, Hz	J_{45}, Hz	Solvent
	CH_3CO	CH_3X	3H	4H	5H			
IIa	2,36	2,52	7,38	6,80	—	4,2	—	CCl_4
IVa	2,39	2,50	—	6,96	7,27	—	5,5	CCl_4
IIIa	2,51	2,57	7,88	—	—	—	—	$CDCl_3$
IIb	2,32	3,91	7,33	6,16	—	4,5	—	CCl_4
IVb†	2,05	4,04	—	7,08	6,40	—	6,0	CCl_4
IIIb	2,45	4,13	7,88	—	—	—	—	$CDCl_3$
IIc	2,25	3,00	7,26	5,72	—	4,0	—	CCl_4

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*The signals of the protons of the CH_3CO, CH_3X, and 3H groups of IIIa and IIIb were singlets while the signals of the ring protons of IIa-c and IVa, b were doublets.

†The data are presented for the spectrum of a mixture with IIb.

It was expedient to compare the data presented above with the results of the acylation of 2-methoxythiophene (Ib) in the presence of both $SnCl_4$ and $AlCl_3$. It has been reported [7] that a mixture of 2-methoxy-3-acetylthiophene and 5-methoxy-2-acetylthiophene is formed in the acylation of 2-methoxythiophene with acetyl chloride in the presence of $SnCl_4$, and the first compound was isolated in a yield of ~1.5% by means of chromatography on Al_2O_3, while the second was isolated in a yield of ~20%. By carrying out the reaction in the presence of $SnCl_4$ but under milder conditions than described in [7], we obtained only 5-methoxy-2-acetylthiophene (IIb), the physical constants of which were in agreement with the data in [7], but not even traces of isomer IVb were found in the reaction product. We also failed to obtain this ketone in the acylation of Ib with acetyl chloride in the presence of $AlCl_3$, and IIb and 5-methoxy-2,4-diacetylthiophene (IIIb) were isolated from the reaction mixture. The structure of the latter was established on the basis of the results of elementary analysis, the PMR spectrum, and a molecular-weight determination. Its melting point (127-128°) coincided with the melting point of the product described by Sicé [7] as 2-methoxy-3-acetylthiophene (IVb). The reason for the error in [7] was that the conclusion regarding the composition of the product was made on the basis of elementary analysis only for C and H, and the results (C 54.07% and H 5.27%) are close to values calculated for both the monosubstituted and disubstituted compounds (see the Experimental section). According to the PMR spectrum, 2-methoxy-3-acetylthiophene is formed in addition to the already-mentioned 5-methoxy-2,4-diacetyl- and 5-methoxy-2-acetylthiophene in the acylation of Ib with acetyl chloride in the presence of $AlCl_3$, and these compounds are present in a ratio of ~20 : 75 : 5, respectively; this confirms the high activity of the 5 position in the Ib molecule. The signals in the PMR spectrum (see Table 1) were assigned on the basis of the data in [6], while the assignment of the ring protons of 2-methoxy-3-acetylthiophene was proposed with allowance for the data for Ib [8].

We acetylated 2-dimethylaminothiophene (Ic) in the presence of excess $AlCl_3$ at −70° in methylene chloride (see [3]). Because of the instability of the reaction product, we were able to isolate it in a yield of only ~ 10%; the results of elementary analysis and the PMR spectrum (see Table 1) are evidence that it is 5-dimethylamino-2-acetylthiophene (IIc). In contrast to sulfide Ia and ether Ib, the formation of other products (IIIc and IVc) was not observed.

The conditions that we used (excess $AlCl_3$ at − 70°) favor the formation of complexes with aluminum chloride at the functional group of the thiophenes. It is natural to assume that complexing with aluminum chloride should lead to overall deactivation of the thiophene ring in the compounds under consideration (Ia-c). For this reason, even a small amount of uncomplexed compound, which is present because of the reversibility of complexing, should have a pronounced effect on the composition of the products formed. This effect apparently should diminish as the stability of the complex increases, and the stability increases in the order sulfide < ether < amine, as can be judged, for example, from the data in [9]. At first glance, the formation of diacetyl-substituted compounds from 2-methylmercapto- and 2-methoxythiophene under mild conditions is surprising. However, it should be borne in mind that the stability of the complex with $AlCl_3$ at the sulfur atom of the CH_3S group or at the oxygen atom of the CH_3O group in the monoacylated molecules should be sharply reduced as compared with starting sulfide Ia or ether Ib. It may therefore be supposed that the diacetyl-substituted compounds are formed as a result of the conversion of uncomplexed [at the CH_3S (CH_3O) group] substrates, in which the thiophene ring is activated by a −I, +M substituent. In the case of amine Ic, one observes the formation of a more stable complex in which the thiophene ring is deactivated; this leads to substitution of only the free α position.

EXPERIMENTAL

The PMR spectra of CCl_4 or $CDCl_3$ solutions of the compounds were recorded with a Varian DA-60-IL spectrometer with an operating frequency of 60 MHz with hexamethyldisiloxane as the internal standard. The chemical shifts are presented on the δ scale relative to tetramethylsilane. The authors thank L. V. Shmelev for recording the PMR spectra.

Acetylation of 2-Methylmercaptothiophene (Ia). A. A solution of 5.2 g (0.04 mole) of Ia [4] in 15 ml of dry CH_2Cl_2 was added by drops to a cooled (−70°) suspension of 40 g (0.3 mole) of $AlCl_3$ in 50 ml of dry CH_2Cl_2, after which 23.1 g (0.3 mole) of CH_3COCl was added, and the resulting mixture was poured into cold water. The product was extracted with chloroform, and the extract was washed successively with water, $NaHCO_3$ solution, and water and dried over $MgSO_4$. The solvent was removed, and the residue (7.8 g of a yellow liquid that crystallized on cooling) was washed several times with small portions of hexane at room temperature. The undissolved light-colored crystalline product (1.18 g) with mp 115-120° was sublimed at 60-70° (20 mm) to give a product with mp 119.5-120.5°; no melting-point depression was observed for a mixture of this product with a genuine sample of 5-methylmercapto-2,4-diacetylthiophene (IIIa) [4]. The combined hexane extracts (~ 100 ml) were evaporated, and the residue was chromatographed on Al_2O_3 (with ether as the eluent) to give keto sulfides IIa and IVa. This procedure yielded 1.6 g (24%) of 5-methylmercapto-2-acetylthiophene (IIa) with mp 51-52°, which did not depress the melting point of IIa obtained by the method in [4].* Oxidation of sulfide IIa with 30% H_2O_2 in acetic acid gave the sulfone with mp 136-137° (from CH_3OH). Found: C 41.4; H 4.3; S 31.4%. $C_7H_8O_3S_2$. Calculated: C 41.2; H 3.9; S 31.4%. 2-Methylmercapto-3-acetylthiophene (IVa) [0.21 g (~3%)] with mp 32-34° was also obtained. The sulfone obtained from IVa had mp 121-121.5° and did not depress the melting point of a sample (mp 121.5-122.5°) obtained by oxidation of sulfide IVa, which was synthesized by the action of butyllithium on 3-acetothienone diethylketal and subsequent treatment of the organolithium compound with sulfur and methyl iodide. A mixture of a sample of this sulfone with the sulfone obtained from IIa had mp 96-98°. Samples of 2-methylmercapto-3-acetylthiophene (IV) and the corresponding sulfone could not be isolated in the analytically pure state.

B. The experiment was carried out as described above but the mixture was held at −70° for 7 h after the addition of CH_3COCl. The usual workup gave 5-methylmercapto-2,4-diacetylthiophene (IIIa) (56%) with mp 104-110°, which had mp 118-119.5° after vacuum sublimation and did not depress the melting point of the sample obtained above.

Acetylation of 2-Methoxythiophene (Ib) in the Presence of $SnCl_4$. A solution of 2.28 g (0.02 mole) of Ib [7] in 5 ml of CH_2Cl_2 was added by drops to a solution of 1.5 ml (0.02 mole) of CH_3COCl and 2.3 ml (0.02 mole) of $SnCl_4$ in 20 ml of CH_2Cl_2 at −70°, after which the mixture was stirred at −70° for 10 min and poured into a mixture of crushed ice and hydrochloric acid (1 : 10). The mixture was extracted with chloroform, and the extract was washed with water, $NaHCO_3$ solution, and water and evaporated. The residue was chromatographed on Al_2O_3 in hexane−ether (4 : 1) to give 0.76 g (24%) of 5-methoxy-2-acetylthiophene (IIb) with mp 33-35°, which was in agreement with the melting point given in [7].

Acetylation of 2-Methoxythiophene in the Presence of $AlCl_3$. A. A solution of 2.85 g (0.025 mole) of Ib in 25 ml of CH_2Cl_2 was added by drops to a cooled (to −70°) suspension of 27 g (0.2 mole) of $AlCl_3$ in 60 ml of dry CH_2Cl_2, and the mixture was immediately poured over ice. The aqueous mixture was extracted with chloroform, and the extract was washed successively with water, $NaHCO_3$ solution, and water and evaporated. The residue was extracted with cold hexane, and the hexane extract was evaporated to give 2 g of a substance which was chromatographed on Al_2O_3 in hexane−ether (1 : 1) to give 0.17 g of 5-methoxy-2,4-diacetylthiophene (IIIb) with mp 123-127° (see below) and 1.08 g of yellow crystals with mp 22-26°, which, judging from the PMR spectra, was 5-methoxy-2-acetylthiophene (IIb) containing ~5-7% 2-methoxy-3-acetylthiophene (IVb). According to the PMR spectra, the mixture of products before separation contained IIIb, IVb, and IIb in a ratio of ~20 :5 :75.

B. The reaction was carried out under the conditions of the preceding experiment, but the mixture was held at −70° for 1 h, during which considerable resinification was observed. The usual workup gave a residue, which was extracted successively with cold and hot hexane. The first extract yielded 5-methoxy-2-acetylthiophene (IIb) with mp 30-33° (from hexane), which, after sublimation at 60-70° (20 mm) had mp 34-35° and did not depress the melting point of a sample obtained by acetylation in the presence of $SnCl_4$ (see above). Found: C 53.8; H 5.1; S 20.6%. $C_7H_8O_2S$. Calculated: C 53.8; H 5.2; S 20.5%. The second

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* The yield of IIa reached 74% when the acetylation of Ia was carried out in the presence of $SnCl_4$ by the method in [4].

extract yielded 5-methoxy-2,4-diacetylthiophene (IIIb) with mp 127-128° (from hexane). Found: C 54.7; H 5.1; S 16.0%; mol. wt. (mass spectrometry) 198. $C_9H_{10}O_3S$. Calculated: C 54.5; H 5.1; S 16.2%; mol.wt. 198.2.

Acetylation of 2-Dimethylaminothiophene (Ic). A solution of 1.27 g (0.01 mole) of 2-dimethylaminothiophene [10] in 20 ml of dry CH_2Cl_2 and 5 ml (0.07 mole) of CH_3COCl were added successively by drops to a cooled (to −70°) suspension of 10 g (0.075 mole) of $AlCl_3$ in 20 ml of CH_2Cl_2, and the mixture was stirred with cooling for 1 h and poured into 60 ml of cooled (to −30°) concentrated HCl (see [3]). The resulting viscous light-green emulsion was extracted successively with chloroform and ether. The aqueous layer was added by drops to a cooled (to −10°) 50% KOH solution (100 ml), after which the mixture was extracted with ether. The extract was dried over $MgSO_4$, the ether was evaporated, and the residue was subjected to low-temperature crystallization from hexane to give 0.15 g (9%) of 5-dimethylamino-2-acetylthiophene (IIc) with mp 65-66°. Found: C 56.7; H 6.7; S 18.7; N 7.8%. $C_8H_{11}NOS$. Calculated: C 56.8; H 6.6; S 18.9; N 8.3%.

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