SYNTHESIS AND ELECTROPHILIC TRICHLOROMETHYLATION OF 2,4-DIALKYLTHIOPHENES. SOME TRANSFORMATIONS OF 2,4-DI-tert-BUTYL-5-(TRICHLOROMETHYL)THIOPHENE

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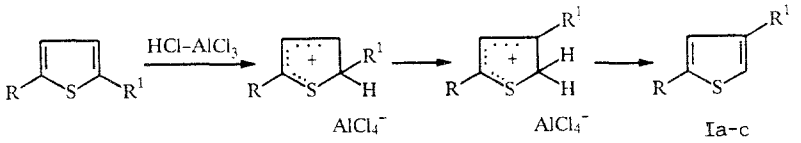
The disproportionation products of the C-protonation of 5-tert-butyl-2-methyl- and 2-ethylthiophene first give 4-tert-butyl-2-methyl- and 2-ethylthiophene. We studied the electrophilic trichloromethylation of a series of 2,4-dialkyl thiophenes and showed that the reaction goes smoothly only for the most sterically hindered 2,4-di-tert-butyl-thiophene. We studied the reaction of 2,4-di-tert-butyl-5-(trichloromethyl)thiophene with some O- and N-nucleophiles.

In [1] we studied the trichloromethylation of 2,4-dichlorothiophene by carbon tetrachloride in the presence of aluminum chloride using methylene chloride or excess carbon tetrachloride as solvent: the result was a high yield of 3,5-dichloro-2-trichloromethylthiophene. Here, steric shielding of the trichloromethyl group by the chlorine atom result in the minimum amount of the undesirable 'coupling' reaction forming the corresponding substituted dithienyldichloromethane. From these results as well as the fact that the volume of the chlorine atom is approximately that of the methyl group, we selected for the present work 2,4-dialkylthiophenes distinguished by differences in the volume of the alkyl group: 2,4-di-tert-butylthiophene (Ia), 4-tert-butyl-2-ethylthiophene (Ib), 4-tert-butyl-2-methylthiophene (Ic), 4-isopropyl-2-ethylthiophene (Id), 2,4-diethylthiophene (Ie), and 2,4-dimethylthiophene (If).

Di-tert-butylthiophene Ia was obtained by disproportionation of the products of α-C-protonation of a mixture of 2,4- and 2,5-di-tert-butylthiophenes, as described in [2]. We also showed that upon disproportionation of analogous σ-complexes obtained from 5-tert-butyl-2-ethylthiophene and 5-tert-butyl-2-methylthiophene, migration of the tert-butyl groups leading after deprotonization to the corresponding 2-alkyl-4-tert-butylthiophenes (Ib, Ic) was observed. The syntheses of the remaining starting 2,4-dialkylthiophenes are given in the experimental part.



Ia R = R^1 = *t*-Bu; b R = Et, R^1 = *t*-Bu; c R = Me, R^1 = *t*-Bu

The 2,4-disubstituted thiophene structure of compounds Ib and Ic follows from the values of the constant J_{35} ~ 2 Hz, and the fact that the molecules have the tert-butyl groups in the β-position is confirmed by the equal chemical shift in the ^{1}H NMR spectrum of the α-C-protonation product of these compounds and the analogous σ-complexes obtained from 2,4-dialkylthiophenes Ia, Ie, and If [3, 4] (see Table 1).

For most of the listed 2,4-dialkylthiophenes, the isolation of the trichloromethylation product was unsuccessful. This required the acidic oligomerization of the starting material under the comparatively severe conditions which this reaction requires (about 40°C in the presence of equimolar or excess amounts of aluminum chloride) and possibly, 'coupling' with the formation of dithienyldichloromethanes. Upon reducing the temperature, the 2,4-dialkylthiophenes did not react and a significant part of

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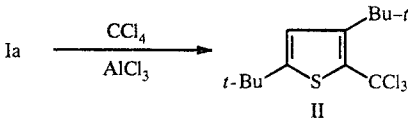
TABLE 1. ^{1}H NMR Spectra of 3,5-Dialkyl-2H-thiophene Ions

Starting 2,4-dialkyl-thiophene	Cation chemical shift, δ, ppm								Literature
	2-H	4-H	3-CH_2	3-Me	3-t-Bu	5-CH_2	5-Me	5-t-Bu	
Ib*	5,10	7,63	—	—	1,51	3,50	1,60	—	—
Ic**	5,10	7,63			1,50	—	3,21	—	—
Ia	4,96	7,67			1,48			1,60	[3]
Ie	5,12	7,64	3,07	1,40		3,47	1,56		[4]
If	5,03	7,53		2,72			3,18		[4]

*Coupling constants for thienylium ion: 2-H, t, J = 4.5 Hz; 4-H, s; 3-tert-butyl, s; 5-CH_2, m; 5-Me, t, J = 7 Hz.

**Coupling constants for thienylium ion: 2-H, q, J = 4 Hz; 4-H, s; 3-tert-butyl, s; 5-Me, t, J = 4 Hz.

the starting material was recovered unchanged. Only in the case of 2,4-di-tert-butyl-5-trichloromethylthiophene Ia, with two voluminous alkyl groups, was oligomerization impeded, the trichloromethylation proceeding sufficiently smoothly to give a 50% yield on the taken and 75% on the reacted starting material of 2,4-di-tert-butyl-5-trichloromethylthiophene (II). Part of the starting di-tert-butylthiophene Ia was recovered after trichloromethylation, apparently because combined under the reaction conditions ($AlCl_3$ and liberated HCl) as stable α-C-protonation products (compare data given in the review [5]). In addition to the trichloromethyl substituted II, a small amount of high-boiling residue was also obtained, containing, as judged by the 1H NMR spectrum, the corresponding substituted dithienyldichloromethane. The structure of the trichloride II was shown by its 1H NMR as well as its chemical transformations.



II

The combination of the data presented and the results published earlier [1] show that the opportunity for electrophilic trichloromethylation in the thiophene series is for the most part more limited than for compounds of the benzene series. It may be assumed that these limitations result from the increased activity of thiophene derivatives with respect to electrophiles and the features of their geometry (larger than the benzene analogs, "external" valence angles), which sharply facilitate oligomerization of the starting compounds under trichloromethylation conditions and further transformations of trichloromethylthiophene leading to dithienyldichloromethanes. Specifically, the trichloromethylation of m-xylene proceeds rather smoothly [6], but its thiophene analog, 2,4-dimethylthiophene, and a series of other 2,4-dialkylthiophenes having large-volume substituents in the 4-position, are subject to 'coupling' and oligomerization. Acidic oligomerization is prevented only for the 2,4-di-tert-butylthiophene, but even in this case the presence of very large substituents apparently does not completely suppress further transformations of the product trichloride II. Taking into account that the interaction with carbon tetrachloride of compounds of the thiophene series carrying electron acceptor substituents requires rather strenuous conditions leading to 'coupling' products [7], prospective subjects for study of electrophilic trichloromethylation are disubstituted thiophenes in which one of the substituents is deactivating and the other is activating, as well as trisubstituted compounds.

The final part of this work is devoted to a study of some chemical transformations of trichloride II. It should be noted initially that purification of the latter from a small admixture of the starting di-tert-butyl thiophene Ia did not succeed because of its exceptionally easy hydrolysis and alcoholysis. Thus, in attempts at chromatographic purification of compound II on silica gel readily gave the corresponding acid (III), and upon treatment with hydroxylamine in alcohol (see [8]), the ethyl ester of 3,5-di-tert-butyl-2-thiophene carboxylic acid (V) was obtained instead of the expected carboximoyl chloride (IV). In this connection it should be pointed out that esters of carboxylic acids form side-by-side with carboximoyl chlorides in the case of trichloromethyl arenes [9]. Apparently the π-donor nature of the thiophene ring, activated in this case by the two tert-butyl substituents, strongly facilitates the hydrolysis and alcoholysis of the trichloromethyl group taking place in the absence of sulfuric

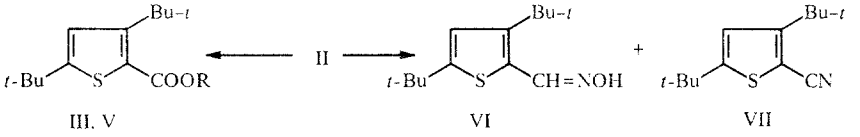
TABLE 2. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp°C or bpr°C (mm Hg)	^{1}H NMR spectrum, δ, ppm (J, Hz)		Yield, %
			ring protons	substituent protons	
Ib	$C_{10}H_{16}S$	78...85 (10)	6,84, d, 5-H 6,79, d, 3-H (2)	2,90, q, $\underline{CH_2}Me$; 1,40, t, $CH_2\underline{Me}$ (7,5); 1,36, s, CMe_3	68
Ic	$C_9H_{14}S$	90(20)	6,78, d, 5-H 6,73, d, 3-H (2)	2,52, s, Me; 1,35, s, CMe_3	70
Id	$C_9H_{14}S$	108...112 (53)	6,90, s (2H), 3-H, 5-H	3,10, m, $\underline{CH}Me_2$; 1,43, d, $CH\underline{Me_2}$ (7); 3,05, q, $\underline{CH_2}Me$; 1,50, t, $CH_2\underline{Me}$ (7)	75
III	$C_{13}H_{20}O_2S$	193	6,90, s, 4-H	11,38, br.s, COOH; 1,47, s and 1,40, s 3- and 5-CMe_3	*
IV	$C_{13}H_{20}ClNOS$	135...138	6,71, s, 4-H	8,22, s, NOH; 1,38, s and 1,36, s, 3- and 5-CMe_3	42
V	$C_{15}H_{24}O_2S$	160(2,5)**	6,85, s, 4-H	4,29, q, $COO\underline{CH_2}Me$; 1,35, t, $COOCH_2\underline{Me}$ (7); 1,46, s and 1,38, s, 3- and 5-CMe_3	86
VII	$C_{13}H_{19}NS$	118...119 (1,5)	6,78, s, 4-H	1,43, s, and 1,38, s, 3- and 5-CMe_3	68
VIII	$C_{25}H_{39}NS_2$	217...219	6,75, s, 4-H 6,62, s, 4'-H	8,66, s, CH=N; 1,48, s, 1,47, s, 1,42, s and 1,38, s, 3-, 5-, 3'- and 5'-CMe_3	4,5

*Acid III was isolated upon attempted purification of trichloride II by TLC on silica gel. Yield not determined.

**Bath temperature.

acid usually used in these cases. The reaction of trichloride II with hydroxylamine in pyridine leads to products of reductive condensation (see [10, 11]): oximes (VI) and nitriles (VII).

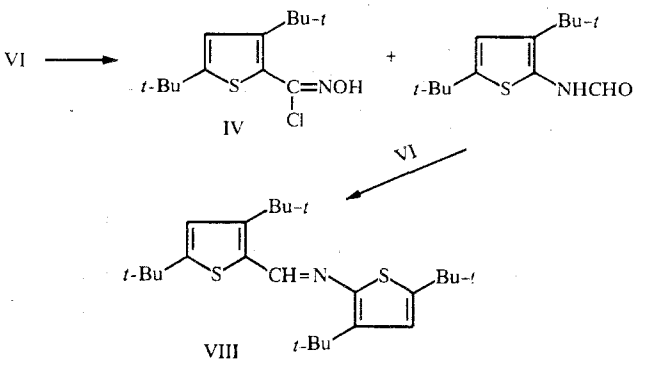


III, V VI VII

III R = H; V R = Et

Use of diethyl ether for extraction of the reductive condensation products VI and VII surprisingly gave an appreciable amount of ester V, which probably arises as a result of the reaction of unreacted trichloride II, or of the partially hydrolyzed acid chloride of III formed from II, with ethanol contained in the normally used amount of ether (0.2-0.3% by GLC). After substitution of methylene chloride for ether the formation of V was not observed.

It also is interesting to note that in the synthesis of the previously-known hydroximoyl chloride IV by the action of nitrosyl chloride on 3,5-di-tert-butyl-2-thiophencarbaldoxime (VI), we observed the formation of a small quantity of the azomethine (VIII) side product. The latter apparently is obtained from the oxime VI and 2-formylamino-3,5-di-tert-butylthiophene, arising as a result of a Beckmann rearrangement of the indicated oxime under chlorination conditions (NOCl and by-product HCl). It should be noted that the formation of N-formylamine together with the nitrile by Beckmann rearrangement of 2,4,6-trimethylbenzaldoxime (structurally related to oxime VI) was described by Hantzsch and Lucas in 1895 [12].



EXPERIMENTAL

The ^1H NMR spectra were obtained on JEOL FX-90Q (90 MHz) and Bruker WM-250 (250 MHz) instruments in $CDCl_3$ for neutral compounds and CD_2Cl_2 for thienyl ions.

Chromatographic analyses were carried out with an LKhM-80 chromatograph ("Chromatograph" plant) with flame-ionization detection, a 2 × 1500 mm column containing 5% SE-30 on Chromosorb R in isothermic (150-160°C) and linearly programmed temperature (130-200°C, 8 deg/min) regimes.

Mass spectra were obtained with a Varian MAT CH-6 mass spectrometer with direct introduction of the sample into the ionization chamber (ionization energy = 70 eV, emission current = 100 μA) and a Varian MAT-111A GLC-mass spectrometer (ionization energy = 70 eV, emission current = 500 μA) with a 25 m capillary column, stationary phase = SE-30.

Elemental analysis data for C, H, and S corresponded with the calculated values for all newly prepared compounds. The characteristics of these compounds are presented in Table 2.

Starting Materials (Ia-f). 2,4-Di-tert-butylthiophene Ia, 2,4-dimethylthiophene If, and 2,4-diethylthiophene Ie were prepared by methods in [2, 3, 4], respectively.

4-Isopropyl-2-ethylthiophene (Id) was synthesized from 2-acetyl-4-isopropylthiophene [13] by Kishner reduction (boiling with hydrazine hydrate in diethylene glycol in the presence of KOH).

4-tert-Butyl-2-ethylthiophene (Ib). Acetylation of 2-tert-butylthiophene [3] with acetyl chloride in the presence of $SnCl_4$ in benzene by the standard method described for the acetylation of thiophene [14] gave 2-acetyl-5-tert-butylthiophene with bp 136-138°C/16 mm Hg. ^1H NMR spectrum: 7.47 (1H, d, 3-H); 6.82 (1H, d, 4-H, $J_{3,4}$ = 4.4 Hz); 2.43 (3H, s, MeCO); 1.31 (9H, s, t-Bu) ppm. Yield, 85%, Kishner reduction of this product analogously to the synthesis of Id gave 5-tert-butyl-2-ethylthiophene with bp 75-80°C/9 mm Hg. ^1H NMR spectrum: 6.68 (2H, br. s, H_{arom}); 2.88 (2H, qu, CH_2); 1.48 (9H, s, t-Bu); 1.38 (3H, t, $MeCH_2$) ppm, J_{Et} = 7.5 Hz. Yield, 68%. A solution of 4.73 g (0.028 mole) of 5-tert-butyl-2-ethylthiophene in 10 ml of dry methylene chloride was added dropwise to a cooled suspension of 4 g (0.03 mole) of aluminum chloride in 50 ml of methylene chloride, previously saturated at −70°C with hydrogen chloride. The mixture was kept at −70°C for 20 min, and then was kept at room temperature for 2 days. The reaction mixture was poured onto ice, the organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined extract was washed with 1% NaOH and water, dried over magnesium sulfate, the solvent was evaporated, and the residue was distilled to give 3.2 g (68%) of product Ib.

4-tert-Butyl-2-methylthiophene (Ic). Kishner reduction of 5-tert-butyl-2-thiophene aldehyde [15] gave 5-tert-butyl-2-methylthiophene, bp 77-79°C/19 mm Hg. ^1H NMR spectrum: 6.51 (2H, br. s, 3-H and 4-H); 2.42 (3H, s, Me); 1.28 (9H, s, CMe_3). The characteristics presented correspond with those given in [16]. The transformation of this product into the 2,4-isomer Ic proceeded analogously to that described above for the conversion of 5-tert-butyl-2-ethylthiophene into compound Ib.

Electrophilic Trichloromethylation of 2,4-Di-tert-butylthiophene Ia. To a suspension of 3.5 g (0.026 mole) of anhydrous $AlCl_3$ in a boiling (40°C), energetically stirred mixture of 10 ml of CCl_4 and 40 ml of CH_2Cl_2 was added dropwise 40 ml of a solution of 2 g (0.01 mole) of compound Ia in a mixture of 6 ml CCl_4 and 7 ml CH_2Cl_2. After boiling for 1 h and standing for 3 h at room temperature, the mixture was added to ice. The organic layer was separated, the aqueous layer was extracted with methylene chloride, and the combined extract was washed with water, 1% NaOH, again with water, and dried over $CaCl_2$. The solvent was removed and the residue was distilled under vacuum to give starting compound Ia, bp 72°C/3 mm Hg, recovery 0.66 g (33%), and 3,5-di-tert-butyl-2-trichloromethylthiophene II, bp 145°C/3 mm Hg, yield 1.6 g (50% based on starting material, 75% based upon conversion of Ia). ^1H NMR spectrum of II: 6.90 (1H, s, 4-H); 1.57 (9H, s, 5-CMe_3);

1.38 (9H, s, 3-CMe_3). ^1H NMR indicated the blue residue to contain II and di-(3,5-di-tert-butyl-2-thienyl)dichloromethane [^1H NMR spectrum: 6.99 (2H, s, 4-H and 4′-H); 1.43 (18H, s, CMe_3); 1.42 (18H, s, CMe_3)] in a ratio of ~6:1.

Trichloromethylation of 2,4-dialkylthiophenes Ib-f proceeded analogously. No other products besides nonreacted starting materials and unidentified tar-forming blue residues were observed.

3,5-Di-tert-butyl-2-thiophenecarboxylic acid (III) was obtained upon TLC of II on Silpearl silica gel eluted with diethyl ether, M^+ 240.

Ethyl 3,5-di-tert-butyl-2-thiophene carboxylate (V) was obtained by boiling II in ethanol in the presence of a catalytic amount of concentrated H_2SO_4, M^+ 268.

3,5-Di-tert-butyl-2-thiophenecarboximoyl Chloride (IV) and N-(3,5-Di-tert-butyl-2-thienyl)-3,5-di-tert-butyl-2-thiophenecarbaldimine (VIII). To a solution of 6 g (0.025 mole) of oxime VI [2] in 40 ml of dry ether was slowly (~10 min) added under a stream of nitrogen with stirring and at a temperature maintained at less than −10°C, a solution of 3.4 g (0.075 mole) of nitrosyl chloride in 30 ml of ether. The mixture was stirred at −10°C for 5 h, then another 30 ml of ether was added and stirring was continued at room temperature until HCl evolution ceased (ca. 1 day). The ether was evaporated under vacuum without heating to give an orange oily residue. From the latter upon treatment with petroleum ether (40-70°C) was obtained 2.9 g of colorless carboximoyl chloride IV, which was additionally purified by recrystallization from hexane. The mother liquor after separation of compound IV was evaporated and the resulting oil containing, according to TLC (silufol, ethyl acetate−hexane, 1:2), in addition to carboximoyl chloride IV a single additional yellow material which was separated by distillation into two fractions: bp 122-126°C/2 mm Hg, 1.24 g and bp 130-132°C/2 mm Hg, 1.24 g. The second fraction upon standing gave 0.15 g of yellow imine VIII, further purified by recrystallization from heptane, M^+ 417.

Reaction of 3,5-Di-tert-butyl-2-trichloromethylthiophene with Hydroxylamine. Hydroxylamine hydrochloride (1.39 g, 0.02 mole) was dissolved with heating in 10 ml of dry pyridine and to the solution was added 0.66 g (0.0021 mole) of trichloride Ia. The resulting solution was boiled for 1 h, cooled, poured into water, and the product was extracted with ether. The ethereal extract was washed with water, dilute sulfuric acid, water again, and then dried over $MgSO_4$. Removal of the solvent gave 0.78 g of viscous orange oil, the composition of which was determined by GLC-MS and TLC. It contained a small quantity of di-tert-butylthiophene Ia (M^+ 196), the oxime of 3,5-di-tert-butyl-2-thiophenealdehyde VI (M^+ 239) identical with a known sample [2], 3,5-di-tert-butyl-2-thiophenecarbonitrile VII (M^+ 221) identical with a sample obtained by dehydration of oxime VI, and the ethyl ester V (M^+ 268). Use of methylene chloride for extraction (see above) gave no ester V.

3,5-Di-tert-butyl-2-thiophenecarbonitrile (VII). A mixture of 3.2 g (0.0134 mole) of aldoxime VI, 2.6 g (0.026 mole) of acetic anhydride, and 0.6 g of sodium acetate was stirred slowly until boiling. After completion the brown mass was kept at the boiling point for 30 min, added to an equal volume of water, boiled for 2-3 min, cooled, and saturated with potassium carbonate. The product was extracted with ether, the extract was dried over magnesium sulfate, and distilled to give 2.0 g of nitrile VII.

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