NUCLEOPHILIC REPLACEMENT OF THE TERT-BUTYLSULFONYL GROUP IN THE THIOPHENE SERIES. IX*

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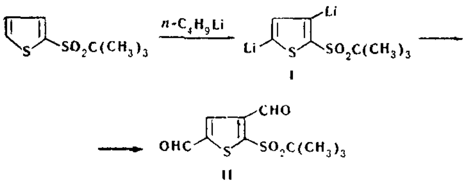
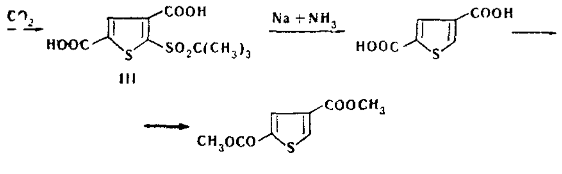
The conditions for dimethylation of tert-butyl-2-thienylsulfone at positions 3 and 5, in 60–70% yield, are determined. In 5-tert-butylsulfonylthiophene-2,4-dialdehyde, the tert-butylsulfonyl group readily undergoes nucleophilic replacement by RS and RO groups. In the case of 3-tert-butylsulfonylthiophene-2,5-dialdehyde, treatment with nucleophilic reagents does not lead to replacement, and only a hemiacetal is formed from one of the aldehyde groups.

It was previously shown [2] that tert-butyl-2-thienylsulfone is immediately metallized by n-butyl lithium at two positions in the thiopene ring, and that replacement of the metal in dilithium compound I by a formyl group gave a dialdehyde, to which structure II was assigned.

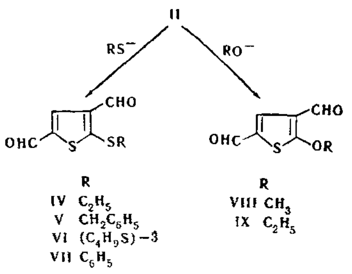


This reaction has now been investigated in somewhat more detail and it has been established that the yield of dilithium compound I depends on the temperature and time of metalation. A temperature of −15 to −20° proved optimum, when there was 68% metallization in 8–10 hours. Reducing the temperature to −60° or less gave a mixture of monolithium substition products. Above −15° the yield of compound I also dropped.

The structure of I was shown by splitting off the tert-butylsulfonyl group from 5-tert-butylsulfonylthiophene-2,4-dicarboxylic acid (III) by sodium in liquid ammonia [3].



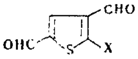
Dimetallization of the thiophene ring offers new synthetic possibilities in the thiophene series. In dialdehyde II the tert-butylsulfonyl group is fairly mobile towards such nucleophilic reagents as alkoxy- and alkyl(aryl)mercaptide anions. A reaction that is obviously related to nucleophilic substitution takes place in the presence of an alkaline reagent (e.g. a tertiary amine), on brief heating in ethanol solution. Under such conditions the aldehyde groups are not affected, and in that way it is possible to obtain 5-alkyl(aryl)mercaptothiophene-2,4-dialdehydes IV–VII [4] and 5-alkoxythiophene-2,4-dialdehydes VII,IX [5], for which it is difficult to suggest any other method of synthesis.



The table gives the yields and physical constants of the compounds obtained. The aldehyde groups were identified by preparing the bisazomethines by reaction with p-toluidine.

It is to be noted that in 5-tert-butylsulfonylthiophene-2,4-dicarboxylic acid (III), the tert-butylsulfonyl group is not, under these conditions, replaced by the alkoxy or alkylmercapto group. This is readily explained by the less powerful electron-accepting properties of carboxyl.

It was of interest to see whether a tert-butylsulfonyl group β to the thiophene ring, was susceptible to nucleophilic replacement. Tert-butyl-3-thienylsulfone (X), perpared by oxidizing the sulfide, was metallized with excess butyl lithium. Treatment of

5-Substituted Thiophene-2,4-Dialdehydes 

Compound	X	Mp, °C	Formula	Found, %			Calculated, %			Yield, %
				C	H	S	C	H	S	
IV	SC_2H_5	103—105	$C_8H_8O_2S_2$	48.12	4.16	32.02	47.98	4.02	32.02	90
V	$SCH_2C_6H_5$	125.5—126.5	$C_{13}H_{10}O_2S_2$	59.57	3.86	24 67	59.51	3.84	24.44	84
VI	$S(C_4H_3S)$-3	121—123	$C_{10}H_6O_2S_3$	47 31	2.69	37.74	47.22	2.38	37.81	70
VII	SC_6H_5	110- 112	$C_{12}H_8O_2S_2$	58.15	3.17	25.84	58.20	3.24	25.84	51
VIII	OCH_3	156—158,5	$C_7H_6O_3S$	49.50	3.43	18.76	49.40	3.55	18.83	41
IX	OC_2H_5	131,5—132,5	$C_8H_8O_3S$	52.44	4.52	17.43	52.20	4.38	17.35	40

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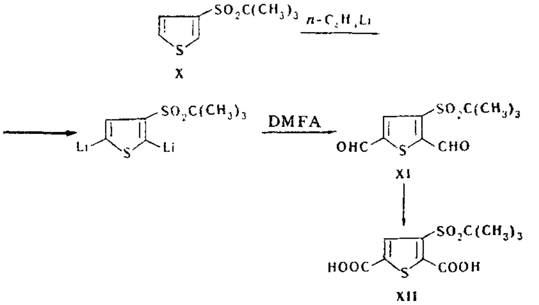
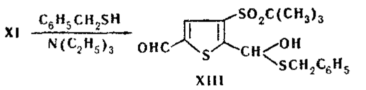
*For Part VIII see [1].

the lithium derivative with dimethylformamide (DFMA) gave a dialdehyde, whose polarographic behavior* led to its being assigned a structure 3-tert-butylsulfonylthiophene-2,5-dialdehyde (**XI**). The latter is oxidized to 3-tert-butylsulfonylthiophene-2,5-dicarboxylic acid (**XII**).



However when dialdehyde **XI** was treated with benzylmercaptan in the presence of triethylamine, it was found that what took place was not replacement of the tert-butylsulfonyl group or any other group, but addition of the mercaptan at the C=O bond of one of the aldehyde groups of dialdehyde **XI**, to give the hemi-thioacetal **XIII**.



The mercaptan more probably adds to that aldehyde group of 3-tert-butylsulfonylthiophene-2,5-dialdehyde (**XI**), whose carbon atom carried a large positive charge, i. e. to the aldehyde group at position 2. Indeed, if the region of carbonyl group valence vibrations of the IR spectrum of dialdehyde **XI** has 2 bands, at 1680 and 1697 cm^{-1}, where obviously the higher frequency corresponds to the 2-aldehyde group, interacting strongly with the tert-butylsulfonyl substituent ortho to it, then the spectrum of compound **XIII** shows, along with the band of valence vibrations of hydroxyl at 3410 cm^{-1}, only one band at 1680 cm^{-1} in the region of carbonyl group frequencies, corresponding to the aldehyde group at position 5.

EXPERIMENTAL

5-Tert-butylsulfonylthiophene-2,4-dialdehyde (II). 12.2 g (0.2 mole) n-BuLi in 150 ml ether was added to 10.2 g (0.05 mole) tert-butyl-2-thienylsulfone in 100 ml tetrahydrofuran, dried over granular KOH, the temperature being −15° to −20°. The mixture of reactants was stirred for 9.5 hr at that temperature, then cooled to −60°, and 30 ml dimethylformamide in 70 ml dry ether added all together, after which the mixture was left overnight. The contents of the flask were poured into 10% AcOH, and extracted with $CHCl_3$. After removing the solvent the residue was diluted with a small amount of ether, then the precipitate formed filtered off. Yield of dialdehyde II 7.7 g (59%), mp 151–152° [2].

Tert-butyl[3,5-bis(p-tolyliminomethylene)-2-thienyl]sulfone. Prepared from 0.52 g aldehyde II and 0.86 g p-toluidine, by heating together for 2 hr in EtOH, yield 84%, mp 207–209°. Found: N 6.42; 6.58%, calculated for $C_{24}H_{21}N_2O_2S_2$: N 6.38%.

5-Tert-butylsulfonylthiophene-2,4-dicarboxylic acid (III). The solution of dilithium compound I, prepared as described above, was poured into a mixture of dry ice and ether. The reaction products were allowed to warm up to room temperature, water added, the ether layer separated off, and the aqueous layer acidified. The acid precipitated was filtered off and dried. Yield 9.96 g (68%) acid **III**, which decomposed without melting above 200°. Found: C 41.23; 41.13; H 4.27; 4.11; S 21.99; 22.08%, calculated for $C_{10}H_{12}O_6S_2$: C 41.08; H 4.14; S 21.95%.

Dimethyl ester: mp 94–95.5° (ex hexane). Found: C 45.20; 45.40; H 5.00; 5.01; S 19.98; 20.21%, calculated for $C_{12}H_{16}O_6S_2$: C 44.99; H 5.03; S 20.01%.

Diamide: decomposes at 225–226°. Found: C 41.48; 41.30; H 4.96; 4.79; S 22.08; 22.02%, calculated for $C_{10}H_{14}N_2O_4S_2$: C 41.36; H 4.86; S 22.06%.

Thiophene-2,4-dicarboxylic acid. 0.23 g Na was added in small pieces to a solution of 1.46 g acid **III** in 30 ml liquid NH_3. After the Na had dissolved the ammonia was removed, and the residue dissolved in water and acidified with dilute HCl. The mixture of acids precipitated was filtered off (mass 0.69 g), and treated with a solution of diazomethane, to give 0.69 g esters, mp 74–83°. Recrystallization from hexane led to the separation of thiophene-2,4-dimethylate, mp 119.5–120°, which proved identical (mixed mp) with a known specimen. Found: C 48.13; 48.41; H 3.90; 4.04; S 15.83; 15.96%, calculated for $C_8H_8O_4S$: C 47.99; H 4.03; 16.01%.

5-Ethylmercaptothiophene-2,4-dialdehyde (IV). 1.3 g (0.005 mole) Dialdehyde II was added to a solution of 1 ml ethylmercaptan in 6 ml EtOH. Then 0.5 g (0.005 mole) Et_3N in 2 ml EtOH was added to the resultant suspension, when the mixture suddenly became clear. The solution was refluxed for 15 min. The crystals that precipitated on cooling were filtered off.

Compounds V–VII were prepared similarly. Yields, physical constants, and analyses of these compounds are given in the table.

5-Methoxythiophene-2,4-dialdehyde (VIII). 0.115 g (0.005 mole) Na was dissolved in 10 ml absolute MeOH. The mixture was refluxed for 15 min. After cooling, the precipitate was filtered off. The same method was used to prepare 5-ethoxythiophene-2,4-dialdehyde (IX, see table).

Benzyl-[2,4-bis(p-tolyliminomethylene)-5-thienyl]sulfide. Prepared from 0.38 g (0.0015 mole) aldehyde V and 0.32 g (0.003 mole) p-toluidine by heating the two together in the presence of a few drops of AcOH. Yield 0.52 g (79%), mp 86–87° (ex EtOH). Found: N 6.71; 6.59%, calculated for $C_{27}H_{24}N_2S_2$: N 6.37%.

Phenyl-[2,4-bis(p-tolyliminomethylene)-5-thienyl]sulfide, was prepared similarly, mp 113.5–114° (ex EtOH). Found: N 6.58%, calculated for $C_{26}H_{22}N_2S_2$: N 6.58%.

3'-Thienyl[2,4-bis(p-tolyliminomethylene)-5-thienyl]sulfide was similarly prepared from 5-[3'-thienylmercapto]thiophene-2,4-dialdehyde (**VI**); mp 85–90° (ex EtOH), found N 6.45; 6.51%, calculated for $C_{24}H_{20}N_2S_3$: N 6.48%.

Tert-butyl-3-thienylsulfide. Prepared similarly to tert-butyl-2-thienylsulfide [2], 48% yield, bp 99–101° (15 mm), n_D^{20} 1.5445, the literature [6] gives 65–67° (1 mm), n_D^{20} 1.5440.

Tert-butyl-3-thienylsulfone (X). 20 g Tert-butyl-3-thienylsulfide, 65 ml 30% H_2O_2, and 100 ml glacial AcOH were heated together for 3 hr at 100°. The mixture was diluted with water, and the sulfone formed filtered off. Yield 18.7 g (79%) sulfone **X**, mp 165–166°. Found: C 46.92; 46.92; H 5.75; 5.81; S 31.33; 31.29%, calculated for $C_8H_{12}O_2S_2$: C 47.03; H 5.92; S 31.39%.

3-Tert-butylsulfonylthiophene-2,5-dialdehyde (XI). This was prepared in the way described above for synthesizing aldehyde **II**, from 5.1 g (0.025 mole) sulfone **X**, 7.6 g (0.12 mole) n-BuLi, in 50 ml tetrahydrofuran, and 70 ml ether. Yield 2.33 g (36%) dialdehyde **XI** mp 148.5–149°, (ex CCl_4). Found: C 45.99; 45.76; H 4.54; 4.48; S 24.92; 24.71%, calculated for $C_{10}H_{12}O_4S_2$: C 46.12; H 4.65; S 24.63%.

Tert-butyl-[2,5-bis(p-tolyliminomethylene)-3-thienyl]sulfone. Prepared in 50% yield similarly to the above-described azomethines mp 292–293.5° (ex EtOH). Found: N 6.04; 5.93%, calculated for $C_{24}H_{21}N_2O_2S_2$: N 6.38%.

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*The polarographic data will be published later.

3-Tert-butylsulfonylthiophene-2,5-dicarboxylic acid (XII). Prepared by oxidizing XI with moist Ag_2O, yield 75%, mp 230° (decomp).

Dimethyl ester. Mp 127–128° (ex heptane). Found: C 44.93; 45.30; H 5.04; 5.14; S 19.98; 19.93%, calculated for $C_{12}H_{16}O_6S_2$: C 44.99; H 5.03; S 20.01%.

Reaction of dialdehyde XI with benzylmercaptan. 0.25 g benzylmercaptan and 0.20 g Et_3N were added to a suspension of 0.53 g XI in 10 ml EtOH, the whole refluxed for 15 min, then evaporated to 4–5 ml, and allowed to stand. After standing for a long time crystals came down, and these were filtered off and recrystallized from EtOH. The 4-tert-butylsulfonyl-5-(1-hydroxy-1-benzylmercaptomethylene)thiophene-2-aldehyde, obtained as colorless crystals, had two mps; it melted first at about 110°, then after being further heated (on a hot stage) mercaptan was evolved, and the residue resolidified and melted at 150°; undepressed mixed mp with the starting aldehyde XI. Found: C 53.07; 53.13; H 5.25; 5.16; S 24.80; 24.84%; calculated for $C_{17}H_{20}O_4S_3$: C 53.10; H 5.23; S 25.01%.

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