Some Substitution Reactions of 3-Phenylthiophene

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The Vilsmeyer formylation of 3-phenylthiophene yields a 94:6
mixture of 3-phenyl-2-thiophene aldehyde and 3-phenyl-5-thiophene
aldehyde. The Friedel-Crafts acetylation with $SnCl_4$ as catalyst is less
selective and yields a 7:3 mixture of 2-acetyl-3-phenylthiophene and
5-acetyl-3-phenylthiophene. Authentic 3-phenyl-4-thiophene aldehyde
and 4-acetyl-3-phenylthiophene were also prepared, but could not be
detected in the reaction products by VPC. Preparatively 3-phenyl-5-
thiophene aldehyde and 5-acetyl-3-phenylthiophene were most con-
veniently obtained by reaction of 5-bromo-3-phenylthiophene with
ethyllithium followed by reaction with N,N-dimethylformamide and
N,N-dimethylacetamide, respectively.

In connection with work on the directing effect of carbocyclic [1] and hetero-
cyclic [2] aromatic rings on aromatic substitution, some reactions of 3-phenyl-
thiophene have been studied. It can be expected that in this compound, for
electrophilic substitution, the activating effect of the phenyl group on the
reactivity on the 2-position is partially cancelled by steric effects so that sub-
stitution is obtained both in the 2- and 5-position, the isomer distribution
being dependent upon the reagent used.

It has been found that bromination of 3-phenylthiophene with bromine
and acetic acid yielded a monobrominated product consisting of 70 % 5-
bromo-3-phenylthiophene and 30 % 2-bromo-3-phenylthiophene, while N-
bromosuccinimide in carbon tetrachloride yielded almost exclusively the 2-
isomer.[3] Further experiments showed that the different solvents and not the
different brominating agents were responsible for the varying isomer distribu-
tion and that the bromination of 3-phenylthiophene under certain conditions
is reversible.[4,5]

The nitration of 3-phenylthiophene has recently been reinvestigated by
us, and we found that 2-nitro-3-phenylthiophene and 5-nitro-3-phenylthiophene
were formed in the ratio 9:1.[1]

We have now continued our investigations of the electrophilic substitution
reactions of 3-phenylthiophene by studying the Vilsmeyer formylation with
N,N-dimethylformamide and $POCl_3$ and the Friedel-Crafts acetylation with
$SnCl_4$ as catalyst.

In order to avoid possible diformylation, a slight excess of N,N-dimethyl-formamide was used. This procedure led to the recovery of about 35 % of the starting 3-phenylthiophene and to the formation of two products in the ratio 94:6 as shown by VPC. Combined mass spectrometry-VPC showed that both were monoformylated 3-phenylthiophenes. Later experiments, however, showed that by doubling the amount of N,N-dimethylformamide the amount of recovered 3-phenylthiophene could be suppressed to about 8 %, giving a 74 % yield of formylated products with the same ratio between the two components. The main component having the lowest retention time could easily be obtained pure through recrystallisation from aqueous ethanol. Its NMR spectrum proved it to be 3-phenyl-2-thiophene aldehyde (I), as the two thiophenic doublets showed a coupling of 5.1 c/s characteristic for J_{45} in thiophenes.[6] The low field band (1.95 τ) is that of hydrogen 5, as it in addition shows a long-range coupling to the 2-formyl group.[6] The minor component had the same retention time as authentic 3-phenyl-5-thiophene aldehyde (II) prepared through halogen-metal interconversion between 5-bromo-3-phenylthiophene [3] and ethyllithium followed by reaction with N,N-dimethylformamide. The thiophenic hydrogen resonances in the NMR spectrum
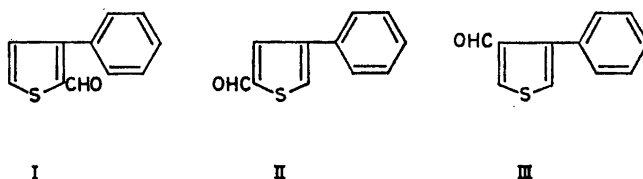

of II showed couplings of 1.5 c/s, characteristic for J_{24} in thiophenes, and in addition the high field resonance occurred as a 1:2:1 triplet due to long-range coupling to the formyl hydrogen.[6] Furthermore, small amounts of the minor component could be isolated by means of preparative VPC, which showed the same IR spectrum as authentic II.

In order to check that the retention time of 3-phenyl-4-thiophene aldehyde (III) was not accidentally the same as that of one of the other aldehydes, it was prepared from 4-bromo-3-phenylthiophene. This compound was obtained by the reaction of 4-bromo-3-thienyllithium [7] with cyclohexanone, followed by aromatization of the intermediate 4-bromo-3-(1-cyclohexenyl)thiophene with dichlorodicyanoquinone. Halogen-metal exhange between 3-phenyl-4-bromothiophene and ethyllithium followed by reaction with N,N-dimethyl-formamide yielded III in good yield. As in the case of 3-bromo-4-thiophene aldehyde, the formyl hydrogen of III did not show any resolvable long-range coupling to the 2-hydrogen.[6] The structure of III was evident from the J_{25}-coupling (3.4 c/s) between the thiophene hydrogens. VPC on a 2 m × 1/8″ column of 5 % NPGS on Chromosorb W (80—100 mesh) at 180°C showed that III had quite a lower retention time than I and II. The retention times of 3-phenylthiophene, III, I, and II were under these conditions 1.7 min, 7.2 min, 9.3 min, and 13.7 min, respectively. Careful VPC analysis of the formylation product thus indicated that if III was formed it was less than 0.1 %.

Formylation with toluene as solvent did not significantly change the proportion of I:II.

Friedel Crafts acetylation of 3-phenylthiophene using $SnCl_4$ as catalyst yielded two monoacetylated 3-phenylthiophenes in the ratio 69:31 as indicated by analytical VPC and mass spectrometry, as well as 3 % of recovered 3-phenylthiophene. Again the main component was well separated from the minor, and could be obtained in a pure state by recrystallisation from aqueous ethanol. Its NMR spectrum, showing two thiophenic doublets with a coupling constant of 5.2 c/s, proved it to be 2-acetyl-3-phenylthiophene (IV). The NMR spectrum of the crude product showed two sets of thiophenic doublets with coupling constants of 5.1 c/s and 1.5 c/s indicating that the second component was 5-acetyl-3-phenylthiophene (V). This was confirmed by preparing authentic V by the reaction of 3-phenyl-5-thienyllithium obtained via low-temperature halogen-metal exchange between 5-bromo-3-phenylthiophene and ethyllithium followed by reaction with N,N-dimethylacetamide.

IV   V   VI
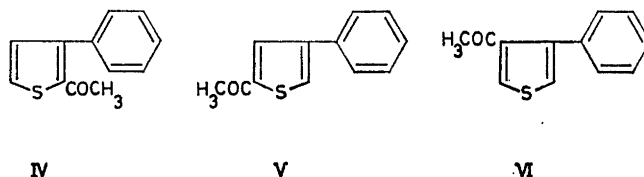
Authentic 4-acetyl-3-phenylthiophene (VI) was prepared by the reaction of 3-phenyl-4-thienyllithium with N,N-dimethylacetamide. The retention time for VI was very similar to that of IV when the same column was used as in the aldehyde case. However, on a 2 m $\times 1/8''$ column of 20 % Apiezon L on Chromosorb P (60—80 mesh) at 250°C, using a Perkin-Elmer model F 11 gas chromatograph, these two components separated, the retention times of VI, IV, and V being 6.6 min, 7.6 min, and 11.7 min, respectively. Due to the near overlap of the VPC peaks for IV and VI, the maximum amount of 4-substituted product present could not be determined as exactly as in the formylation reaction, but it must in any case be very small. NMR analysis of the $COCH_3$ region showed that the crude acetylation product contained less than 0.5 % of the 4-isomer, if any.

The rather large amount of 5-substitution in the acetylation of 3-phenylthiophene is not unexpected, as it is well-known that this reaction is very sensitive to steric effects. Negligible amounts of *ortho* isomers are obtained in the acetylation of alkylbenzenes or biphenyl.[8]

The very small amount of 4-isomer formed in these reactions is of some interest. Also in the nitration of 3-phenylthiophene with cupric nitrate in acetic anhydride, no 4-isomer was found, although due to the analytical technique used (TLC) minor amounts could have been overlooked. In the nitration of 3-methylthiophene with nitric acid in acetic anhydride the amount of 4-isomer is small (3 %), the main nitration products being 2-nitro- (79 %) and 5-nitro- (18 %) 3-methylthiophene.[9] With *"meta"*-directing —I—M-substituents the amount of 4-isomer is larger. Östman recently found that in

the nitration of 3-thiophenealdehyde and 3-cyanothiophene with nitric acid in trifluoroacetic acid 7—8 % of the 4-nitro isomer was obtained.[10]

The isomer distributions obtained in some electrophilic substitution reactions of 3-phenylthiophene and also in the metalation of this compound with alkyllithium derivatives [11] are given in Table 1. The accuracy of the isomer distribution in the bromination is not as high as in the other substitution reactions.

Table 1. Isomers formed during substitution reactions of 3-phenylthiophene.

Reagent	2-Position	5-Position
$Br_2(HOAc)$	33 %	67 % [a]
$NBS(CCl_4)$	98 %	2 % [b]
$Cu(NO_3)_2, Ac_2O$	90 %	10 %
$(CH_3)_2NCHO, POCl_3$	94 %	6 %
$CH_3COCl, SnCl_4$	69 %	31 %
$n\text{-}C_4H_9Li$	45 %	55 %

[a] Equilibrium position after five hours of reaction.

[b] In an earlier paper it was stated that only 3-phenyl-2-bromothiophene was formed.[3] Several later experiments, however, disclosed the presence of about 2 % of 5-bromo-3-phenylthiophene.

EXPERIMENTAL

Formylation of 3-phenylthiophene. To a mixture of 2.00 g (12.5 mmole) of 3-phenylthiophene [1] containing less than 0.1 % of 2-phenylthiophene and 1.16 g (16 mmole) of N,N-dimethylformamide 1.2 g (8.0 mmole) of phosphoroxychloride was added dropwise with stirring and ice-cooling. After stirring for 0.5 h the mixture was heated to 75°C, whereupon an exothermic reaction set in which caused the temperature of the reaction mixture to rise to 110°C. The temperature was then kept at 100—105°C for 0.5 h, the mixture cooled and poured onto ice. Sodium acetate was added to adjust the pH to 5. The mixture was allowed to stand overnight, was then extracted with ether and the combined ether phases were washed with water and dried over $MgSO_4$. The ether was distilled off, leaving 1.59 g of a yellow solid. Analytical VPC on a 2 m × 1/8″ column packed with 5 % NPGS on Chromosorb W (80—100 mesh) at 180°C using a Perkin-Elmer model 900 gas chromatograph indicated that the product contained about 35 % 3-phenylthiophene and two other components with retention times of 9.3 min and 13.7 min, respectively, and in the ratio 94:6. Combined mass spectrometry-gas chromatography showed both components to be formylated phenylthiophenes. The main component, *2-formyl-3-phenylthiophene*, was obtained pure by recrystallisation of the crude product from aqueous ethanol. M.p. 36.0—36.5°C. NMR (acetone): $\tau_5 = 1.94$ ppm, $\tau_4 = 2.61$ ppm, $\tau_{C_6H_5}$ ca 2.40 ppm, $\tau_{CHO} = 0.07$ ppm. $J_{45} = 5.1$ c/s, $J_{5\text{-}CHO} = 1.2$ c/s. [Found: C 70.52; H 4.39; S 16.75. Calc. for $C_{11}H_8OS$ (188.3): C 70.18; H 4.28; S 17.03].

The second peak yielded on preparative gas chromatography 5-formyl-3-phenyl-thiophene having the same IR spectrum as an authentic sample described below.

Using 2.0 g (12.5 mmole) of 3-phenylthiophene, 2.3 g (32 mmole) of N,N-dimethyl-formamide and 2.4 g (16 mmole) of $POCl_3$ yielded 1.88 g (80 %) of product containing 8 % of 3-phenylthiophene as well as 3-phenyl-2-thiophene aldehyde and 3-phenyl-5-thiophene aldehyde in the ratio 94:6.

5-Formyl-3-phenylthiophene. To a stirred solution of 1.00 g (4.20 mmole) of 5-bromo-3-phenylthiophene [3] in 20 ml of anhydrous ether cooled to −60°C, 7.5 ml of 0.80 N ethyl-lithium was added under nitrogen. After 5 min. 0.5 g (7 mmole) of N,N-dimethyl-

formamide in 5 ml of ether was added and the mixture stirred at $-60°C$ for 30 min and then allowed to stand at room temperature for 4 h. The mixture was poured into water, the ether layer separated and the water layer extracted with ether. The combined ether phases were washed with 1 N hydrochloric acid, sodium bicarbonate, and water and dried over magnesium sulphate. Evaporation of the ether yielded 691 mg of a light-yellow product, 500 mg of which was chromatographed on silica gel. Elution with hexane yielded 103 mg of a 3:2 mixture of 5-bromo-3-phenylthiophene and 3-phenylthiophene. Combined elution with a 1:1 hexane-benzene mixture yielded 345 mg (60 %) of 5-formyl-3-phenylthiophene, m.p. $67-68°C$ after recrystallisation from aqueous ethanol. NMR (acetone): $\tau_4 = 1.72$ ppm, $\tau_2 = 1.85$ ppm, $\tau_{C_6H_5} = 2.17-2.72$ ppm, $\tau_{CHO} = -0.01$ ppm. $J_{24} = 1.5$ c/s, $J_{2-CHO} = 1.2$ c/s. [Found: C 69.3; H 4.30; S 16.85. Calc. for $C_{11}H_8OS$ (188.3): C 70.18; H 4.28; S 17.03].

4-Bromo-3-(1-cyclohexenyl)thiophene. To 400 ml 0.77 N ethyllithium cooled to $-70°C$, 60.0 g (0.25 mole) of 3,4-dibromothiophene [12] in 50 ml of anhydrous ether was added in a slow stream with stirring and under nitrogen. After a few minutes 24.5 g (0.25 mole) of cyclohexanone in 50 ml of anhydrous ether was rapidly added. The mixture was stirred for an additional hour at $-70°C$ and then allowed to stand overnight at room temperature. It was then cooled to $-10°C$ and 150 ml of 6 N hydrochloric acid was added dropwise with vigorous stirring and the mixture stirred at $-10°C$ for 0.5 h. The ether phase was separated, washed with sodium bicarbonate and water, dried over magnesium sulphate and fractionated to yield 48.1 g (79 %) of 4-bromo-3-(1-cyclohexenyl)thiophene, b.p. $156-158°C/16$ mm Hg. NMR ($CDCl_3$): $\tau_{2,5} = 2.81$ ppm and 3.02 ppm. $J_{25} = 3.5$ c/s, $\tau_{CH=} = 3.33$ ppm, τ_{CH_2} between 7.5–8.5 ppm (8H). [Found: C 49.1; H 4.68; Br 32.95; S 13.45. Calc. for $C_{10}H_{11}BrS$ (243.2): C 49.39; H 4.56; Br 32.86; S 13.19].

4-Bromo-3-phenylthiophene. 20.0 g (0.082 mole) of 4-bromo-3-(1-cyclohexenyl)-thiophene, 37.2 g (0.16 mole) of dichlorodicyanoquinone and 250 ml of benzene were mixed with stirring. The mixture grew warm and the temperature rose to 40°C. After stirring for 2 h, the temperature had sunk to room temperature, so the mixture was refluxed for 5 h and allowed to stand overnight. The precipitate was filtered off and the mixture washed several times with 2 N sodium hydroxide until no more precipitate was formed in the aqueous layer. The organic phase was then washed with N hydrochloric acid and water and dried over magnesium sulphate. The benzene was distilled off and the residue was chromatographed on alumina (Fluka, type 507 c, neutral) using hexane as eluent. Evaporation of the hexane yielded 14.0 g (71 %) of 4-bromo-3-phenylthiophene, m.p. $71-72°C$ after recrystallisation from aqueous ethanol. NMR (DMSO): $\tau_{2,5} = 2.27$ ppm, 2.42 ppm. $J_{25} = 3.45$ c/s, $\tau_{C_6H_5} = 2.60$ ppm. [Found: C 50.2; H 3.20; Br 33.2; S 13.4. Calc. for $C_{10}H_7BrS$ (239.1): C 50.23; H 2.95; Br 33.41; S 13.41].

4-Formyl-3-phenylthiophene was prepared analogously to 5-formyl-3-phenylthiophene from 3.00 g (12.6 mmole) of 4-bromo-3-phenylthiophene, 20 ml 0.8 N ethyllithium and 1.5 g (20 mmole) of N,N-dimethylformamide. Chromatography on silica gel using hexane as eluent gave a forerun containing mostly 4-bromo-3-phenylthiophene. Continued elution with hexane-benzene (2:1) yielded 4-formyl-3-phenylthiophene, m.p. $30-31°C$ after recrystallisation from aqueous ethanol; yield 51 %. NMR ($CDCl_3$): $\tau_5 = 1.81$ ppm, $\tau_2 = 2.77$ ppm, $\tau_{C_6H_5} = 2.62$ ppm, $\tau_{CHO} = 0.18$ ppm. $J_{25} = 3.35$ c/s. [Found: C 69.5; H 4.40; S 16.9. Calc. for $C_{11}H_8OS$ (188.3): C 70.18; H 4.28; S 17.03].

Acetylation of 3-phenylthiophene. To a mixture of 1.50 g (9.4 mmole) of 3-phenylthiophene [1] and 0.73 g (9.4 mmole) of acetyl chloride in 15 ml of benzene, cooled to about 0°C, 2.44 g (9.4 mmole) of tin tetrachloride was added dropwise. The mixture was then stirred at room temperature for one hour and hydrolysed by the addition of 20 ml of 1.2 N hydrochloric acid. The benzene layer was separated, washed with water and dried over MgSO₄. Removal of the solvent *in vacuo* yielded 1.51 g (80 %) of product. VPC on the same column (temperature 200°C) as described in the formylation reaction indicated that the product contained 3 % 3-phenylthiophene and two other components with retention times of 4.3 min and 9.1 min, respectively, and in the ratio 69:31. Similar proportions were also found by integration of the COCH₃ resonances in the NMR spectrum of the crude product. Preparative VPC yielded pure 2-acetyl-3-phenylthiophene, m.p. $61.8-62.3°C$ after recrystallisation from aqueous ethanol. NMR (CH_3NO_2): $\tau_5 = 2.24$ ppm, $\tau_4 = 2.81$ ppm, $\tau_{C_6H_5} = \sim 2.48$ ppm, $\tau_{CH_3} = 7.81$ ppm. $J_{45} = 5.2$ c/s. [Found: C 70.86; H 4.90; S 16.09. Calc. for $C_{12}H_{10}OS$ (202.3): C 71.26; H 4.98; S 15.85].

The second peak yielded on preparative VPC 5-acetyl-3-phenylthiophene having the same IR spectrum as an authentic sample described below.

5-Acetyl-3-phenylthiophene. To 1.50 g (6.3 mmole) of 5-bromo-3-phenylthiophene in 20 ml of anhydrous ether at −60°C, 10 ml of 0.90 N ethyllithium was added with stirring in a slow stream under nitrogen. After 5 min, 1.6 g (18 mmole) of *N,N*-dimethylacetamide in 10 ml of ether was added dropwise. The reaction mixture was stirred at −60°C for 1 h, then at room temperature for the same time and finally poured into 160 ml of 10 % hydrochloric acid. The ether phase was separated, the aqueous layer extracted with ether and the combined ether phases washed with bicarbonate solution and water and dried over magnesium sulphate. The ether was removed and the residue chromatographed on silica gel. Elution with hexane, which yielded 94 mg of 3-phenylthiophene, was followed by elution with benzene, which yielded 822 mg (65 %) of 5-acetyl-3-phenylthiophene, m.p. 56−57°C after recrystallisation from aqueous ethanol. NMR (CH_3NO_2): $\tau_4 = 1.91$ ppm, $\tau_2 = 2.15$ ppm, $\tau_{C_6H_5} \approx 2.2 - 2.7$ ppm, $\tau_{CH_3} = 7.44$ ppm. $J_{24} = 1.4$ c/s. [Found: C 71.0; H 5.08; S 15.75. Calc. for $C_{12}H_{10}OS$ (202.3): C 71.26; H 4.98; S 15.85].

4-Acetyl-3-phenylthiophene. This compound was prepared in 9 % yield, analogously to the isomer described above from 3.00 g (12.6 mmole) of 4-bromo-3-phenylthiophene in 30 ml of ether, 20 ml of 0.84 N ethyllithium and 2.1 g (24 mmole) of *N,N*-dimethyl-acetamide, m.p. 56−58°C after recrystallisation from aqueous ethanol. NMR (CH_3NO_2): $\tau_5 = 1.89$ ppm, $\tau_2 = 2.77$ ppm, $\tau_{C_6H_5} = 2.67$ ppm, $\tau_{CH_3} = 7.66$ ppm. $J_{25} = 3.25$ c/s. [Found: C 70.2; H 5.00; S 15.35. Calc. for $C_{12}H_{10}OS$ (202.3): C 71.26; H 4.98; S 15.85].

NMR spectra were recorded with a Varian A 60 NMR spectrometer. Mass spectra were recorded on an LKB A-9000 mass spectrometer and correct molecular weights were obtained for all compounds. The formylated and acetylated products were injected into the mass spectrometer through a gas chromatograph using an NPGS 5 % column. Pure compounds were injected through the direct inlet.

The gas chromatographic work was carried out with a Perkin-Elmer model 900 gas chromatograph, a Perkin-Elmer model F 11 gas chromatograph and an Aerograph Autoprep model A-700 gas chromatograph. For analysis the various peaks were calibrated with known amounts.

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