A NEW SYNTHESIS OF 3-THIENYLACETONITRILE BASED ON THE PHOTO-STIMULATED REACTION OF 3-BROMOTHIOPHENE WITH THE CYANO-METHANIDE ION

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The photochemical substitution reactions in aromatic and heteroaromatic compounds have been widely investigated in recent years. Some of these reactions are of interest not only from the theoretical but from the synthetic standpoint. Special attention is drawn to the transformations of aryl halides, which are regarded by Bunnett as radical-nucleophilic substitution $S_{RN}1$ (see [1] and the references therein). For reactions of this type a chain mechanism has been proposed [2], according to which the radical anion of the halogenoaromatic compounds formed at the initiation stage eliminates the X^- anion (stage 1), and the aryl radical which forms gives a new radical anion with the nucleophilic agent (stage 2); the latter is then stabilized by reaction with the aryl halide, and the initial radical anion is regenerated (stage 3):

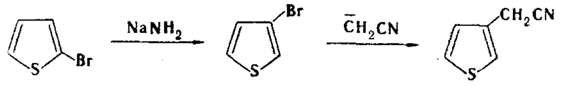
$$(ArX)^{\overline{\cdot}} \longrightarrow Ar^{\cdot} + X^- \tag{1}$$

$$Ar^{\cdot} + Nu^- \longrightarrow (ArNu)^{\overline{\cdot}} \tag{2}$$

$$(ArNu)^{\overline{\cdot}} + ArX \longrightarrow ArNu + (ArX)^{\overline{\cdot}} \tag{3}$$

The initiation of such reactions is usually realized either by a photochemical method or by means of solvated electrons. The role of the nucleophilic agent in reactions of this type can belong both to anions, in which the negative charge is localized at the heteroatom (e.g., the amide or thiolate anion), and to carbanions stabilized by functional groups (e.g., $\bar{C}H_2COR$, $R\bar{C}H_2CN$). In this connection interesting synthetic possibilities are created.

The aim of the present work was to investigate the reaction of 3-bromothiophene with the cyanomethanide ion. Here we aimed by a simple method to synthesize 3-thienylacetonitrile, which is an important intermediate product in the production of one of the types of modified penicillins. The reaction was carried out in liquid ammonia, and the carbanion was generated from acetonitrile by the action of sodium or potassium amide. By such conditions it was possible to use not only 3-bromothiophene but also the more readily obtainable 2-bromothiophene, which (as known [3, 4]) is converted into the 3-bromo isomer with a high yield by the action of sodium or potassium amide in liquid ammonia, as the starting compound.



Thus, the whole process can be realized in a single operation. The yields of 3-thienylacetonitrile by the method which we developed with both 3- and 2-bromothiophene as starting compounds amounted to 30-40% in the case of photoinitiation and 10-15% in the case of initiation by solvated electrons (sodium in liquid ammonia). The decrease in the yield in the latter case was evidently due to side processes initiated by the solvated electrons [5]; among the products by GLC we detected, in particular, thiophene, 3-methylthiophene, and also 1,2-di(3-thienyl)ethane. The last compound is also formed in an appreciable amount during photoinitiation on account, probably, of recombination of 3-thienyl radicals formed from the radical anion of 3-thienylacetonitrile (cf. [5, 6]).

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EXPERIMENTAL

The chromatographic analyses were performed on an LKhM-8MD chromatograph with a flame-ionization detector and with nitrogen as carrier gas. The columns were of stainless steel: A) 3000 × 3 mm, 5% SE-30 on Chromaton N-AW (0.2-0.25 mm); B) 2700 × 2 mm, 7% polyethylene-glycol adipate on Chromosorb P (120-140 mesh). The quantitative determinations were realized with diphenylmethane as internal standard.

The PMR spectra were recorded on a Tesla BS-497 radiospectrometer at 100 MHz in carbon tetrachloride with HMDS as internal standard.

The UV-initiated reactions were realized in a quartz reactor in apparatus for photochemical investigations [7], provided with three mercury tube lamps of the DRT-220 type and a magnetic stirrer for effective agitation of the reaction mass. For the reactions initiated by solvated electrons we used flasks of molybdenum glass. All the reactions were carried out in a stream of dry argon.

Reagents. The 3-bromothiophene, obtained by the method in [8], was distilled on a fractionating column, and the fraction boiling at 157-158°C was used. According to GLC, it contained 0.6% of the 2-bromo isomer. 2-Bromothiophene was obtained by the method in [9]; n_D^{20} 1.5861, bp 149-152°C. The acetonitrile was dried over anhydrous potassium carbonate, boiled with phosphorus pentoxide, and distilled. The middle fraction boiling at 81.6°C was collected. The ammonia was dried by dissolving sodium in it and was then redistilled into the reaction vessel. The sodium and potassium amides for the reactions were obtained by the reaction of the respective metal with liquid ammonia in the presence of a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$. The cyanomethanide ion was obtained by the addition of a small excess of acetonitrile to sodium or potassium amide in liquid ammonia at −70°C.

Reaction of 3-Bromothiophene with Cyanomethanide Ion with UV Irradiation. To a suspension of potassium amide, obtained from 2.2 g (56.3 mmole) of potassium in 100 ml of ammonia, at −70°C we added successively 2.54 g of acetonitrile (62 mmole) in 5 ml of absolute ether and 1.80 g (11.05 mmole) of 3-bromothiophene in 7 ml of absolute ether. The mixture was irradiated with stirring for 45 min (−70°C), 5 g of ammonium chloride was added, and as the ammonia evaporated 50 ml of ether and 50 ml of an aqueous solution of ammonium chloride were added in portions. The ether layer was removed, and the aqueous layer was extracted with ether (3 × 50 ml). The ether extracts were combined, washed with water (3 × 20 ml), 1 N hydrochloric acid (3 × 15 ml), and again with water (3 × 15 ml), and dried. After a sample had been taken for GLC analysis (1/50 of the extract, to which a sample of diphenylmethane had been added) the ether was distilled. The residue was dissolved in 40 ml of alcohol, 10 ml of 40% potassium hydroxide solution was added, and the mixture was boiled for 3 h. The alcohol was then distilled, 40 ml of water was added to the residue, and the mixture was extracted with ether. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with chloroform (3 × 30 ml). The extract was washed with water (2 × 20 ml). After distillation of the chloroform the residue contained 0.56 g of 3-thienylacetic acid; mp 78°C (from alcohol). Published data [10]: mp 79-80°C (from petroleum ether). By GLC analysis (column B) of the sample (see above), apart from the initial 3-bromothiophene (0.25 g) (14% recovery) and diphenylmethane, we found thiophene, 3-methylthiophene (the amounts of which were not determined), 3-thienylacetonitrile (0.51 g, yield 37.5%), and 1,2-bis(3-thienyl)ethane (0.07 g, yield 6.5%) (mol.wt. 194, by chromatomass spectrometry, column A).

In order to isolate the 3-thienylacetonitrile the ether extracts of the reaction products, obtained in several analogous experiments (total amount of 3-bromothiophene used 13.2 g), were not subjected to alkaline hydrolysis but were combined and redistilled twice. A fraction boiling at 118-122°C (15 mm Hg) was obtained (2.7 g). According to GLC, it contained 3-thienylacetonitrile and 1,2-bis(3-thienyl)ethane in a ratio of 96:4. By chromatography of this fraction on aluminum oxide (170 g, with a 1:4 mixture of chloroform and petroleum ether as eluent) we isolated 0.5 g of 3-thienylacetonitrile; bp 120-121°C (15 mm Hg), n_D^{20} 1.5425. PMR spectrum (in carbon tetrachloride), δ: 7.20 (2H, two q, 2-H and 5-H, overlapping), 6.93 (1H, q, 4-H), 3.62 ppm (4H, s, CH_2), $J_{4.5}$ = 5.2 Hz, $J_{2.4}$ = 2 Hz. Published data [11]: bp 124-125°C (16 mm Hg), n_D^{20} 1.5422.

The ether extracts from the alkaline solution (see above), obtained in several analogous experiments during the hydrolysis of 3-thienylacetonitrile, were combined, washed with water, and evaporated under vacuum. After fractional crystallization of the residue from alcohol we isolated 1,2-bis(3-thienyl)ethane; mp 65-66°C. PMR spectrum (in carbon tetrachloride), δ: 7.10 (2H, q, 5-H), 6.79 (4H, q, 2-H and 4-H, overlapping), 2.92 ppm (4H, s, CH_2); $J_{2.5}$ = 3 Hz, $J_{4.5}$ = 4.7 Hz. Found %: C 62.0; H 5.3; S 32.9. $C_{10}H_{10}S_2$. Calculated %: C 61.8; H 5.2; S 33.0. Published data [10]: mp 64-65°C (from methanol).

Reaction of 3-Bromothiophene with the Cyanomethanide Ion, Initiated by Sodium in Liquid Ammonia. To a suspension of sodium amide, obtained from 1.87 g (81 mmole) of sodium in 120 ml of ammonia, at −68°C we added successively 3.34 g (81 mmole) of acetonitrile and 3.14 g (19.2 mmole) of 3-bromothiophene in 3 ml of absolute ether. To the obtained dark suspension at a temperature between −65 and −68°C we added three 1.18-g portions of sodium at intervals of 15 min. When the last portion of sodium had dissolved, an excess (∿ 10 g) of ammonium chloride was added to the yellowing mass, and the mixture was then treated as described above. According to GLC analysis, 0.36 g of 3-thienylacetonitrile (yield 15%) and 83 mg (4.5%) of 1,2-bis(3-thienyl)ethane were formed. The reaction products contained thiophene, 3-methylthiophene, and the initial 3-bromothiophene.

Isomerization of 2-Bromothiophene (cf. [3]) and the Subsequent Reaction with Cyanomethanide Ion with UV Irradiation. To a suspension of sodium amide, obtained from 1.2 g (52 mmole) of sodium in 100 ml of ammonia, we added 1.68 g (10.3 mmole) of 2-bromothiophene in one portion. The mixture was boiled for 18 min and cooled to a temperature between −65 and −68°C, 3.3 ml (62.5 mmole) of acetonitrile in 8 ml of absolute ether was added, and the mixture was irradiated at −68°C for 1 h. To the stirred mixture we added 5 g of ammonium chloride. The mixture was then treated as described above. According to GLC, the reaction products contained 0.43 g of 3-thienylacetonitrile (35% yield) and 0.06 g (6%) of 1,2-bis(3-thienyl)ethane.

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