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ELECTROCHEMICAL SYNTHESIS OF 5-AMINO-4-BENZOYL-3-PHENYLFURAN-2-CARBONITRILE

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Abstract-Cathodic reduction of 2-bromo-2-cyanoacetophenone afforded 5-amino-4-benzoyl-3-phenylfuran-2-carbonitrile in an one pot reaction. The process is discussed and all the secondary products are isolated and characterized.

2-Aminofurancarbonitriles are useful compounds from a synthetical point of view. Some of them react with vinyl ketones to afford anthranilic acid,[1] with malonic acid to form pyridines,[2] or with urea to give pyrrols.[2]

Contrary to the widely accepted theory that the mutagenic and carcinogenic activity of 2-substituted 5-nitrofuran derivatives is due to the reduction of the nitro group into active amino metabolites, their direct isolation and identification have shown major problems.[3] Only one attempt at preparative-scale to the corresponding 5-aminofurans *via* cathodic reduction involving 2-substituted 5-nitrofurans has been reported.[4]

Catalytic reduction of 2-nitrofurans gives low yields of 2-aminofurans which have not been isolated but were trapped using ethyl ethoxymethylenecyanoacetate or ethoxymethylenemalononitrile.[5] However, their stability was greatly improved by introduction of electron withdrawing groups to the ring.[6] There are several studies on synthetic procedures towards these systems.[7,8,9]

RESULTS AND DISCUSSION

The cathodic reduction of 2-bromo-2-cyanoacetophenone (**1**) (obtained from phenacyl cyanide by bromination [10]) at a mercury cathode using DMF/$LiClO_4$ as solvent supporting electrolyte, affords 5-amino-4-benzoyl-3-phenylfuran-2-carbonitrile (**2**) as the main product (67% yield)

together with 5-amino-4-bromo-2-phenylfuran-3-carbonitrile (**3**) (8% yield), dibenzoylacetonitrile (**4**) (14% yield) and traces of phenacyl cyanide.

The characterization of **2** was made based on the following spectroscopic and spectrometric data.

A carbonyl band at 1644 cm^{-1}, two primary amine signals at 3396 and 3247 cm^{-1} and a strong cyano band at 2224 cm^{-1} appeared in IR. MS spectrometry (electronic impact) showed a molecular ion M^+ with a m/z value of 288 units. In ^{1}HNMR spectrum a broad singlet corresponding to the amine protons at 6.61 ppm disappeared in the presence of D_2O. The relationship between the integration of this singlet and the corresponding to the aromatic signals was 1:5. In ^{13}CNMR the more indicative signals appeared at 189.3 ppm (correlating to a carbonyl group), at 162.1 ppm (due to the carbon directly linked to NH_2 and to the oxigen in the furan ring) and at 151.1 ppm, which corresponds to the other carbon atom, directly linked to the oxigen and to the cyanide group, in the furan ring. The carbon of the cyano group appeared at 113.7 ppm.

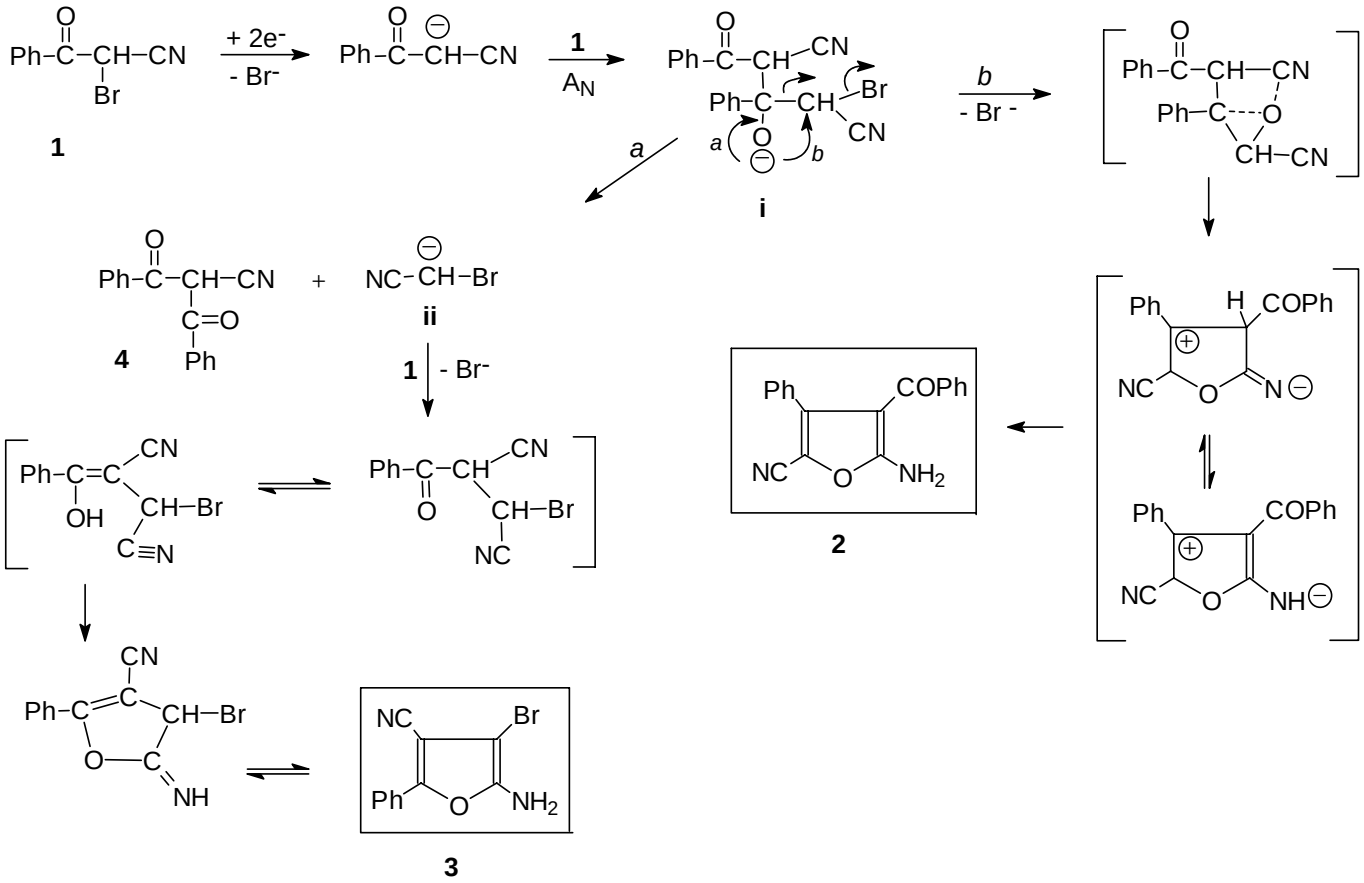
Related to the spectroscopical properties of **3**, a molecular M^+ and a M^+ +2 ions with the same intensity, typical of a monobrominated compound, appeared in MS with a m/z values of 262 and 264 units respectively. The IR of **3** showed no carbonyl bands, two primary amine bands at 3438 and 3347 cm^{-1} and a nitrile band at 2199 cm^{-1}. In ^{1}HNMR a broad singlet corresponding to the amine protons at 4.1 ppm disappeared in the presence of D_2O.

MS of **4** showed a molecular ion M^+ with a m/z value of 249 units and a base peak (100% relative intensity) of 105 m/z units. Physical and spectroscopical properties of **4** are the same as those described in the literature.[11]

The formation of these compounds can be explained as follows. In the first step, the cleavage of the C-halogen bond takes place in a $2e^-$/ molecule process to afford the corresponding enolate under a constant cathodic potential of -0.25V (vs. SCE) (see Scheme). This enolate adds to the carbonyl group of another substrate molecule to give the intermediate (**i**), which can follow different pathways. The main process is the nucleophilic attack to the halogenated carbon losing a bromide anion to form **2** as shown in the Scheme.The expected 2,4-diphenylfuran-3,5-carbodinitrile was not obtained, due to the hindered aproximation of the bulky groups in the addition step. However, the intermediate (**i**) can regenerate the second carbonyl group (pathway *a*) affording **4** and anion (**ii**), which attacks, *via* a nucleophilic substitution, the C-halogen bond of another substrate molecule giving **3**. The total experimental consumption of charge was arround 320 C (slightly lower than $1e^-$/ 1 substrate molecule) due to the fact that, according to the proposed mechanism the major product (**2**) (67%) needs $2e^-$/ 2 substrate molecule to be formed, the

secondary product (**4**) (14%) needs 2e$^-$/ 2 substrate molecule to be obtained, and the minoritary product (**3**) (8%) needs 2e$^-$/ 3 substrate molecule.

On the other hand, the electroreduction of phenacyl cyanide in DMF-Et_4NBr on mercury cathode afforded **2** (5%). This can be explained as the bromide migration towards the anodic compartment, where it is oxidized to bromine cation. Subsequent attack to the electrogenerated enolate gives 2-bromo-2-cyanoacetophenone (**1**) which is further reduced to **2** as described before. When solid sodium thiosulfate was added into the anodic compartment, no aminofuran (**2**) was observed.



Scheme. Proposed route for the formation of the aminofurans (**2**,**3**).

Electrolysis in DMF-$LiClO_4$ on graphite working electrode and at a constant applied potential of -1.5V (vs. SCE) did not yield **2**, as expected; the main product was lithium enolate of the starting phenacyl cyanide which was regenerated when salt was poured onto acidic water. Finally, when phenacyl cyanide was reduced in MeCN-Bu_4NBr at more negative potential (-1.8V (vs. SCE)), the corresponding pinacol: [Ph-C(OH)-CH_2-CN]$_2$ (**5**) was obtained as a secondary product (10% yield) due to carbonyl reduction.

EXPERIMENTAL

The electrolyses were carried out using an Amel potentiostat Model 552 with an electronic integrator Amel Model 721. MS spectra (EI, ionizing voltage 70 eV) were determined using a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-Packard MS Chem Station. IR spectra were obtained, as dispersions in KBr, on a Perkin-Elmer Model 583 spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity 300 apparatus with deuteriochloroform or CD_3OD as internal standard. The chemical shifts are given in ppm. Melting points were determined on a Reichert Thermovar microhot stage apparatus, and are uncorrected. Elemental analyses were performed on a Perkin-Elmer Model 240-B analyzer. Polarography was carried out on a Metrohm apparatus Model 663 VA Stand and a Scanner 626 Polarecord. $E_{1/2}$ of **1** in DMF/$LiClO_4$(0.1M) is –0.2 V (reference electrode: Ag/Ag^+, 5 mV/s). Analytical HPLC was performed on a Hewlett-Packard 5033 instrument, using a reverse phase column and 80% methanol/ water as the eluent. The temperature was maintained constant by use of a criostat Grant, Model LTD6G. The products were purified by silica gel 60 (230-400 mesh) in a (25 × 3 cm) column, using Hexane/EtOAc (5:1) as eluent.

Treatment of 2-bromoacetophenone with potassium cyanide gave rise to 2-cyanoacetophenone. The electroactive 2-bromo-2-cyanoacetophenone (**1**) was prepared according to the literature [9] with some modifications: the reaction was carried out by adding the bromine (1.6 g, 0.01 mol) in $CHCl_3$ (10 mL)as solvent into a 2-cyanoacetophenone (1.45 g, 0.01 mol) chloroform solution (40 mL) in the presence of pyridine (0.8 g, 0.01 mol) during 2 h at 45 ºC. The mixture was maintained on stirring for 12 h. When the reaction was finished the precipitation was filtered and the organic $CHCl_3$ solution, was washed with water and dried with sodium sulfate. The expected 2-bromo-2-cyanoacetophenone (98% yield) was obtained when the chloroform was evaporated.

General Electrochemical Procedure.

The electrochemical reduction was carried out under the following conditions:

Anode: Platinum. Anolyte: lithium perchlorate (0.53 g, 5.10^{-3} mol) in DMF (10 mL) Cathode: mercury pool. Catholyte: $LiClO_4$ (1.6 g, 0.015 mol) in DMF (25 mL) and **1** (0.9 g , 4.10^{-3} mol) Electrolysis cell: divided cell equipped with a magnetic stirrer containing a piece of glass tubing with a glass frit of medium porosity at one end (anodic compartment). Solid sodium carbonate (2 g, 1.42 mmol) was added to the anodic compartment for "*in situ*" neutralization of the generated perchloric acid. Solid sodium thiosulphate (1 g, 6.3 mmol) was added to the anodic

compartment to avoid bromine generation. A constant cathodic potential of -0.25 V (vs. SCE) was applied. The temperature during the electrolysis was 15 ºC, and the reaction time about 1 h. At the end of this time the cathodic solution was poured over ice water. The precipitated solid was filtered after 12 h and dried under reduced pressure.
The crude was chromatographed and the obtained products characterized.

5-Amino-4-benzoyl-3-phenylfuran-2-carbonitrile (2). 67% yield; mp 200-202 ºC (EtOH); IR (KBr) : 3396, 3247, 2224, 1644, 1598, 1488, 920, 752, 688 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$) δ : 6.61 (br s, 2H, NH_2), 7.35-7.65 (m, $6H_{Ar}$), 7.70 (d, J= 6.8 Hz, $2H_{Ar}$), 7.70 (d, J= 6.8 Hz, $2H_{Ar}$). ^{13}CNMR (75.4 MHz, $CDCl_3$) δ : 90.6, 97.5, 113.7 (CN), 124.7, 126.9, 127.8, 127.9, 128.7, 129.5, 131.6, 138.2, 151.1, 153.7, 162.1, 189.3 (C=O). MS m/z (rel. inten.) : 289 (M^++1, 10), 288 (M^+, 56), 287 (M^+-1, 74), 105 (100), 77 (82), 51 (14). Anal. Calcd for $C_{18}H_{12}N_2O_2$: C,75; H, 4.16. Found: C, 74.88; H, 4.13.

5-Amino-4-bromo-2-phenylfuran-3-carbonitrile (3). 8% yield; mp 180-182 ºC (EtOH); IR (KBr) : 3438, 3347, 2199, 1635, 1446, 950, 686 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$) δ : 4.10 (br s, 2H, NH_2), 7.40-7.50 (m, $3H_{Ar}$), 7.90-8.00 (m, $2H_{Ar}$).^{13}CNMR (75.4 MHz, $CDCl_3$) δ : 90.1, 107.8, 111.8 (CN), 125.9, 127.8, 128.4, 129.6, 144.3, 152.1. MS m/z (rel. inten.): 264 (M^++2, 20), 262 (M^+, 20), 183 (M^+-Br, 60), 128 (78), 105 (100), 77 (72), 51 (39). Anal. Calcd for $C_{11}H_7N_2OBr$: C, 50.19; H, 2.66. Found: C, 50.31; H, 2.63.

3,4-Diphenyl-3,4-dihydroxyhexanedinitrile (5). 10% yield; mp 230 ºC (EtOH); IR (KBr): 3407, 2261, 1338, 1252, 1068, 700 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$) δ : 2.34 (d, 2H, J=17 Hz), 3.43 (d, 2H, J=17 Hz), 7.20-7.35 (m, $6H_{Ar}$), 7.47-7.57 (m, $4H_{Ar}$).^{13}CNMR (75.4 MHz, $CDCl_3$) δ : 29.3, 113.9 (CN),128.4, 129.1, 134.3, 134.7. MS m/z (rel. inten.): 293 (M^++1, 3), 292 (M^+, 12), 234 (11), 105 (100), 77(84), 51 (34). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.97; H, 5.47. Found: C, 73.81; H, 5.63.

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