Preparation of 2,6-Dimethyl-4-arylpyridine-3,5-dicarbonitrile: A Paired Electrosynthesis†

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Abstract: Electrolysis of benzylthiocyanate, benzyl chloride, *p*-methylbenzyl chloride, *p*-methoxybenzyl chloride, or toluene in acetonitrile, at platinum electrodes in a two compartments cell divided by a glass-frit diaphragm, affords 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitrile as major product.

The synthesis of polysubstituted pyridines,[1] particularly the 3,5-dicarbonitrile, has received considerable attention due to its chemistry[1] and photochemistry,[2] but also to its antibacterial activity as nifedipine analogue,[3] as intermediate in thrombin inhibition,[4] or its use to avoid the prion replication through structure-based drugs design.[5] On the other hand, polysubstituted 1,4-dihydropyridines are interesting as pharmacologically active substances, antioxidants, and NADH coenzyme analogues that mediate the hydrogen transfer in biological systems.[6]

The highest electric current efficiency is one of the aims of the organic electrochemists. It is known that the number of electrons added at the cathode (for reduction) must simultaneously be removed at the anode (for oxidation). For instance, to obtain a product into the anodic compartment it is necessary for another to be formed into the cathode. Unfortunately, in most of the processes the product in one of the compartments is undesirable. Herein, we describe the paired electrosynthesis of the 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitrile. There are few examples in the literature where both compartments show a cooperative action to lead simultaneously to interesting products.[7]

Results and Discussion

The anodic oxidation of benzylthiocyanate (5 mmol) at platinum net anode and a platinum plate as cathode, in dry acetonitrile−Bu_4NBF_4 or $LiClO_4$ (0.05 M), using a two-compartment cell separated by a glass-frit diaphragm (D3), at constant temperature of 15 °C and under controlled potential of +2.5V (vs SCE), determined by voltammetry, afforded in good yield (70%) a crystalline product (**1**). The same reaction carried out in a one-compartment cell led to a mixture of products and the yield in our crystalline product was poor.

The solid presented a melting point of 174 °C. In its IR spectrum the band at 2156 cm^{-1} corresponding to the SCN group of the starting molecule had disappeared, and simultaneously, another band appeared at 2230 cm^{-1} that could be assigned to a CN group joined to an aromatic ring. In the proton NMR spectrum, a singlet assigned to two equivalent methyl groups, which integrated for 6 hydrogen atoms, appeared at 2.87 ppm and also showed a multiplet centered at 7.57 ppm corresponding to the, almost equivalent, five aromatic protons. The ^{13}C NMR confirms the previous data and shows the presence of carbon−nitrogen double bond. Moreover, the elemental analysis together with the molecular weight obtained by mass spectrometry led to the molecular formula $C_{15}H_{11}N_3$.

With these data and having in mind the nature of the starting material, it was not possible to establish the structure of the final compound, as it was necessary to apply an X-ray analysis. The molecular structure of **1** can be described as a central pyridine ring with two methyl and two cyanide groups located in a symmetrical fashion, and a tilted phenyl ring (torsion angle C2−C1−C7−C8 124.8(3)°) as substituents.[8] The X-ray study was in agreement with the compound 2,6-dimethyl-4-phenyl-3,5-pyridinedicarbonitrile (**1**), a known compound[9] whose formation was very surprising.

The cathodic reduction of acetonitrile in absence of water leads to 3-aminocrotonitrile anion (**i**), as proposed by Pons et al.[10] (see Scheme 1).

IR spectroscopy of **i** showed a band at 2151 cm^{-1} corresponding to the CN group in the anion. This CN band appears at 2181 cm^{-1} in 3-aminocrotonitrile. It is noticeable that we observed both bands in the IR spec-

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† In Memory of Prof. Lennart Eberson.

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(8) X-ray data for $C_{15}H_{11}N_3$: colorless crystals, orthorhombic, *Pnab*, $a = 8.165(2)$ Å, $b = 11.075(2)$ Å, $c = 13.999(3)$ Å, $V = 1265.9(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.224$ Mg/m^3. All data were collected on an Enraf Nonius CAD4 diffractometer at room temperature, Kα Mo = 0.710 73 Å. The structure was solved, using the WINGX package (Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837), by direct methods (SHELXS-97) and refined by least-squares against F_2 (SHELXL-97). Intensity measurements were performed by $\omega - 2\theta$ scans in the range $3° < 2\theta < 46°$, of the 1093 measured reflections, 883 were independent; R1 = 0.058 and wR2 = 0.161 (for 717 reflections with $F > 4\sigma(F)$). The values of R1 and wR are defined $R1 = \sum||F_o| - |F_c||/[\sum|F_o|]$; $wR2 = [[\sum w(F_o^2 - F_c^2)^2]/[\sum w(F_o^2)^2]]^{1/2}$. Largest difference: peak and hole 0.274 and −0.210 e·Å^{-3}. All non-hydrogen atoms were anisotropically refined.

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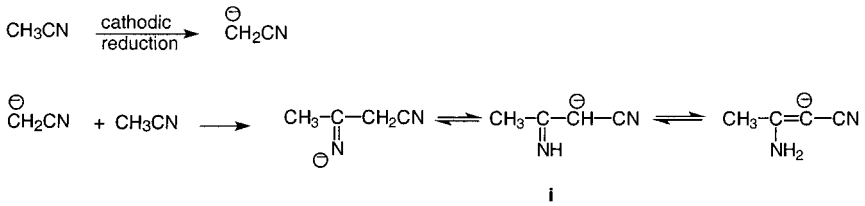
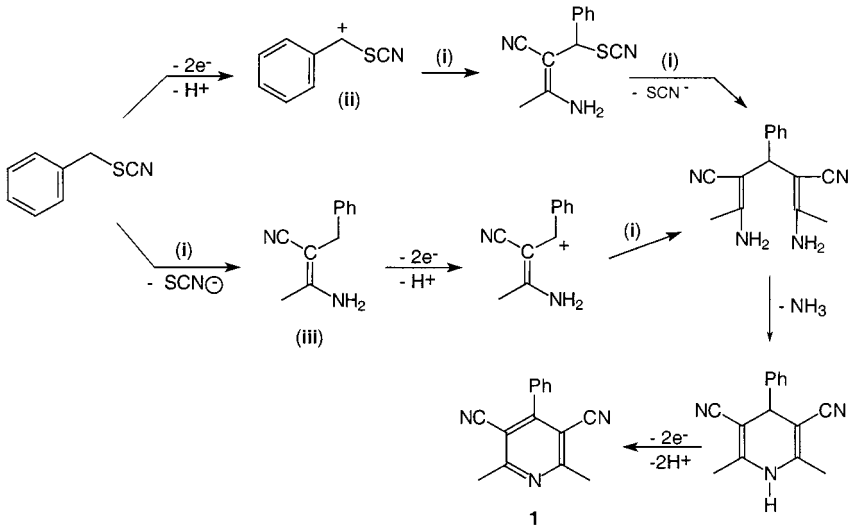
Scheme 1. Cathodic Formation of 3-Aminocrotonitrile Anion



Scheme 2. Proposed Route for the Paired Reaction



trum of the catholyte. If we assume that the anion **i** goes through the glass-frit diaphragm to the anodic compartment, it can be explained the formation of **1** in agreement with the route proposed in Scheme 2.

Two concurrent routes are proposed to explain the formation of **1**. In both cases, intermediates have been isolated. The only difference between these routes is whether the oxidation step takes place before or after the substitution reaction. In the first case the cation **ii** does not react with acetonitrile, and only a small trace of $PhCH(SCN)NHCOCH_3$, formed by a Ritter reaction with the acetonitrile (acetamidation reaction), was detected by mass spectrometry EI: 206 (M^+, 6), 148(100), 121 (46), 91 (55).

On the other hand 3-amino-2-benzylcrotonitrile (**iii**) has been prepared by addition of **i** (obtained by treatment of 3-aminocrotonitrile with NaH in hexane) to a solution of substrate, MS *m/e* (relative intensity) EI: 172 (M^+, 47), 171 (23), 157 (8), 145 (10), 103 (10), 91(100), 65 (26), 51 (19), IR showed bands at 3478, 3380, and 2185 cm^{-1}. The oxidation potential of **iii** was +1.15V (vs SCE) determined by voltammetry in $CH_3CN/LiClO_4$. This value is less positive than that of the substrate, and it is immediately oxidized under the applied potential. A small amount of 1,4-dihydropyridine, was obtained when the reaction was stopped before its conclusion. Mp: 209−211 °C (lit.[11] mp 211−212 °C). MS *m/e* (relative intensity) EI: 235 (M^+, 10), 158 (100), 91 (13), 77 (15). ^{1}HNMR ($CDCl_3$) δ: 2.1 (s, 6H), 4.35 (s, 1H), 5.9 (bs, 1H), 7.2−7.5 (m, 5H). The oxidation potential of the 1,4-dihydropyridine, determined by voltammetry[12] with a rotated platinum electrode in acetonitrile/TBAHFP, was +1.34V vs SCE. This value is again less positive than that of the substrate.

To confirm the proposed routes, an electrolysis using a cationic Nafion 450 membrane, instead of the glass-frit diaphragm, was carried out. Under the same experimental conditions, **1** was not obtained and **i** was isolated into the catholyte. In the anodic compartment, all of the substrate was converted into benzaldehyde. This fact supports the formation of **ii**, which affords benzaldehyde in the presence of water during the workup.

Despite benzylthiocyanate is consumed after $2e^-$ per substrate molecule passed over the solution, the reaction proceeds until $4e^-$ per substrate molecule are circulated. At the end of the reaction, in the cathodic compartment there is an excess of **i** (precipitated solid when lithium perchlorate is used as electrolyte or in solution when Bu_4NBF_4 is employed). It has to be mentioned that when $4e^-$ per substrate molecule have been circulated, the current does not go down to zero, because molecules of **i** going through the diaphragm are oxidized into the anodic compartment.

When benzyl chloride is oxidized instead of benzylthiocyanate, under the same experimental conditions, the yield in **1** was 74%.

To make the reaction more general other substrates (*p*-methylbenzyl chloride and *p*-methoxybenzyl chloride) have been employed. In both cases, the corresponding pyridines and their 1,4-dihydro derivatives were obtained.

2,6-Dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarbonitrile (67% yield). Mp: 232−234 °C. IR (KBr) ν = 3039, 2925, 2223, 1611, 1573, 1552, 1540, 1513, 822, 774, 518 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35−7.43 (m, 4H), 2.85 (s, 6H), 2.44 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.7, 24.9, 107.5, 115.6, 128.8, 130.1, 130.2,

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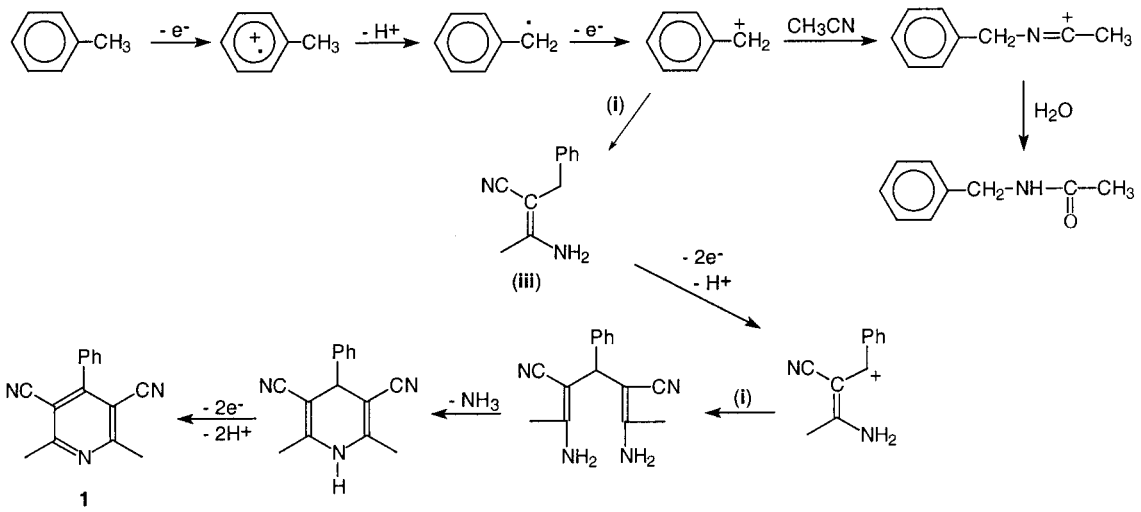
Scheme 3. Proposed Alternative Route to 1 in the Anodic Oxidation of Toluene



141.8, 157.1, 165.3. MS *m/e* (relative intensity) EI: 248 ($M^+ + 1$, 18), 247 (M^+, 100), 246 (27), 232 (9), 219 (9), 205 (15), 151 (9), 140 (9), 91 (8).

2,6-Dimethyl-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (62% yield). Mp: 182 °C (Lit.[11] mp 181−183 °C). IR (KBr) ν = 3070, 2945, 2845, 2225, 1610, 1578, 1540, 1520, 1271, 1189, 1027, 835 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.5 (d, 2H, J = 8.9 Hz), 7.1(d, 2H, J = 8.9 Hz), 3.9 (s, 3H), 2.9 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 24.9, 55.7, 107.4, 114.8, 115.8, 125.1, 130.7, 156.8, 162.0, 165.3. MS *m/e* (relative intensity) EI: 264 ($M^+ + 1$, 19), 263 (M^+, 100), 262 (11), 248 (7), 232 (8), 220 (13), 205 (10), 192 (13), 152 (12), 114 (13), 76 (10).

2,6-Dimethyl-4-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. Mp: 218−222 °C. IR (KBr) ν = 3313, 3123, 2856, 2192, 1668, 1504, 1273, 1021, 787 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.9−7.2 (m, 4H), 6.3 (s, 1H), 4.3 (s, 1H), 2.35 (s, 3H), 2.0 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 18.4, 21.4, 41.8, 84.8, 119.1, 127.6, 129.8, 137.9, 139.9, 145.7. MS *m/e* (relative intensity) EI: 249 (M^+, 9), 248 (5), 234 (4), 159 (11), 158 (100), 91 (9), 65 (13).

2,6-Dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarbonitrile. Mp: 216−217 °C. IR (KBr) ν = 3317, 3128, 2924, 2204, 1668, 1509, 1244, 1023, 849 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.17 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.6 Hz), 6.1 (s, 1H), 4.3 (s, 1H), 3.8 (s, 3H), 2.1 (s, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 18.8, 41.5, 55.5, 85.9, 114.6, 118.8, 129.0, 135.0, 144.7, 159.6. MS *m/e* (relative intensity) EI: 265 (M^+, 13), 264 (10), 250 (4), 234 (5), 159 (10), 158 (100), 108 (19).

On the other hand, it is well-known that the anodic oxidation of toluene in acetonitrile in a one-compartment cell affords *N*-benzylacetamide as major product.[13] When this reaction is carried out under our experimental conditions, again *N*-benzylacetamide (54%) is the major product, but **1** (38%) is also obtained. In this case, the electrogenerated benzyl cation can react either with acetonitrile, via a Ritter reaction, to give *N*-benzylacetamide or with the anion **i** affording **iii**, which is immediately oxidized at the applied working potential to the corresponding cation, as has been previously demonstrated. Subsequent attack of **i** leads to the dihydropyridine. Since **i** is a stronger nucleophile than acetonitrile one would expect the benzyl cation to react faster with **i** than with acetonitrile; however, the acetamide is the main product. This effect was observed by Eberson[13] and by Nyberg.[14] They postulated that "as the cation becomes more stable, the selectivity is toward the weaker nucleophile".

On the other hand, by linear free energy relatioship[15] has been determined that $PhCH_2^+$ is more stable than $PhCH^+SCN$ or $PhCH^+Cl$. In both cases $\mathcal{J}_I$ value is higher than the $\mathcal{J}_R$ value. For this reason and due to the fact that both cations are harder acids than the benzyl cation, they react preferently with the harder base **i**.

The radical route is not discarded, as a side pathway, in the oxidation of these compounds. Having in mind that **i** can be oxidized to radical in the anodic compartment, subsequent coupling with electrogenerated benzyl radicals can take place.

As conclusion, all substrates able to be oxidized to a benzyl cation will lead under the described experimental conditions to 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitrile.

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Supporting Information Available: Crystal data and structure refinement for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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