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Electrosynthesis of pyridines from 'only acetonitrile'

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Abstract—2,4,6-Trimethylpyridine-3,5-dicarbonitrile has been obtained as the main product after the electrolysis of acetonitrile in the presence of tetrabutylammonium bisulfate as supporting electrolyte using a divided cell with a medium porosity diaphragm. 2,6-Dimethylpyridine-3,5-dicarbonitrile and 2,6-dimethylpyridine-3,4,5-tricarbonitrile have also been obtained in minor quantity. This process, which takes place with participation of both electrodes, is an example of a paired electrosynthesis.

Polysubstituted pyridines-3,5-dicarbonitrile have received considerable attention due to their pharmacological and biological activity.[1,2]

On the other hand, the cathodic reduction of acetonitrile in the absence of water leads to 3-aminocrotonitrile anion,[3] while the positive potential limit of acetonitrile solutions is fixed by the anodic oxidation of the supporting electrolyte anion.

In the present letter, a paired electrosynthesis of substituted pyridines: 2,4,6-trimethylpyridine-3,5-dicarbonitrile (**1a**) (as main product), 2,6-dimethylpyridine-3,5-dicarbonitrile (**1b**) and 2,6-dimethylpyridine-3,4,5-tricarbonitrile (**1c**) is described.

Constant current electrolyses of acetonitrile-electrolyte solutions, in a divided cell with a medium porosity diaphragm, afforded pyridines **1a–c** in the anodic compartment. It is important to notice that no pyridines were found in the cathodic side, and that if the reaction is performed in an undivided cell, under the same experimental conditions, pyridines were not obtained.

In Table 1 the improvement on the yield of pyridine mixture with the current density is observed, after 4000 C circulated through the cell.

As higher current density is applied and larger amount of charge is circulated through the cell, higher yield of pyridines is achieved (Table 2).

The proposed mechanism to explain these results is as follows: 3-aminocrotonitrile anion, formed into the cathodic compartment, can react with acetonitrile either before or after the migration through the diaphragm to the anodic site. This reaction in the cathodic compartment is displaced to the left side, for this reason, experimentally no traces of imine **i**, neither its hydrolysis products, were found in this compartment. However, in the anodic compartment, the attack of 3-aminocrotonitrile anion to the solvent becomes irreversible as a result of the subsequent in situ protonation of the anionic intermediate to give imine **i** (Scheme 1). It is supported by the fact that no pyridines were obtained into the cathodic compartment.

The protons source is generated by anodic oxidation of the electrolyte anion and further reaction with acetonitrile.[4]

$$HSO_4^- \xrightarrow{-e^-} HSO_4^{\bullet} \xrightarrow{CH_3CN} H_2SO_4 + {}^{\bullet}CH_2CN$$

Table 1. Increase of the pyridines yield with the current density

Circulated charge (C)	*I* (mA)	Current density (mA/cm^2)	Pyridine mixture (mg)	Yield (%) **1a**	Yield (%) **1b**	Yield (%) **1c**
4000	300	22.5	273	50	28	22
4000	900	67.6	380	54	31	15
4000	1200	90.2	537	57	33	10

Keywords: 2,4,6-Trimethylpyridine-3,5-dicarbonitrile; Paired electrochemical reaction; Acetonitrile; Constant current.
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Table 2. Increase of the pyridines yield with the circulated charge

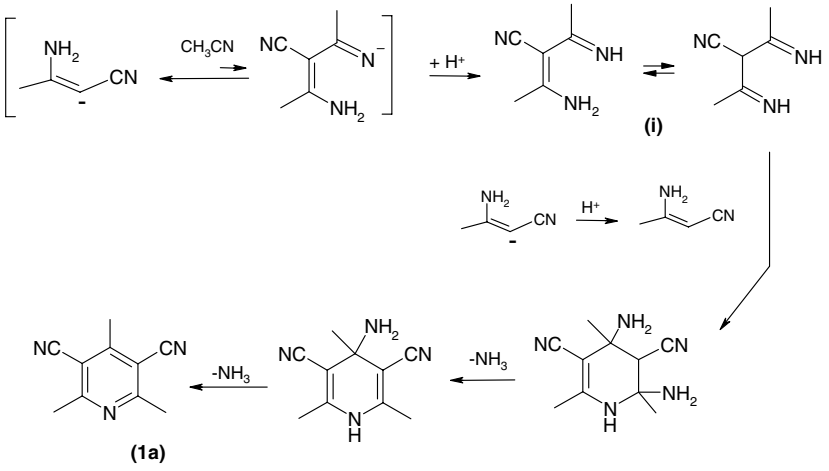
Circulated charge (C)	*I* (mA)	Current density (mA/cm^2)	Pyridine mixture (mg)	Yield (%) **1a**	Yield (%) **1b**	Yield (%) **1c**
10000	1200	90.2	1440	71	22	7
20000	1200	90.2	2570	79	17	4
40000	1200	90.2	4710	84	13	3

Reaction of **i** with 3-aminocrotonitrile leads, after loss of two ammonia molecules, to 2,4,6-trimethylpyridine-3,5-dicarbonitrile (**1a**).

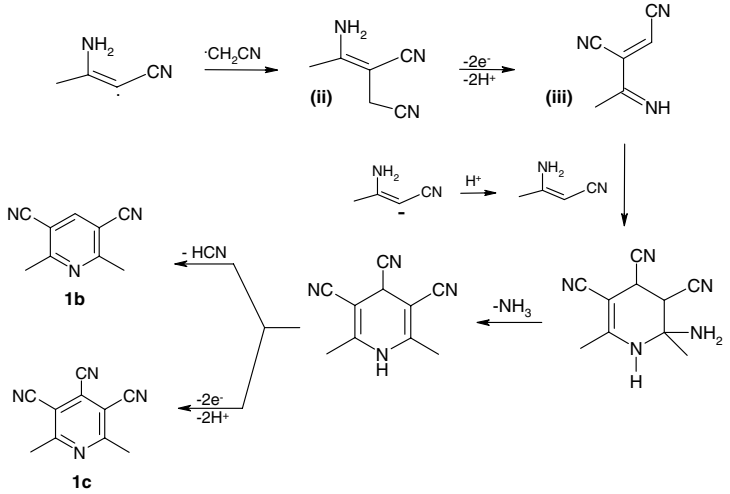
The formation of the secondary products, pyridines **1b** and **1c**, can be rationalized as follows: some 3-aminocrotonitrile anion molecules arrive to the anode surface where they are oxidized to the corresponding radicals, which are further coupled with the acetonitrile radicals $^{\cdot}CH_2CN$, whose formation is described above and well known in the literature.[4] This coupling affords enamine **ii**, which is immediately oxidized to the α,β-unsaturated imine **iii**. α,β-Unsaturated imines have already been postulated as intermediates in the synthesis of substituted pyridines[5] and polysubstituted pyrimidines.[6] The reaction of **iii** with 3-aminocrotonitrile allows the obtention of pyridines **1b** and **1c**, as indicated in Scheme 2.

The obtained yield of each pyridine is directly related to the theoretical charge consumption postulated for their formation.

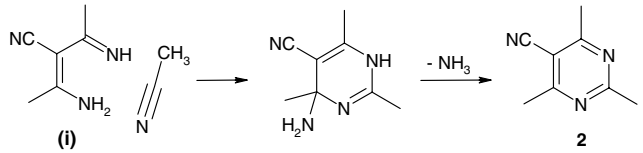
When the electrolysis is performed using a low porosity diaphragm (D4), the migration of 3-aminocrotonitrile anion to the anode is hindered, and a large amount of this compound is found into the catholyte. In this case, only traces of pyridines are obtained in the anodic compartment while 2,4,6-trimethylpyrimidine-5-carbonitrile (**2**) is isolated as the main product. The regioselective formation of **2** can be rationalized (Scheme 3) as a reaction between acetonitrile and the intermediate **i**, already postulated in the formation of pyridine **1a**. This reaction only takes place when the concentration of 3-aminocrotonitrile anion into the anolyte is too low, due to the low porosity of the diaphragm employed.



Scheme 1.



Scheme 2.



Scheme 3.

The anodic obtention of pyrimidine **2** supports the postulated mechanism (Scheme 1) to explain the formation of pyridine **1a**.

Experimental: Electrolyses of dry acetonitrile were carried out under constant current conditions at a platinum mesh anode (13.3 cm^2) and a platinum plate cathode, using Bu_4NHSO_4 (0.05 M) as electrolyte, which is the cheapest tetraalkylammonium salt. A refrigerated (15 °C) two-compartment cell with a medium porosity glass-frit diaphragm (D2) was employed. After the desired charge was circulated through the cell, the solvent in the anodic solution was removed under reduced pressure, the residue was extracted with ether/water and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid was chromatographed on silica gel (18 × 3 cm) column, using CH_2Cl_2–hexane (9:1) as eluent. A mixture of **1a**, **1b** and **1c** was obtained. Spectroscopical and physical description of the obtained pyridines **1a** (mp 115–117 °C [lit.[7] 116–118 °C]) and **1b** (mp 116–118 °C [lit.[8] 117–118 °C]) coincided with those from the literature.

2,6-Dimethylpyridine-3,4,5-tricarbonitrile (**1c**): Mp 100 °C (hexane). IR (KBr) $\nu = 2921$, 2233, 1569, 1412, 1222, 1021, 916 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.87 (s, 2Me). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 24.9, 109.3, 111.6, 112.7, 127.5, 166.28. MS *m/e* (relative intensity) EI: 183 (M^++1, 12), 182 (M^+, 100), 167 (2), 155 (5), 141 (7), 114 (4), 88 (5). Anal. Calcd for $C_{10}H_6N_4$: C, 65.93; H, 3.30; N, 30.77. Found: C, 65.81; H, 3.39, N, 30.67.

2,4,6-Trimethylpyrimidine-5-carbonitrile (**2**): Mp 134–135 °C (hexane). IR (KBr) $\nu = 2926$, 2226, 1562, 1434, 1137, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.65 (s, 6H, 2Me), 2.68 (s, 3H, Me). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 23.6, 26.6, 105.3, 115.4, 169.4, 170.0. MS *m/e* (relative intensity) EI: 148 (M^++1, 11), 147 (M^+, 100), 120 (54), 119 (92), 105 (20), 90 (9), 78 (16), 66 (14), 51 (12). Anal. Calcd for $C_8H_9N_3$: C, 65.31; H, 6.12, N, 28.57. Found: C, 65.13; H, 6.17, N, 28.71.

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