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Electroorganic synthesis of 6-aminonicotinic acid from 2-amino-5-chloropyridine

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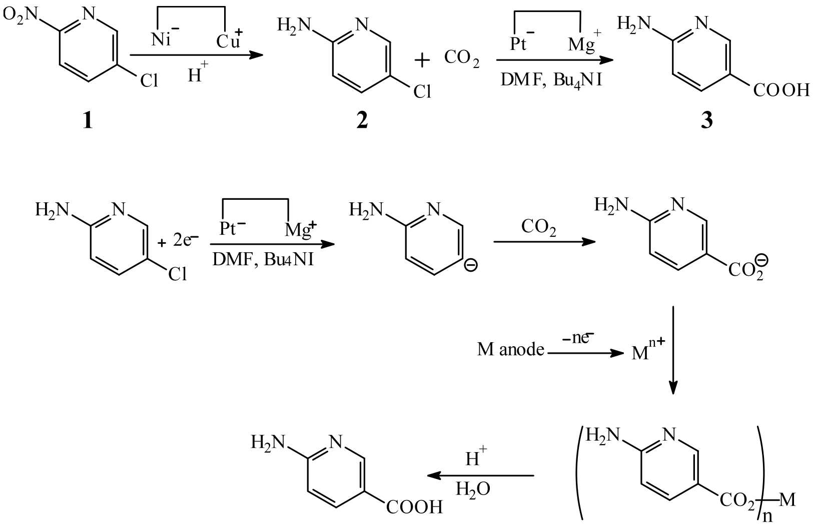
Abstract—A synthesis of 6-aminonicotinic acid by electrochemical hydrogenation of 5-chloro-2-nitropyridine and electrochemical carboxylation of 2-amino-5-chloropyridine at a cathode surface in the presence of sulphuric acid and carbon dioxide in a dimethylformamide (DMF) solution at an apparent current density of 10 mA/cm^2 using an undivided cell with good yields is reported. © 2003 Elsevier Science Ltd. All rights reserved.

6-Aminonicotinic acid, a main constituent of the 'B_3' vitamin, is used to cure pellagra disease.[1] The conventional synthesis of 6-aminonicotinic acid reported[2–4] in the literature has certain drawbacks such as the formation of hazardous chemicals including cyanide and ammonia gas and low yields due to the high temperatures required. Electrochemical hydrogenation and carboxylation are used for the synthesis of many organic compounds[5–8] and include hydrogenation of nitro compounds[9] and carboxylation of halogenated derivatives.[10–12] In this paper, we wish to report a new method for the synthesis of 6-aminonicotinic acid, which involves the combination of electrochemical hydrogenation and carboxylation.

The six-electron reduction of a nitro group to the corresponding amine is well known[13] and the electrochemical conversion of 5-chloro-2-nitropyridine **1** to 2-amino-5-chloropyridine **2** at a nickel cathode and copper anode in the presence of acid proceeded in up to 84% yield.[14–16] Reductive-carboxylation of this then gave 6-aminonicotinic acid **3** in 78% yield.



Scheme 1.

Keywords: 6-aminonicotinic acid; 5-chloro-2-nitropyridine; 2-amino-5-chloropyridine; electroorganic synthesis.

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Table 1. Electrochemical hydrogenation of 5-chloro-2-nitropyridine[a,b]

Experiment no.	Temperature (°C)	Substrate concentration (g/dm^3)	Yield of 2-amino-5-chloropyridine (%)
1	25	2.0	84
	30		83
	40		81
	60		80
2	40	4.0	78
	60		74
3	40	6.0	68
	60		65
4	40	8.0	64
	60		60

[a] At current density of 100 A/m^2.

[b] Charged passed 2F.

Table 2. Electrochemical carboxylation of 2-amino-5-chloropyridine[a,b,c]

Experiment no.	Temperature (°C)	Substrate concentration (g/dm^3)	Yield of 6-aminonicotinic acid (%)
1	5	2.0	78
2	5	4.0	77
3	5	6.0	76
4	5	8.0	73

[a] $P_{CO_2} = 1$ atm.

[b] Current density = 10 mA/cm^2.

[c] Charge passed = 2F.

The mechanism of reductive-carboxylation is outlined in Scheme 1. The two-electron reduction of 2-amino-5-chloropyridine produced an intermediate carbanion which attacks carbon dioxide to give a carboxylate anion. Capture of the anion by metal ions generated by the dissolution of the anodic metal, gives a metal carboxylate. Finally, treatment of the metal carboxylate with acid gives 6-aminonicotinic acid.[17]

To optimise the electroreductive reactions (hydrogenation and carboxylation) of 5-chloro-2-nitropyridine and 2-amino-5-chloropyridine they were carried out at different electrodes in the presence of supporting electrolytes with different substrate concentrations and reaction temperatures. The experimental results presented in Tables 1 and 2, demonstrate the variation in the yields of product due to changes in the initial concentrations of the substrates which were reduced at fixed current densities, and also from changes in temperature at a given substrate concentration. The conditions that favoured the formation of good yields of the products were low concentrations of substrate, low temperatures and proper selection of the electrode material. The yields were strongly dependent on the electrolysis conditions and the selectivity for the desired product was found to be sensitive to the nature of the cathode material and solvent. Electrolyses with platinum and nickel cathodes and dimethylformamide (DMF) as solvent gave good yields of the reductive carboxylation.

In conclusion, the electroorganic synthesis of 6-aminonicotinic acid from 2-amino-5-chloropyridine can be achieved at a cathode surface in good yield. This electrolytic procedure is an alternative route for the synthesis of 6-aminonicotinic acid which needs only a current generator and is especially easy to work-up.

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16. *Experimental procedure for 2-amino-5-chloropyridine*: The electrochemical hydrogenation was carried out by dissolving 5-chloro-2-nitropyridine (5.0 g) in ethanol (50 mL) containing 10% sulphuric acid (15 mL) at a constant current density of 100 A/m^2 in an undivided cell equipped with a nickel cathode (3×4 cm^2) and a copper anode (3×4 cm^2). These electrodes were connected to a dc power supply and 2F of charge passed. The cell was then kept under an atmosphere of nitrogen and the contents were stirred using a magnetic stirrer. At the end of the reaction, the electrolyte solution was diluted with water, the product was extracted into ether, washed with water, dried over anhydrous magnesium sulphate and the evaporation of the solvent gave 4.1 g of 2-amino-5-chloropyridine in 82% isolated yield; mp 136–138°C; ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, $J=2.1$ Hz), 7.45 (dd, 1H, $J=8.3$ Hz), 6.48 (d, 1H, $J=8.4$ Hz), 6.2–7.8 (brs, 2H, $N\underline{H}_2$); IR (neat): ν 3226, 3130, 1713, 1635, 795 cm^{-1}.
17. *Experimental procedure for 6-aminonicotinic acid*: The electrochemical carboxylation was carried out in an undivided cell equipped with a platinum cathode (20 cm^2) and magnesium anode (20 cm^2). The cell was charged with a dimethylformamide (50 mL) solution containing Bu_4NI (0.04 mol/dm^3) and 2-amino-5-chloropyridine (20 mmol) was added to the cell. Then, the cell was immersed in cold water to dissipate the heat evolved during the electrolysis and to keep the temperature near 5°C. Before electrolysis, the oxygen in the system was removed by passing nitrogen gas through the solution. After that, the stirred mixture was saturated by bubbling carbon dioxide gas. In this saturated state, the system was electrolysed by supplying regulated dc power at 10 mA/cm^2 until 2F had been passed through the cell at 5°C. The usual work-up of the electrolysed solution afforded 3.2 g of 6-aminonicotinic acid in 78% isolated yield; mp 244–246°C; ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 1H, $J=2.1$ Hz), 8.0 (dd, 1H, $J=8.3$ Hz), 6.26 (d, 1H, $J=8.4$ Hz), 7.36 (brs, 2H), 11.64 (brs, 1H); IR (neat): ν 3250, 3130, 1724, 1638, 1540 cm^{-1}.