ELSEVIER

Electrocatalytic synthesis of 6-aminonicotinic acid at silver cathodes under mild conditions

Armando Gennaro [a,*], Carlos M. Sánchez-Sánchez [b], Abdirisak Ahmed Isse [a], Vicente Montiel [b]

[a] *Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, 35131 Padova, Italy*
[b] *Departamento de Química Física, Instituto de Electroquímica, Universidad de Alicante, Ap. 99, 03080 Alicante, Spain*

Abstract

The feasibility of electrosynthesis of 6-aminonicotinic acid by electrochemical reduction of 2-amino-5-bromo and 2-amino-5-chloropyridine in the presence of CO_2 has been investigated in DMF and CH_3CN at glassy carbon (GC), Hg, Pt and Ag electrodes. Reduction of both halides at GC, Hg and Pt electrodes occurs at potentials only slightly more positive than E_p of CO_2. These electrodes are not appropriate for a simple and clean electrocarboxylation of the halides to 6-aminonicotinic acid. The silver electrode shows a remarkable electrocatalytic effect for the reduction of only the bromo derivative. Reduction of 2-amino-5-bromopyridine at such an electrode occurs at potentials 0.5–0.8 V more positive than at the other electrodes. The electrosynthesis process was investigated at Ag using only the bromo derivative as the starting substrate. The process was investigated both in a divided and an undivided cell with Al sacrificial anode under constant potential or current density. In all cases fairly good yields of 6-aminonicotinic acid (48–82%) with moderate quantities of 2-aminopyridine were obtained in DMF. Instead, the principal reduction product in CH_3CN is 2-aminopyridine with yields >80% while only very small quantities of the acid are formed.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Halopyridines; Aminonicotinic acid; Electrocarboxylation; Electrocatalysis; Silver electrode

1. Introduction

The syntheses of 6-aminonicotinic acid (6-ANA) and its amide derivative are of interest due to their biochemical properties as protein synthesis inhibitor, vitamin B_3 antagonist and modulating agent in chemotherapy treatment for some types of cancer. These compounds are the analogues of nicotinic acid (vitamin B_3) and nicotinamide (Niacin), respectively, and were originally synthesised as antagonists of Niacin [1], which is used by the body to form the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). The 6-aminonicotinamide antagonist inhibits NADP production because it is a specific pentose pathway inhibitor [2]. 6-Aminonicotinamide is

also a potential agent for modulating the cytotoxicity of antineoplastic drugs. In particular, it has been found that this pyridine nucleotide enhances the accumulation of cisplatin (*cis*-diamine-dichloroplatinum) in a variety of tumour cell lines [3,4]. Recent results have indicated that 6-aminonicotinamide sensitises a number of human tumour cell lines to the cisplatin in vitro [3]. Another pharmaceutically interesting derivative of 6-ANA is its ethyl ester, which is a nontoxic compound used for the treatment of psoriasis [5].

The conventional synthesis of 6-ANA, based on hydrolysis of the corresponding nitrile, suffers from several drawbacks such as the use of hazardous chemicals, the high temperatures required for the reactions and the low yields in acid [6–8]. It is well known, on the other hand, that the electrocarboxylation of organic halides is a powerful pathway for the production of carboxylic acids [9–13]. This methodology has been extensively used for

obtaining alternative synthetic routes to the manufacture of pharmaceutical industrial products [14,15].

The electrochemical reduction of halobenzenes and halopyridines goes through a two-electron irreversible bond cleavage in organic solvents [16,17]. More than ten years ago, Zylber et al. [18] studied the electrochemical carboxylation of several halogenated N-heteroaromatic compounds. They tested as possible substrates for carboxylation also 2-amino-5-chloropyridine (2-ACP) and 2-amino-5-bromopyridine (2-ABP). The reactions were carried out at stainless steel cathode in an undivided cell at constant current density until 2.1 e⁻/molecule of halide were passed, but the expected 6-ANA was not found in the reaction mixture. Recently, Raju et al. [19] have reported a new method for the synthesis of 6-ANA, which involves the electrochemical hydrogenation of 5-chloro-2-nitropyridine followed by electrocarboxylation of the formed 2-ACP. Their carboxylations were conducted in an undivided cell at constant current density, until 100 e⁻/molecule of halide were passed. Despite the excessive charge consumption, good yields of acid were obtained.

These different results are probably attributable to the highly negative reduction potential of the pyridine halides and the pre-eminent reduction of CO_2. In this study, we explore a new approach for the synthesis of 6-ANA, based on the electrocatalytic reduction of 2-ABP at silver cathodes in CO_2-saturated nonaqueous solvents. Owing to its remarkable electrocatalytic activity towards the reduction of organic halides [20–23], use of a Ag cathode will make possible the selective reduction of the halide, thus avoiding the concomitant reduction of CO_2, which takes place during the electrochemical carboxylation at the most commonly used cathodes. In fact, at Ag cathodes we found that the process requires only the stoichiometric charge (2 e⁻/molecule of substrate) and gives good yields of 6-ANA.

2. Experimental

2.1. Chemicals

N,N-Dimethylformamide (DMF) (Janssen, 99%) was kept over anhydrous Na_2CO_3 for several days and stirred from time to time. It was then fractionally distilled twice under reduced pressure under N_2 and stored in a dark bottle under N_2. Acetonitrile (BDH, 99.9%) was distilled over CaH_2 and stored under argon atmosphere. Tetra-n-butylammonium perchlorate (Fluka 98%) was recrystallized twice from a 2:1 water–ethanol mixture and dried at 60 °C under vacuum. The 2-amino-5-halopyridines and all other compounds used for the identification and quantification of the reduction products were commercially available and were used as received.

2.2. Instrumentation

Electrochemical measurements were carried out by using an EG&G Princeton Applied Research potentiostat/coulometer Model 173/179 equipped with an EG&G universal programmer Model 175 and a LeCroy LT322 oscilloscope. Cyclic voltammetry measurements were made at glassy carbon (GC), Pt, Ag and Hg electrodes. The counter-electrode and the reference electrode were a Pt wire and Ag|AgI| 0.1 M n-Bu₄NI in DMF, respectively. The latter was calibrated after each experiment against the ferricenium/ferrocene couple. All potentials are reported versus the KCl saturated calomel electrode (SCE), using $E^o_{Fc+/Fc} = 0.391$ V vs. SCE in $CH_3CN + 0.1$ M TBAP and 0.475 V vs. SCE in DMF + 0.1 M TBAP. Controlled-potential electrolyses were carried out at a silver foil of area 8 cm², using two different cells: a two-compartment cell with a Pt anode separated from the cathode compartment by glass frits and Tylose-TBAP-saturated bridge or an undivided cell with a sacrificial Al anode. The silver electrode was pretreated by immersion in HNO_3 65% for 2 min. The Al anode was activated by immersion in a HCl 35% + H_2O (1/1, v/v) solution for 2 min. All experiments were performed at 25 °C. Before starting an electrolysis, a solution of the substrate was saturated with CO_2 by bubbling the gas through the electrolyte for ca. 30 min, after which the gas stream through the cell was closed and a constant potential or current density applied. In each case, the electrolysis was interrupted after the passage of 2 e⁻/molecule of substrate.

The electrolysis products were analysed by using an HPLC JASCO 2075 liquid chromatograph, equipped with a UV detector and a 25 cm × 4.6 mm RP-Amide C16 Supelco column. The eluent was a mixture (20/80, v/v) of CH_3CN and a KH_2PO_4/K_2HPO_4 buffer at pH 6.4. The eluent flow was 1 ml min⁻¹ and the detection wavelength was 255 nm. At the end of the electrolysis a sample of solution was withdrawn from the electrochemical cell and analysed by HPLC after appropriate dilution.

3. Results and discussion

The electrochemical reduction of 2-ACP and 2-ABP was investigated by cyclic voltammetry at four electrodes, namely GC, Hg, Pt and Ag, and in two solvents containing tetra-n-butylammonium perchlorate (TBAP) as supporting electrolyte. Under all experimental conditions, both halides give an irreversible reduction peak at quite negative potentials. Fig. 1 shows examples of the voltammetric response of 2-ABP at two different electrodes in DMF. The peak potentials (E_p) measured for the reduction of the two compounds at all electrodes are collected in Table 1. The reduction potentials of
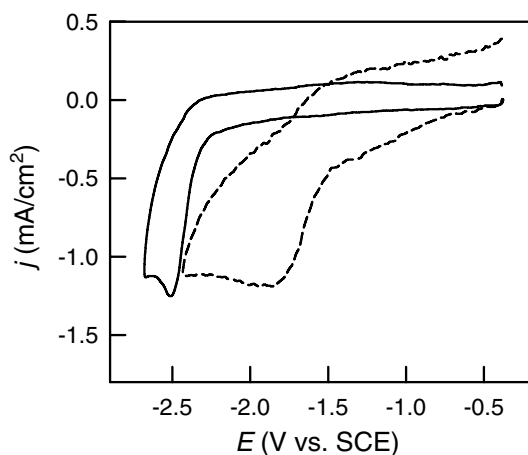
Fig. 1. Cyclic voltammetry of 2-amino-5-bromopyridine 2.85 mM in DMF + 0.1 M TBAP at a GC (——) or Ag (- - -) electrode at $v = 0.2$ V/s.

Table 1
Reduction potentials of 2-amino-5-halopyridines at different cathodes[a]

Solvent	Electrode	2-ACP E_p vs. SCE	2-ABP E_p vs. SCE	CO_2 E_p vs. SCE
DMF	GC	−2.54	−2.48	<−3
	Hg	−2.53	−2.48	−2.58
	Pt	−2.55	−2.38	−2.9[b]
	Ag	−2.52	−1.92	−2.63
CH₃CN	GC	−2.62	−2.58	−2.88
	Hg	−2.67	−2.68	−2.63
	Ag	−2.64	−1.81	−2.64

[a] Other conditions: 0.1 M TBAP supporting electrolyte; $v = 0.2$ V s^{-1}; $T = 25$ °C.
[b] Taken from [25].

these compounds in CH₃CN could not be reliably measured at Pt because their voltammetric peaks merged with the cathodic limiting discharge. With the exception of Ag, the cathode material does not affect strongly the E_p values of the two compounds whereas a slight positive shift is observed in DMF with respect to CH₃CN. At GC, Hg and Pt there is a very small difference between the E_p values obtained for the two compounds, the reduction potentials of 2-ABP being slightly more positive. The negligible effects of the nature of the cathode material and halogen atom on E_p suggest that reduction of the halides at such electrodes proceeds without appreciable interaction between the electrode and the substrate and/or its reduction products and intermediates.

The mechanism of the electrochemical reduction of halopyridines has been previously studied at GC and Hg electrodes [16,17]. The overall process involves a 2e$^-$ reductive cleavage of the carbon–halogen bond and is kinetically controlled by the first electron transfer to RX. According to the well-established reaction mechanism for the dissociative electron transfer to aromatic
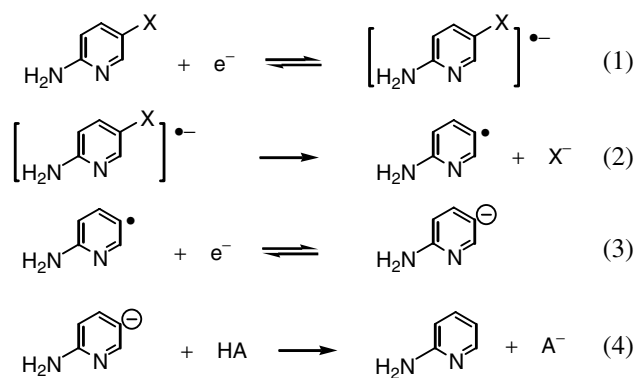
and heteroaromatic halides [24], reduction of amino-halopyridines at inert electrodes can be described by the reaction sequence shown in Scheme 1, where HA stands for any proton donor present in the reaction medium. The formed product 2-aminopyridine shows no reduction peaks up to the cathodic limiting discharge, so only the irreversible reduction peak of the starting halide could be observed in cyclic voltammetry.

Reduction of 2-ACP at silver occurs at potentials similar to those required for its reduction at the other cathodes (Table 1). Instead, the reduction potentials measured for the 2-ABP at Ag are considerably more positive than the E_p values obtained at the other cathodes. Compared to GC, for example, positive shifts of 0.77 and 0.56 V were observed at Ag in CH₃CN and DMF, respectively. The electrocatalytic activity of Ag towards the reduction of organic halides is well documented in the literature and it is assumed to be related to the affinity of Ag for the halide ions [20–23]. Indeed, such an effect decreases in the order I > Br > Cl, which is the same order of the interaction between the halide ions and the metal. There are no literature data for the catalytic reduction of heteroaromatic halides at silver cathodes. The results reported in Table 1 indicate that there is a remarkable electrocatalytic effect only in the case of 2-ABP.

According to the reaction mechanism shown in Scheme 1, reduction of 2-amino-5-halopyridines leads to a carbanion that readily reacts with any electrophile or proton donor present in solution. Thus, 6-aminonicotinate is expected to be formed in the presence of CO_2 (Eq. (5)). It

Scheme 1.

(5)
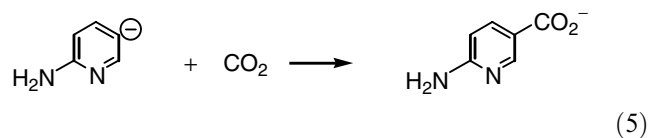
should be stressed, however, that a crucial requirement for a successful electrocarboxylation is that the halopyridine derivative should be more easily reducible than CO_2. The reduction potentials of CO_2 measured under the same experimental conditions used for the 2-amino-5-halopyridines are included in Table 1 for comparison.

Table 2
Electrocarboxylation of 2-amino-5-bromopyridine at a silver cathode

Type of cell	Solvent[a]	c_{2-ABP} (mM)	E_{app} (V vs. SCE)	Conversion[b] (%)	RCOOH[c] (%)	RH[c] (%)
Undivided	DMF	51.5	−2.0	85	74	22
Undivided[d]	DMF	49.1		57	82	14
Divided	DMF	51.6	−2.0	74	48	26
Undivided	CH$_3$CN	51.7	−1.9	80	2	95
Undivided[d]	CH$_3$CN	52.1		36	16	83
Divided	CH$_3$CN	51.6	−1.9	98	2	82

[a] In the presence of 0.1 M TBAP and CO_2 under 1 atm pressure.
[b] Conversion is defined as the fraction of reactant consumed during the electrolysis.
[c] Yield is calculated with respect to 2-ABP consumed.
[d] Constant current electrolysis ($j = 8$ mA/cm^2).

When comparing the peak potentials, we should keep in mind that the electrosynthesis experiments are carried out in CO_2-saturated solvents where the concentration of the gas reaches 0.2 M in DMF and 0.28 M in CH$_3$CN at 25 °C [25]. Under such conditions, reduction of CO_2 starts at potentials much more positive than its peak potential. Comparison of the E_p values reported for the 2-amino-5-halopyridines and CO_2 reveals that electrocarboxylation of 2-ABP may be easily performed at silver cathodes in both solvents. Also GC and Pt may be used for the electrocarboxylation of this compound but only in DMF. In the case of 2-ACP, we see that its reduction potentials are quite similar with those of CO_2. Actually, in most cases, the E_p values of CO_2 are more negative than those of 2-ACP but the difference is so small that concomitant reduction of the two reagents takes place under the electrosynthesis conditions.

The foregoing considerations point out electrocarboxylation of 2-ABP at silver cathodes as the best conditions for electrosynthesis of 6-ANA. We therefore examined this electrocarboxylation process under different experimental conditions. The results of the electrolyses are collected in Table 2. First of all, it should be pointed out that under the investigated experimental conditions the synthesis of 6-ANA does not require excessive charge consumption as has been recently reported using 2-ACP at Pt cathode in DMF [19]. The controlled-potential electrolyses, which were performed at a potential just beyond E_p of the halide, require ca. 2 e$^-$/molecule of 2-ABP whereas a somewhat higher charge consumption is observed when a constant current density is imposed. The excess charge consumed in the latter case is probably due to the concomitant reduction of CO_2, which becomes particularly important during the last stage of the electrolysis when the concentration of 2-ABP decreases drastically. As shown in Table 2, the principal reduction products of 2-ABP were always 6-ANA and 2-aminopyridine. These products are formed according to the two competitive reactions of the aminopyridyl carbanion. In DMF the process leads mainly to the acid, with fairly good chemical and faradaic yields, whereas the yields of 2-aminopyridine are always

low. In this solvent, the electrophilic attack of CO_2 predominates in the carbanion reactions. Instead, in CH$_3$CN the inverse situation prevails; the carbanion is now almost exclusively protonated and the process gives 2-aminopyridine with yields as high as 95% together with very small amounts of 6-ANA. The aminopyridyl carbanion will be protonated by any proton donor present in the reaction medium, presumably the residual water. The observed change of selectivity in favour of the protonation reaction on passage from DMF to CH$_3$CN may be explained by the fact that water is a better proton donor in CH$_3$CN than in DMF [26,27]. It is also possible that CH$_3$CN itself acts as a proton donor since its pK_a is practically the same as that of H_2O in DMSO [28] and presumably this is also the case in CH$_3$CN. Several electrochemical processes in which, besides being the solvent, it plays also the role of proton source have been reported [13,29,30].

4. Conclusions

The electrochemical reduction of 2-amino-5-halopyridines in the presence of CO_2 is an interesting method for the synthesis of 6-aminonicotinic acid. We have shown that in CH$_3$CN and DMF reduction of the halides at the commonly used electrodes such as GC, Hg and Pt requires very negative potentials (< -2.4 V vs. SCE), which are only slightly more positive than that of CO_2. The unavoidable concomitant reduction of CO_2 under the electrosynthesis conditions makes the process at these electrodes less attractive. We found that silver has a remarkable electrocatalytic effect on the reduction of 2-ABP. The E_p of 2-ABP at Ag is 0.71–0.83 V more positive than that of CO_2 at the same electrode, which makes possible the selective reduction and, hence, carboxylation of the compound in CO_2-saturated solvents. The process in both solvents consumes ca. 2 e$^-$/molecule of 2-ABP and gives 6-ANA and 2-aminopyridine as principal reduction products. However, good results in terms of acid yield are obtained only in DMF (48–82%); the process in CH$_3$CN leads mainly to 2-aminopyridine, protonation of the

intermediate carbanion, probably by the residual water or the solvent itself, outrunning the carboxylation reaction.

Acknowledgements

References

[1] W.J. Johnson, J.D. McColl, Science 122 (1955) 834.
[2] J.S. Hothersall, M. Gordge, A.A. Noronha-Dutra, FEBS Lett. 434 (1998) 97.
[3] D.L. Walker, J.M. Reid, P.A. Svingen, R. Rios, J.M. Covey, M.C. Alley, M.G. Hollingshead, I.I. Budihardjo, S. Eckdahl, S.A. Boerner, S.H. Kaufmann, M.M. Ames, Biochem. Pharmacol. 58 (1999) 1057.
[4] I.I. Budihardjo, S.A. Scott, S. Eckdahl, P.A. Svingen, R. Rios, M.M. Ames, S.H. Kaufmann, Mol. Pharmacol. 57 (2000) 529.
[5] R.J. Yu, E.J. Van Scott, US Patent 4258052, 1981.
[6] R.J. Dummel, H.S. Mosher, J. Org. Chem. 24 (1959) 1007.
[7] J.R. Cobb, S.C. Pearcy, R.K. Gholson, J. Bacteriol. 131 (1977) 789.
[8] J. Zanon, A. Klapars, S.L. Buchwald, J. Am. Chem. Soc. 125 (2003) 2890.
[9] J. Chaussard, J.C. Folest, J.Y. Nédélec, J. Périchon, S. Sibille, M. Troupel, Synthesis (1990) 369.
[10] A.A. Isse, A. Gennaro, E. Vianello, J. Chem. Soc., Dalton Trans. (1996) 1613.
[11] A. Gennaro, A.A. Isse, F. Maran, J. Electroanal. Chem. 507 (2001) 124.
[12] A.A. Isse, A. Gennaro, J. Electrochem. Soc. 149 (2002) D113.
[13] A.A. Isse, A. Gennaro, Ind. J. Chem. A 42 (2003) 751.
[14] J.D. Genders, D. Pletcher, Chem. Ind. 682 (1996).
[15] A.A. Isse, M.G. Ferlin, A. Gennaro, J. Electroanal. Chem. 541 (2003) 93.
[16] C.P. Andrieux, C. Blocman, J.-M. Dumas-Bouchiat, J.-M. Savéant, J. Am. Chem. Soc. 101 (1979) 3431.
[17] M.S. Mubarak, D.G. Peters, J. Electroanal. Chem. 425 (1997) 13.
[18] N. Zylber, A. Druilhe, J. Zylber, J. Perichon, New J. Chem. 13 (1989) 535.
[19] R.R. Raju, S.K. Mohan, S.J. Reddy, Tetrahedron Lett. 44 (2003) 4133.
[20] S. Rondinini, P.R. Mussini, F. Crippa, G. Sello, Electrochem. Commun. 2 (2000) 491.
[21] S. Rondinini, P.R. Mussini, M. Specchia, J. Electrochem. Soc. 148 (2001) D102.
[22] S. Rondinini, P.R. Mussini, P. Muttini, G. Sello, Electrochim. Acta 46 (2001) 3245.
[23] A.A. Isse, A. Gennaro, Chem. Commun. (2002) 2798.
[24] J.-M. Savéant, in: P.S. Mariano (Ed.), Advances in Electron Transfer Chemistry, vol. 4, JAI Press, New York, 1994, pp. 53–116.
[25] A. Gennaro, A.A. Isse, E. Vianello, J. Electroanal. Chem. 289 (1990) 203.
[26] J.R. Jezorek, H.B. Mark, J. Phys. Chem. 74 (1970) 1627.
[27] A.J. Fry, Synthetic Organic Electrochemistry, second ed., Wiley, New York, 1989, p. 105.
[28] F.G. Bordwell, Acc. Chem. Res. 21 (1988) 456.
[29] D.A. Koch, B.J. Henne, D.E. Bartak, J. Electrochem. Soc. 134 (1987) 3062.
[30] B. Batanero, C.M. Sánchez-Sánchez, V. Montiel, A. Aldaz, F. Barba, Electrochem. Commun. 5 (2003) 349.