Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2008**, *61*, 526–530 www.publish.csiro.au/journals/ajc

Electrochemical Reduction of Cinnamonitrile in the Presence of Carbon Dioxide: Synthesis of Cyano- and Phenyl-Substituted Propionic Acids

Huan Wang,[A] *Mei-Yu Lin,*[A] *Kai Zhang,*[A] *Su-Jiao Li,*[A] *and Jia-Xing Lu*[A,B]

[A]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry,
East China Normal University, Shanghai 200062, China.
[B]Corresponding author. Email: jxlu@chem.ecnu.edu.cn

Cyano- and phenyl-substituted propionic acids were synthesized simply and efficiently by electrocarboxylation of cinnamonitrile in undivided cells using the non-noble metal nickel as cathode and magnesium as the anode. The radical anion generated by the electroreduction of cinnamonitrile in the absence of CO_2 is involved in several competitive reactions that lead to the formation of linear hydrodimers, cyclic hydrodimers, saturated dihydro products, and glutaronitrile derivatives. While under 101.325 kPa of CO_2, the electrocarboxylation could easily be carried out in the absence of additional catalysts, and with good yield (84.8%). The influence of various synthetic parameters, such as the nature of the electrode, the working potential, the concentration, and the temperature, on the electrocarboxylation reaction was investigated.

Manuscript received: 4 March 2008.
Final version: 16 April 2008.

Introduction

The syntheses of cyano- and phenyl-substituted propionic acids and their esters are of interest owing to their biochemical properties as inhibitors of bovine carboxypeptidase A.[1] They are also key molecules in the synthesis of γ-aminobutyric acid (GABA),[2,3] an important inhibitory neurotransmitter in the central nervous system.[4] The conventional synthesis of cyano- and phenyl-substituted propionic acids and their esters, based on the condensation reaction of ethyl cyanoacetate with aldehydes or ketones combined with the simultaneous reduction of the C=C bond,[5–7] suffers from several drawbacks such as expensive and complicated catalysts, and high pressure of hydrogen.

It is well known, however, that electrocarboxylation is a powerful pathway for the production of carboxylic acids.[8–12] This methodology has been extensively used for obtaining alternative synthetic routes to the manufacture of pharmaceutical industrial products.[13,14] Gennaro[15] and Filardo[16] et al. also have reported the electrocarboxylation of chloroacetonitrile to cyanoacetic acid. To achieve high yield of the electrocarboxylation, sacrificial anodes were normally used.[8–16]

In general, platinum is the most commonly used working electrode in the electrocarboxylation reaction, but it is very expensive for industrial production. Thus we are interested in using a non-noble metal or other cheap material as a cathode. Recently, we reported the electrochemical carboxylation of activated olefins in ionic liquid,[17] cinnamate esters,[18] and styrene[19] in MeCN, using titanium, nickel, etc., as a cathode electrode. As one of our continuing studies on electrochemical carboxylation, we succeeded in an efficient electrochemical fixation of CO_2 molecules to cinnamonitrile to give cyano- and phenyl-substituted propionic acids in moderate to high yield with a Ni electrode. In the present paper, electroreduction of cinnamonitrile was studied by cyclic voltammetry and controlled-potential electrolysis first. Then electrocarboxylation was carried out in an undivided cell and synthesis conditions were optimized.

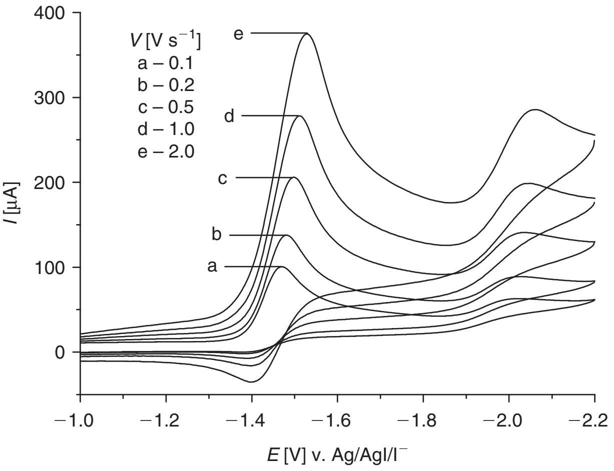


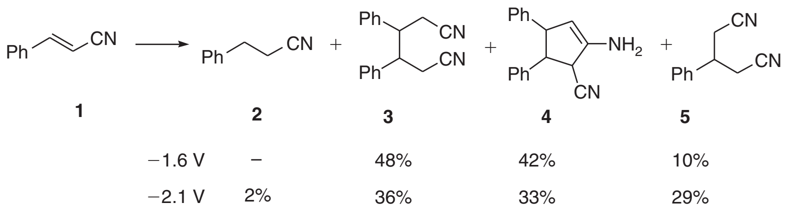
Fig. 1. Cyclic voltammograms obtained at a glass carbon electrode in MeCN–0.1 M Et_4NBF_4 for 5 mM cinnamonitrile with scan rates of 0.1–2.0 V s^{-1}.

Results and Discussion

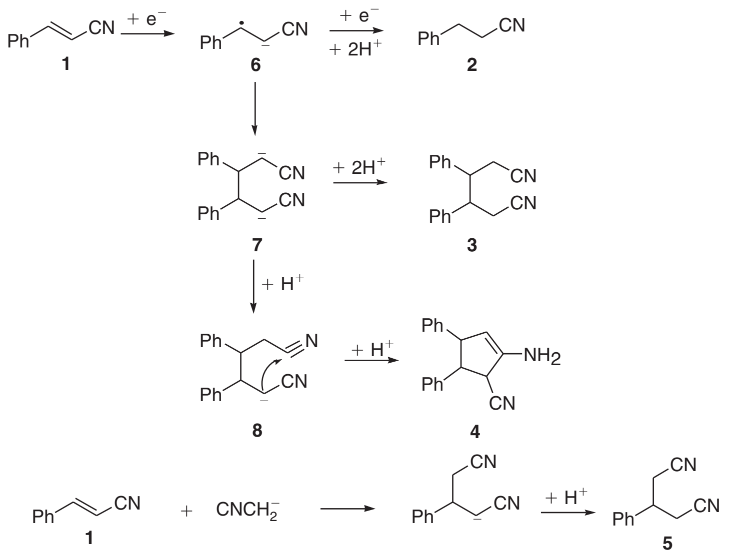
Electrochemical Reduction of Cinnamonitrile

The cyclic voltammetric behaviour for reduction of cinnamonitrile at a glass carbon (GC) electrode in MeCN is shown in Fig. 1. A one-electron reduction peak at −1.46 V (v. Ag/AgI/I^-) and a second chemically irreversible reduction at −2.0 V

10.1071/CH08092 0004-9425/08/070526



Scheme 1.



Scheme 2.

(v. Ag/AgI/I$^-$) are observed at a scan rate of 0.1 V s^{-1}. When the scan rate is increased, the first peak becomes partially reversible, whereas the second remains irreversible (Fig. 1). This behaviour is indicative of a chemical reaction following the first electron transfer reaction.

To understand the process, preparative-scale electrolysis of cinnamonitrile in MeCN was carried out at the two reduction peaks, respectively (Scheme 1). The electroreduction at −1.6 V (v. Ag/AgI/I$^-$) resulted in two forms of hydrodimer, the linear hydrodimer **3** (48%), and a cyclic hydrodimer **4** (42%), with a small amount of glutaronitrile derivative **5** (10%). At −2.1 V (v. Ag/AgI/I$^-$), the saturated dihydro product **2** (2%) was formed by the electroreduction (together with 36% of **3**, 33% of **4**, and 29% of **5**). This indicates that the electron transfer numbers for these two reductions are both one.

According to the literature,[20–23] the experimental results are consistent with the reaction mechanism depicted in Scheme 2. Electroreduction of cinnamonitrile gives rise to the corresponding radical anion **6**. After another one-electron reduction of **6** and further protonation, the saturated dihydro product **2** is obtained. Meanwhile, alkene radical anion **6** could also go through a dimerization process, with the formation of the dimerized dianion **7**, which could be involved in two kinds of protonation processes. In the first route, **7** gets two protons to produce the linear hydrodimer **3**. The other involves a Dieckmann condensation process of anion intermediate **8**, protonated from dimerized dianion **7**, to cyclic hydrodimer **4**. However, because the acidity of MeCN, the conjugate base of MeCN, CNCH$_2^-$, can react with the unreacted substrate by Michael addition, followed by proton transfer from another solvent molecule, to produce the glutaronitrile derivative **5** via canomethylation.

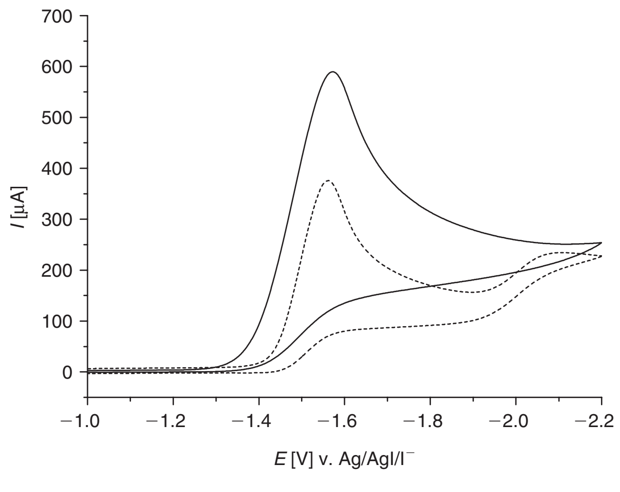
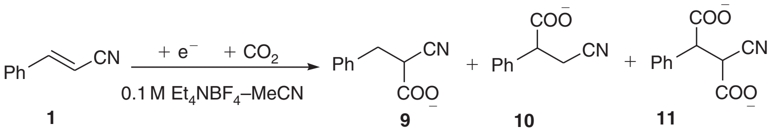


Fig. 2. Cyclic voltammograms obtained at a glass carbon electrode in MeCN–0.1 M Et_4NBF_4 for 25 mM cinnamonitrile with scan rates of 0.1 V s^{-1} in the absence (- - -) and presence (—) of saturated CO_2.

Electrochemical Carboxylation of Cinnamonitrile

When the cyclic voltammograms were obtained in MeCN saturated with CO_2, different behaviours were observed (Fig. 2).



Scheme 3.

Table 1. Electrocarboxylation of cinnamonitrile under various conditions

Solution of cinnamonitrile in MeCN–Et_4NBF_4, undivided cell, CO_2 atmosphere, 2 F mol^{-1} of cinnamonitrile

Entry	Electrodes	E [V]	Concentration [mM]	T [K]	Yield [%][A]	Ratio **9**:**10**:**11**
1	Stainless steel–Mg	−1.70	100	298	67.1	71:13:14
2	Cu–Mg	−1.70	100	298	62.4	35:18:48
3	C–Mg	−1.70	100	298	35.4	79:21:00
4	Ti–Mg	−1.70	100	298	47.8	65:6:29
5	Ni–Mg	−1.70	100	298	71.7	81:1:18
6	Ni–Zn	−1.70	100	298	50.7	54:17:29
7	Ni–Mg	−1.60	100	298	64.8	79:14:7
8	Ni–Mg	−1.65	100	298	68.5	80:11:9
9	Ni–Mg	−1.75	100	298	72.6	74:6:20
10	Ni–Mg	−1.80	100	298	72.5	60:12:28
11	Ni–Mg	−1.85	100	298	72.1	62:7:31
12	Ni–Mg	−1.90	100	298	72.8	59:13:28
13	Ni–Mg	−1.75	50	298	72.3	71:8:21
14	Ni–Mg	−1.75	75	298	71.7	67:26:7
15	Ni–Mg	−1.75	125	298	72.1	82:14:4
16	Ni–Mg	−1.75	150	298	72.4	77:16:7
17	Ni–Mg	−1.75	175	298	73.1	58:23:19
18	Ni–Mg	−1.75	200	298	72.0	57:12:31
19	Ni–Mg	−1.75	250	298	56.7	50:25:25
20	Ni–Mg	−1.75	300	298	47.9	48:19:33
21	Ni–Mg	−1.75	100	288	75.2	56:10:34
22	Ni–Mg	−1.75	100	278	80.3	42:8:50
23	Ni–Mg	−1.75	100	273	84.8	38:8:54

[A] Gas chromatography yield.

The firstreduction peak current increased, whereas the second peak disappeared. Hence, carboxylation between the electrogenerated intermediate and CO_2 is presumably more rapid than dimerization of the radical anion.

To support this assumption, the controlled-potential electroreduction of cinnamonitrile in MeCN saturated with CO_2 was carried out using a stainless steel plate as the cathode and an Mg rod as the anode. 2-Cyano-3-phenylpropionic acid **9** was obtained as the principal product, accompanied by 3-cyano-2-phenylpropionic acid **10** and 2-cyano-3-phenylsuccinic acid **11** (Scheme 3).

With the aim of optimizing the yields, we focussed our attention on the influence of various synthetic parameters on the process, such as the nature of the electrode, the electrolysis potential, the concentration and the temperature. The results of the electrolyses are reported in Table 1.

Influence of the Nature of the Electrode

The reaction yield and selectivity were shown to be dependent on the reaction conditions, particularly on the nature of the electrodes. Therefore, we first investigated the effect of different electrode materials on the electrocarboxylation of cinnamonitrile keeping other reaction conditions the same. Table 1 (entries 1–5) presents the results obtained with the use of different materials (stainless steel, Cu, C, Ti, Ni) as the cathode and the same Mg anode. The yield of carboxylic acids decreased depending on the cathode materials employed in the following order: Ni (71.7%) > stainless steel (67.1%) > Cu (62.4%) > Ti (47.8%) > C (35.4%). As nickel complexes can catalyze electrochemical incorporation of CO_2 into alkenes, the excellent result from the nickel cathode may be associated with its catalytic activation for substrates. This will be pursued in more detail in the future.

In addition, the nature of the anodic material strongly determined the yield or reactivity of this electrocarboxylation reaction. The replacement of the Mg by a Zn anode (with a Ni cathode, entry 6) made the global carboxylation yield drop from 71.7 to 50.7%. This is attributed to the different reducibility of the metal cation generated at the anode. The reduction formal potential of Zn^{2+} ($E^o_{Zn^{2+}/0} = -0.7626$ V v. normal hydrogen electrode (NHE)) is much more positive than Mg^{2+} ($E^o_{Mg^{2+}/0} = -2.356$ V v. NHE).[24] It indicates that Zn^{2+} is reduced more easily on the cathode, which will compete with the electrocarboxylation reaction, causing the decrease of the electrocarboxylation yield. Actually, Zn particles were found on the cathode surface after electrolysis.

According to the above experimental results, the most effective electrode couple is Ni as cathode and Mg as anode. Hence, this electrode couple was applied in the following investigations.

Influence of the Electrolysis Potential

Electrocarboxylation of cinnamonitrile under various electrolysis potentials was examined. As shown in Table 1 (entries 5 and 7–9), the carboxylation yield increased from 64.8 to 72.6% when the electrolysis potential changed from -1.60 to -1.75 V, indicating that a more negative potential favours electrocarboxylation of cinnamonitrile in this region. However, the sensitivity of global yield becomes negligible at potentials more negative than -1.80 V (Table 1, entries 10–12). Considering minimizing energy costs for this electrocarboxylation in practical applications, -1.75 V is the best working potential for further investigation.

Influence of Concentration

Electrocarboxylation of cinnamonitrile with different initial concentrations was performed to investigate the influence of concentration. As shown in Table 1 (entries 9 and 13–18), the global electrocarboxylation yield was almost the same with low initial amounts of substrate (50–200 mM). When the electrolysis was carried out in a more concentrated solution (more than 200 mM of cinnamonitrile), the carboxylation yield decreased dramatically with increasing the concentration (Table 1, entries 19–20). According to our experimental results, the concentration of cinnamonitrile that favoured the electrocarboxylation in good yield is within the range 50–200 mM.

Influence of Temperature

It is well known that CO_2 solubility depends on temperature, which is larger at lower temperatures.[25] The solubility may also affect the electrocarboxylation reaction. So to investigate the effect of temperature on the electrocarboxylation of cinnamonitrile, a set of electrolyses was performed at different temperatures. A strong increase in the global yield was observed at lower temperatures (Table 1, entries 9 and 21–23), in agreement with the CO_2 solubility.

Conclusions

The electroreduction of cinnamonitrile was carried out in MeCN, giving a linear hydrodimer and cyclic hydrodimer as the major products, with small amount of glutaronitrile derivative and saturated dihydro product. The reaction mechanism has also been proposed.

Cyano- and phenyl-substituted propionic acids and their esters (valuable inhibitors of bovine carboxypeptidase A) have been obtained, under mild conditions, in good to high yields by electrochemical reduction (under a CO_2 atmosphere) of cinnamonitrile. The influence of the electrolysis conditions on the yields has been studied. Lower temperature, lower substrate concentrations, and a suitable potential were effective in increasing dramatically the global yields (84.8%).

Experimental

General

^{1}H NMR spectra were recorded on an AVANCE 500 (500 MHz, Bruker, Germany) spectrometer in $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were obtained on a 5973N spectrometer connected with an HP 6890 gas chromatograph (Agilent, USA). Electrochemical measurements were carried out using a CHI 650 instrument (CHI 650 Instruments, USA). Acetonitrile (MeCN) and dimethylformamide (DMF) were kept over 4-Å molecular sieves. Tetraethylammonium tetrafluoroborate (Et_4NBF_4) was prepared according to the literature.[26] Other reagents were used as received.

Electroanalytical Experiments

The electroanalytical experiment was carried out in a dry MeCN solution containing Et_4NBF_4 as a supporting electrolyte in a one-compartment electrochemical cell equipped with a gas inlet, a glassy carbon electrode as the working electrode, a platinum spiral as the counter-electrode and an Ag|AgI|0.1 M *n*-Bu_4NI in DMF as the reference electrode. Potential scan was performed by a CHI 650 instrument.

Electrochemical Reduction of Cinnamonitrile

The controlled-potential electroreduction was carried out in a mixture of cinnamonitrile (0.1 M) and Et_4NBF_4 (0.1 M) in 10 mL dry MeCN under a slow stream of N_2 in a one-compartment electrochemical cell equipped with a Mg sacrificial anode and a stainless steel cathode (8 cm^2) at 298 K, until 2 F mol^{-1} of charge was passed. The identification and quantification of the products was done by gas chromatography–mass spectrometry (GC–MS).

Electrochemical Carboxylation of Cinnamonitrile (Typical Procedure)

Cinnamonitrile (0.1 M) was electroreduced as described above under a slow stream of CO_2.

The reaction mixture was distilled under reduced pressure. The residue was esterified in 10 mL DMF by adding anhydrous K_2CO_3 (1 mmol) and MeI (3 mmol) and stirring the mixture at 323 K for 5 h. The solution was hydrolyzed and extracted with Et_2O, and the organic layers were washed with H_2O, dried over $MgSO_4$, and evaporated. The methyl esters were isolated by column chromatography with petroleum spirit/ethyl acetate as eluent. After isolation and identification of the products, working curves were used with biphenyl as internal standard for analysis of the electrochemical carboxylation.

In some reactions, nickel (Ni), copper (Cu), titanium (Ti), and graphite (C) were also used as cathode, and zinc (Zn) was used as anode.

Acknowledgements

The present work was supported by the National Natural Science Foundation of China (no. 20573037), the Natural Science Foundation of Shanghai (no. 05JC1470), a Shanghai Leading Academic Discipline Project (B409), and PhD Program Scholarship Fund of ECNU 2007.

References

[1] L. D. Byers, R. Wolfenden, *Biochemistry* **1973**, *12*, 2070. doi:10.1021/BI00735A008

[2] M. Calmes, F. Escale, J. Martinez, *Tetrahedron Asymmetry* **2002**, *13*, 293. doi:10.1016/S0957-4166(02)00075-7

[3] P. Camps, D. Munoz-Torrero, L. Sanchez, *Tetrahedron Asymmetry* **2004**, *15*, 311. doi:10.1016/J.TETASY.2003.10.035

[4] P. Krogsgaard-Larsen, *Compr. Med. Chem.* **1990**, *3*, 493.

[5] K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett.* **2005**, *46*, 5507. doi:10.1016/J.TETLET.2005.06.053

[6] M. Baidossi, A. V. Joshi, S. Mukhopadhyay, Y. Sasson, *Tetrahedron Lett.* **2005**, *46*, 1885. doi:10.1016/J.TETLET.2005.01.092

[7] F. Goettmann, D. Grosso, F. Mercier, F. Mathey, C. Sanchez, *Chem. Commun.* **2004**, 1240. doi:10.1039/B403491K

[8] M. Tokuda, A. Yoshikawa, H. Suginome, H. Senboku, *Synthesis* **1997**, 1143. doi:10.1055/S-1997-1327

[9] H. Senboku, H. Komatsu, Y. Fujimura, M. Tokuda, *Synlett* **2001**, 418.

[10] F. Koster, E. Dinjus, E. Dunach, *Eur. J. Org. Chem.* **2001**, 2507. doi:10.1002/1099-0690(200107)2001:13<2507::AID-EJOC2507>3.0.CO;2-P

[11] H. Senboku, H. Kanaya, M. Tokuda, *Synlett* **2002**, 140. doi:10.1055/S-2002-19350

[12] O. Scialdone, M. A. Sabatino, C. Belfiore, A. Galia, M. P. Paternostro, G. Filardo, *Electrochim. Acta* **2006**, *51*, 3500. doi:10.1016/J.ELECTACTA.2005.09.044

[13] J. Damodar, S. R. K. Moha, S. R. J. Reddy, *Electrochem. Commun.* **2001**, *3*, 762. doi:10.1016/S1388-2481(01)00263-6

[14] A. K. Datta, P. A. Marron, C. J. H. King, J. H. Wagenknecht, *J. Appl. Electrochem.* **1998**, *28*, 569. doi:10.1023/A:1003289800341

[15] A. A. Isse, A. Gennaro, *J. Electrochem. Soc.* **2002**, *149*, D113. doi:10.1149/1.1490358

[16] O. Scialdone, A. Galia, C. Belfiore, G. Filardo, G. Silvestri, *Ind. Eng. Chem. Res.* **2004**, *43*, 5006. doi:10.1021/IE034275+

[17] H. Wang, G.-R. Zhang, Y.-Z. Liu, Y.-W. Luo, J.-X. Lu, *Electrochem. Commun.* **2007**, *9*, 2235. doi:10.1016/J.ELECOM.2007.06.031

[18] H. Wang, K. Zhang, Y.-Z. Liu, M.-Y. Lin, J.-X. Lu, *Tetrahedron* **2008**, *64*, 314. doi:10.1016/J.TET.2007.10.104

[19] H. Wang, M.-Y. Lin, F.-J. Fang, T.-T. Chen, J.-X. Lu, *Chin. J. Chem.* **2007**, *25*, 913. doi:10.1002/CJOC.200790177

[20] J. H. P. Utley, M. Gullu, M. Motevalli, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1961. doi:10.1039/P19950001961

[21] I. Fussing, M. Gullu, O. Hammerich, A. Hussain, M. F. Nielsen, J. H. P. Utley, *J. Chem. Soc., Perkin Trans. 2* **1996**, 649. doi:10.1039/P29960000649

[22] I. Fussing, O. Hammerich, A. Hussain, M. Nielsen, J. H. P. Utley, *Acta Chem. Scand.* **1998**, *52*, 328.

[23] N. Kise, S. Iitaka, K. Iwasaki, N. Ueda, *J. Org. Chem.* **2002**, *67*, 8305. doi:10.1021/JO026183K

[24] A. J. Bard, L. R. Faulkner, *Electrochemical Methods: Fundamentals and Applications, 2nd edn* **2001** (John Wiley & Sons: New York, NY).

[25] A. Gennaro, A. A. Isse, E. Vianello, *J. Electroanal. Chem.* **1990**, *289*, 203. doi:10.1016/0022-0728(90)87217-8

[26] D. T. Sawyer, J. L. Robert, Jr, *Experimental Electrochemistry for Chemists* **1974** (Wiley-Interscience, New York, NY).