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Study on Electrocarboxylation of [(4-Methoxy-Benzylidene)-Amino] - Acetic Acid Ester

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In an undivided cell, the electrocarboxylation of [(4-methoxy-benzylidene)-amino] - acetic acid ester bearing an aliphatic substituent on the amine fragment was first investigated in the DMF solution under the atmospheric pressure of carbon dioxide using magnesium rod as the sacrificial anode. As a result, C-carboxylated, N-carboxylated and C,N-dicarboxylated products were isolated as their methyl esters whose yields were influenced by various reaction conditions including the supporting electrolyte, cathode material, current density, charge passed and temperature. Using glassy carbon as the working electrode, the electrochemical behavior of the aryl alkyl substrate was studied by cyclic voltammetry. Based on the character in the absence and presence of carbon dioxide, the possible electrocarboxylation mechanism was postulated accordingly.

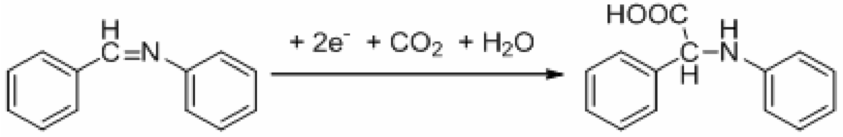
Keywords: Carbon dioxide; electrocarboxylation; aryl alkyl imine; cyclic voltammetry

1. INTRODUCTION

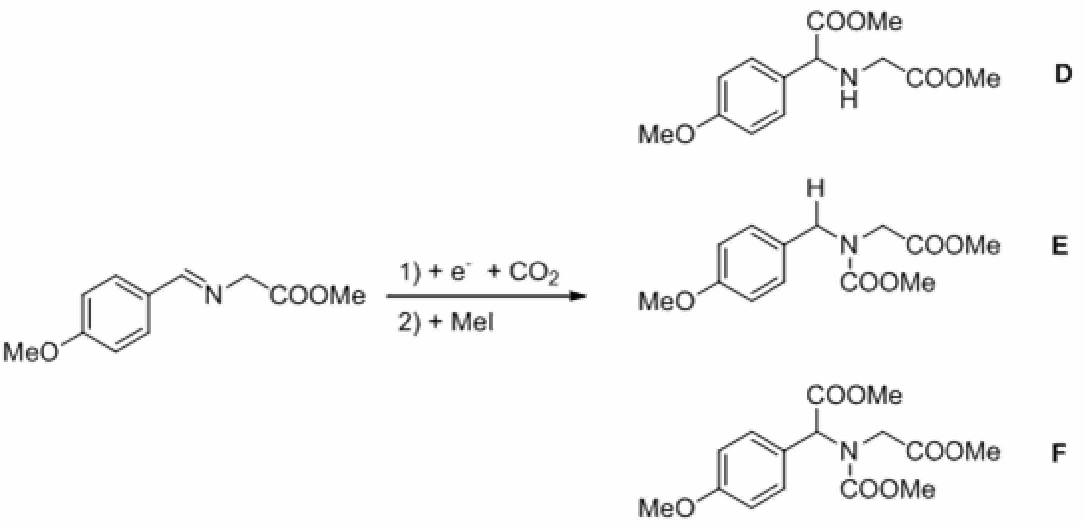
Electrocarboxylation is one of the most practical routes for the introduction of carbon dioxide, which is the largest contributor to the green house effect and also to the corrosion of carbon steel pipelines in the petroleum production [1], into a variety of organic starting materials such as benzyl or aliphatic halides [2-4], vinyl triflates [5], carbonyl compounds [6-8], alkenes [9], alkynes [10-11] etc., because it is a clean and environmentally benign process. It takes place efficiently even in an atmospheric pressure of CO_2 under neutral and mild conditions and opens up broad possibilities for preparation of various mono or polycarboxylic acids. Among these reactions, the electrochemically activated insertion of CO2 to the unsaturated carbon-nitrogen double bond is of considerate interest, as important intermediates for pharmaceutical synthesis, like N-substituted α-amino acids, can be achieved (Eq 1).

$$R_1R_2C{=}NR_3+CO_2 \rightarrow R_1R_2COOHNHR_3 \qquad \text{Eq 1}$$

This kind of reaction, according the stoicheiometry in Scheme 1 was reported for the first time by Giuseppe Silvestri *et al* [12]. The electrochemical reductive carboxylation of benzalaniline was performed in an organic low-melting salt (tetraethylammonium p-toluenesulfanate) to obtain N-phenylphenylglycine in a yield of 60 %. A more detailed investigation on the electrocarboxylation of a series of benaylamines bearing substituents on the aromatic moiety or on the benzyl carbon atom was later reported by U. Hess and coworkers [13-14]. Taking the electronegativity resemblance between carbon and nitrogen into consideration, the synchronous reactions of carboxylation at the nitrogen atom, dicarboxylation, hydrogenation and dimerization could also be expected besides the carboxylated product of N-substituted α-amino acid at the carbon atom. We are concerned about the electrocaboxylation law for the imine with the aliphatic group localized on the either side of the unsaturated C=N since the substituent effect may play an influential role. However, no examples of such electroreductive coupling with CO_2 have yet been reported to the best of our knowledge. Herein, we wish to present our original studies on the electrocarboxylation of aryl alkyl imine of [(4-methoxy-benzylidene)-amino] - acetic acid ester in the presence of CO_2. The radical anion generated by the electroreduction of the substrate is involved in several competitive reactions to lead to the formation of C-carboxylated (**D**), N-carboxylated (**E**) and C, N-carboxylated products (**F**) eventually (Scheme 2).



Scheme 1.

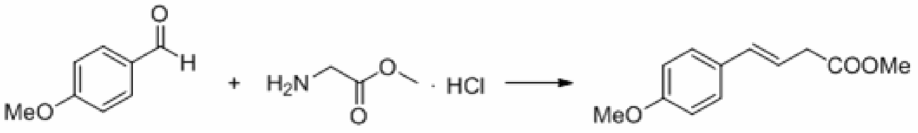


Scheme 2.

2. EXPERIMENTAL

2.1. Synthesis of the substrate of [(4-methoxy-benzylidene)-amino] - acetic acid ester

The substrate was synthesized as previously described [15-16]. A suspension of methyl alaninate hydrochloride (1.5 equiv), $MgSO_4$ (1.5 equiv) and triethylamine (1.5 equiv) in dry CH_2Cl_2 was stirred at room temperature for 5 h under a nitrogen atmosphere. Then *p*-methoxybenzaldehyde (1.0 equiv) was added and the flask was heated to 30 °C. Conversion was followed by TLC and the mixture was filtered off immediately upon completion. The filtrate was transferred to a separatory funnel where the organic layer was washed twice with saturated sodium carbonate. The aqueous phase was extracted once with a small volume of CH_2Cl_2 and the combined organic portions dried ($MgSO_4$), filtered and concentrated to afford the aryl alkyl imine **A** which was further purified by twice recrystallization from CH_2Cl_2/ethyl acetate (yellow solid, 72 %).



Eq 2

2.2. Cyclic voltammetry and general electrosynthesis

Cyclic voltammetric measurements were carried out with a CHI650C electrochemical station at potential sweep rates in the range of 0.05-0.5 V s^{-1} at room temperature in a solution of dimethylformamide (DMF, kept over 4Å molecular sieves) containing 0.1 M of $TEABF_4$ (prepared according to literature [17]) in a three-electrode cell with a glassy-carbon disk (r = 1.5 mm) as working electrode, a spiral platinum wire as auxiliary electrode, and Ag/AgI/0.1 M n-Bu_4NI in DMF reference electrode.

Controlled-current electrolysis using a dc regulated power supply HY 3002D was performed mainly in a mixture of [(4-methoxy-benzylidene)-amino] - acetic acid ester (0.1 M) and TEABr (0.1 M) in 20 mL dry DMF under a slow stream of CO_2 in a one compartment electrochemical cell equipped with a metallic ring cathode and a sacrificial magnesium anode until 2 F mol^{-1} of charge was passed. Before each experiment, all the electrodes were carefully cleaned and activated. The Mg anode was treated with a 20 % (w/w) aqueous HCl, then rinsed with distilled water and acetone and finally dried with a stream of warm air. The cathode of stainless steel (Ss), for example, was mechanically polished with sand paper followed by washed with distilled water and acetone. The electrolyte solution was stirred by a teflon-coated stirred bar and by the continuous bubbling of CO_2. After the electrolysis, the reaction mixture was esterified directly in DMF by adding K_2CO_3 (0.1 M) and CH_3I (0.3 M) and stirring the mixture at 60 °C for 5 h. To isolate and quantitatively determine the product as its corresponding methyl ester DMF was distilled in vacuo, the residue was hydrolyzed with and extracted three times with CH_2Cl_2. The organic extracts were collected, dried with $MgSO_4$ and then concentrated. For final purification, products were isolated by column chromatography with petroleum ether/ethyl acetate mixtures as eluent.

After identification by ^{1}H NMR spectra (recorded on an AVANCE 500 (500 MHz) spectrometer in $CDCl_3$) and mass spectra (obtained on a 5973 N spectrometer connected with an HP 6890 gas chromatograph), working curves were applied with n-decane/1,4-dioxane as an internal standard for determination of the GC yields for each electrolysis product.

(Methoxycarbonylmethyl-amino)-(4-methoxy-phenyl)-acetic acid methyl ester (D): GC-MS (m/z, %): 266(M^+, 0.2), 250(100), 219(14), 191(97), 161(9), 148(10), 132(33), 117(16.4), 89(23), 75(12), 59(14); ^{1}H NMR ($CDCl_3$): δ 3.63(3H, s), 3.81(3H, s), 3.83(3H, s), 3.90(1H, s), 3.97(1H, s), 6.90(2H, d, *J*=9 Hz), 6.95(1H, s), 7.21(2H, d, *J*=9 Hz).

[(4-Methoxy-benzyl)-methoxycarbonyl-amino]-acetic acid methyl ester (E): GC-MS(m/z, %): 266(M^+, 0.1), 250(84), 222(54), 191(100), 161(11), 148(13), 132(49), 117(23), 89(41), 75(19), 59(23); ^{1}H NMR ($CDCl_3$): δ 3.40(3H, s), 3.61(3H, s), 3.70(3H, s), 3.72(2H, s), 3.75(1H, s), 3.88(1H, s), 6.75(2H, d, *J* = 9 Hz), 7.24(2H, d, *J* = 9 Hz).

(Methoxycarbonyl-methoxycarbonylmethyl-amino)-(4-methoxy-phenyl)-acetic acid methyl ester (Mixture of two isomers) (F): GC-MS(m/z, %): 326(M^+, 2), 299(100), 240(3), 225(3), 179(100), 165(4), 151(30), 135(5), 108(1); ^{1}H NMR ($CDCl_3$): δ 3.68(6H, s), 3.71(6H, s), 4.16(2H, s), 6.23(1H, s), 6.68(2H, d, *J* = 9 Hz), 6.94(2H, d, *J* = 9 Hz).

3. RESULTS AND DISSCUSION

3.1. Electrocarboxylation of [(4-methoxy-benzylidene)-amino] - acetic acid ester

At first, the galvanostatic electrolysis was carried out at a constant current of 2.95 mA cm^{-2} in 0.1 M TBAI supporting MeCN solution containing 0.1 M [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester and saturated with atmospheric pressure of carbon dioxide at 0 ^{o}C in an undivided cell equipped with magnesium sacrificial anode and copper (Cu) cathode.

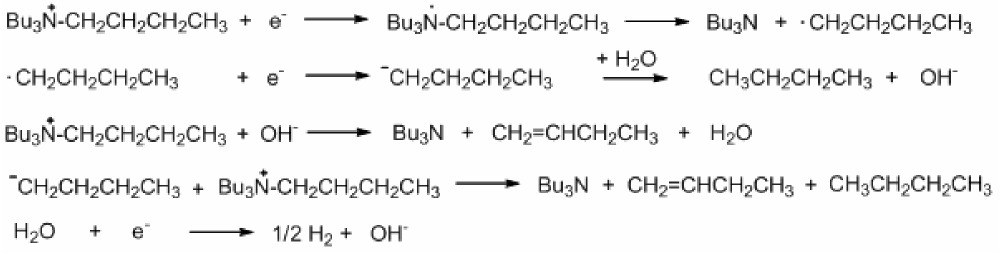
After 2.0 F mol^{-1} charge was passed, 17 % carboxylation yield with a distribution ratio of 5.7:9.4:1.6 was received (Table 1, Entry 1). Through this electrolysis, the imine substrate partially aroused hydrolyzation owing to its not enough stability to result *p*-methoxybenzaldehyde **A**. Actually, partial electrocarboxylation and hydrogenation corresponding to **A** could always be found and the availability of **B** and **C** could be reasonably forecast in the gas chromatography. When the solvent was changed to DMF, the total carboxylated yield was increased to 20 % (Entry 2). So DMF was used as the solvent for the following studies.

Table 1. Effect of various conditions on electrocarboxylation of [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester [a]

Entry	Supporting Electrolyte	Cathode	J / mA cm^{-2}	Q / F mol^{-1}	Yield [b] / %	Ratio D:E:F
1 [c]	TBAI	Cu	2.95	2.0	17	5.7 :9.4: 1.6
2	TBAI	Cu	2.95	2.0	20	7.4 :8.8: 4.1
3	TBAI	Ti	2.95	2.0	16	4.2 :8.6: 3.0
4	TBAI	Ss	2.95	2.0	20	7.9 :9.6: 2.1
5	TEABF$_4$	Ss	2.95	2.0	18	7.0 :5.1: 5.7
6	TEAI	Ss	2.95	2.0	24	7.8 :9.4: 7.0
7	TEABr	Ss	2.95	2.0	32	8.5:2.9:20.3
8	TEABr	Ss	2.05	2.0	29	6.3:3.2:19.2
9	TEABr	Ss	2.50	2.0	30	8.3:3.6:18.1
10	TEABr	Ss	3.40	2.0	25	8.8:4.4:11.5
11	TEABr	Ss	3.84	2.0	21	5.3 :2.9:12.3
12	TEABr	Ss	2.95	3.0	34	14.1:5.7:13.8
13	TEABr	Ss	5.00	3.0	30	12.4:5.7:12.0
14 [d]	TEABr	Ss	2.95	2.0	35	8.6 :3.5:22.4

a : Anode: sacrificial magnesium rod; Temperature: 0°C; Substrate concentration: 0.1 mol L^{-1}; P_{CO2} = 1atm. b: Yields were calculated based on the consumed material. c: The solvent was replaced by MeCN. d: This electrolysis was conducted at lower temperature of -10°C.

For the sake of further optimization, the influence of cathode material, supporting electrolyte, current density, amount of electricity and temperature on the electrocarboxylation was then investigated. Using TBAI supported system, the carboxylation yields obtained on copper and stainless steel cathodes were appreciably superior to the one on titanium (Ti) with the N-carboxylation proportion all higher than C-carboxylation and C, N-dicarboxylation (Table 1, Entries 2-4). One reason for the unconspicuous difference in yield on varied cathodes could be the singularities of the imine's adsorption on them which affects subsequent electrochemical and chemical processes [18]. Considering the economic advantage, the stainless steel was preferred to be chosen. One point to be noted is that electroreduction of tetrabutylammonium cations could be observed (Scheme 3) [19-20]. Overmuch tri-n-butylamine engendered almost depressed the veracity of the aimed products in gas chromatograms and consequentially reduce the current efficiency.



Scheme 3.

Hence several quaternary ammonium salts involving TEA$^+$ were then investigated and common inorganic salts were ignored since alkali metal cations involved salts may imply an unfavorable influence on electrocarboxylation [21-22]. Among chosen electrolytes, TEABr was found to be most efficient to afford a carboxylated yield of 32 % and lead to a significant ratio enhancement for the C, N-dicarboxylation (Entry 7). Whereas, both the yield values showed some decline when $TEABF_4$ and TEAI were applied (Entries 5-6). It became to be understood that the employing of TBAI could not facilitate the electrochemical carboxylation of imine as expected [23-24] in contrast with those involving TEA^+ cations.

The current density remarkably determined the reactivity in CO_2 activation and fixation under otherwise identical conditions. As it follows from Fig.1 and Entries 3, 8-11 in Table 1, besides the N-carboxylation yield varying around 3~4 %, C-carboxylated, C, N-dicarboxylated yields as well as the total value all exhibited an increase-before-decrease trend. In specific, 3.40 mA cm^{-2} gave the best yield of C-carboxylated N-substituted α-amino acid ester while the highest C,N-dicarboxylated and total yields were both obtained at 2.95 mA cm^{-2}. The larger the current density was, the more negative the electrode potential would be. Thus some undesirable reactions could occur on the electrode surface like the reduction of CO_2 or dissolved Mg^{2+}, which would decrease the carboxylation yield. On the other side, the lower the current density was, the more positive the electrode potential would be. So the share of the Faradaic current would be declined, which decreased the carboxylation yield too [25].

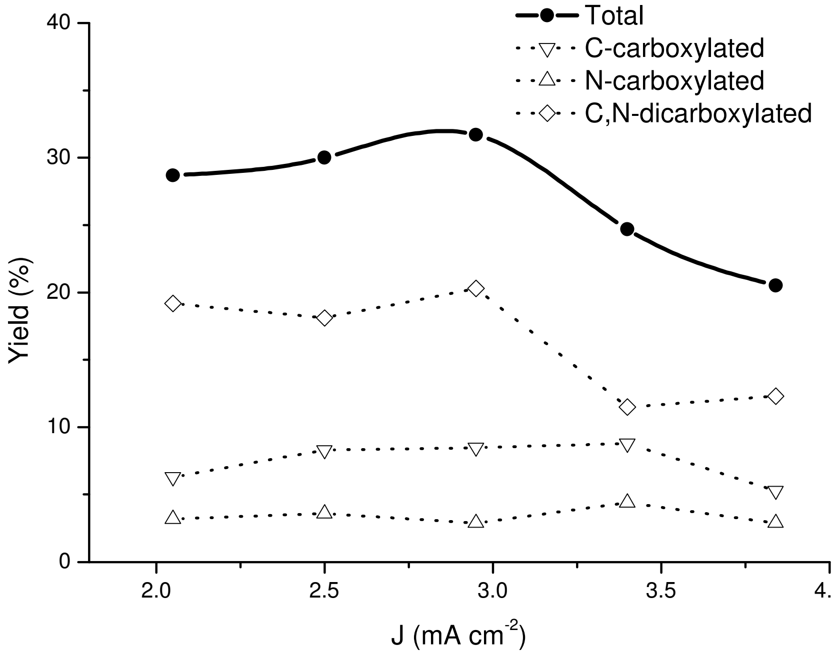


Figure 1. Influence of the current density on the carboxylation yields

Due to the presence of non-Faradaic current, the Faradaic efficiency can not achieve 100 %. Hence, more over the theoretical charge of 2.0 F mol^{-1} was passed to improve the yield. As presented in Table 1, the carboxylated yield increased to 34 % after 3.0 F mol^{-1} charge passed. A similar accretion could also be indicated when the electrolysis was conducted under an even higher current density of 5.0 mA cm^{-2} (Entries 12-13). Quite interestingly, C-carboxylation and N-carboxylation went more effective when the charge passed evidently increased. This fact could be reasonably explained that the electron cloud of the imine radical anion was strengthened via obtaining a further electron to make its nucleophilitic attack towards carbon dioxide more powerfully and easily. Hence, increased the charge to 3.0 F mol^{-1} endued the carboxylation either at carbon or nitrogen atom more abundant time to realize the first electron uptake followed by coupling with one molecule of CO_2 and then improve the corresponding carboxylated yields.

The next experiment was performed at -10 °C under the optimal galvanostatic control, an enhanced yield of 35 % was reached due to the better solubility of CO_2 in DMF at lower temperature (Entry 14) [26].

3.2. Cyclic voltammetry of [(4-methoxy-benzylidene)-amino] - acetic acid ester

The cyclic voltammetric path of [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester tested in the absence of carbon dioxide present two successive and irreversible cathodic peaks (Fig. 2, curve a).

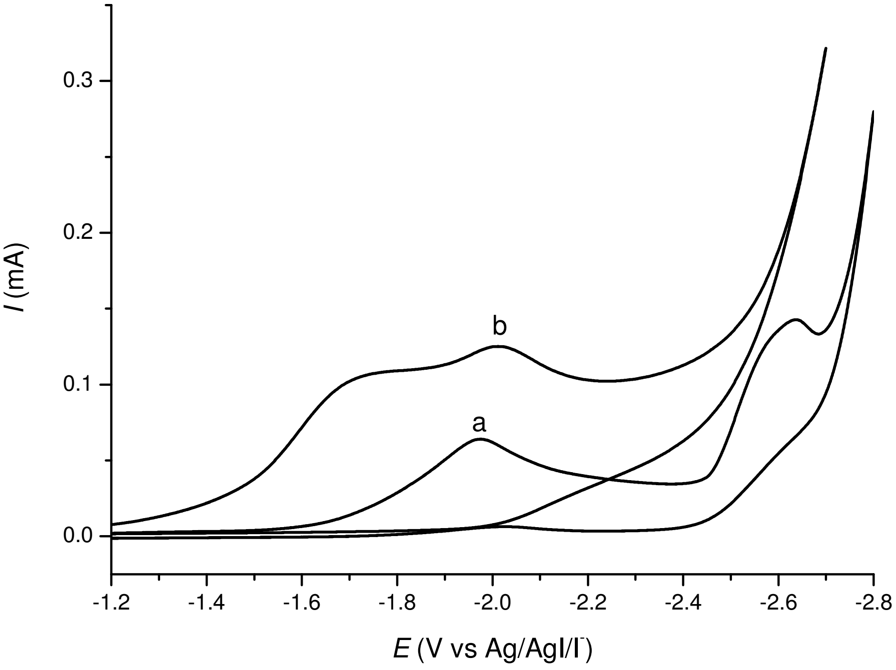


Figure 2 Cyclic voltammetry of [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester in DMF-0.1 mol $L^{-1}$$TEABF_4$ solution on the GC electrode. (a): with 5.7 mmol L^{-1} substrate in the presence of N_2; (b): in the presence of saturated CO_2. Scan rate: 0.1V s^{-1}.

It can be inferred that [18, 27] the first stage of the electrochemical activation of the unsaturated imine is one-electron reduction to the corresponding radical-anion and the second cathodic peak results from subsequent reduction of the radical-anion with the formation of the dianion of the imine. By increasing the sweep rate from 0.05 to 0.5 V s^{-1}, both reduction peaks shifted to more negative place, and their peak currents increased concomitantly (Fig. 3). Plotting the peak current as a function of square root of scan rates equally gave rise to ideal linear behavior, which reveals the reduction processes were both diffusion controlled [28].

Addition of saturated CO_2 to the solution depicted by curve b in Fig.2 results a modified cyclic voltammogram. The new cyclic voltammogram exhibits an increase of the current value of first reduction peak, which is 1.68 times that of the initial value, and an obvious positive shift of its potential by 220 mV at the scan rate of 0.1 V s^{-1}. Moreover, the second reduction peak disappears and another new one can be observed at -2.01 V. This indicates a fast reaction between the radical anion of the substrate and carbon dioxide to form a coupled intermediate which can be reduced at a much less negative potential than the radical anion.

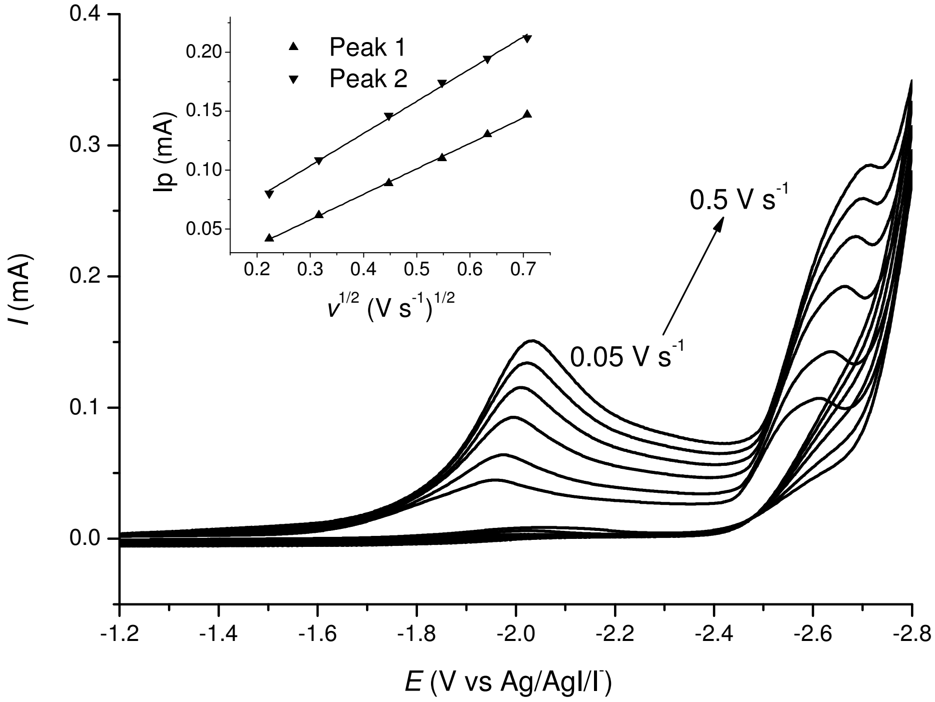
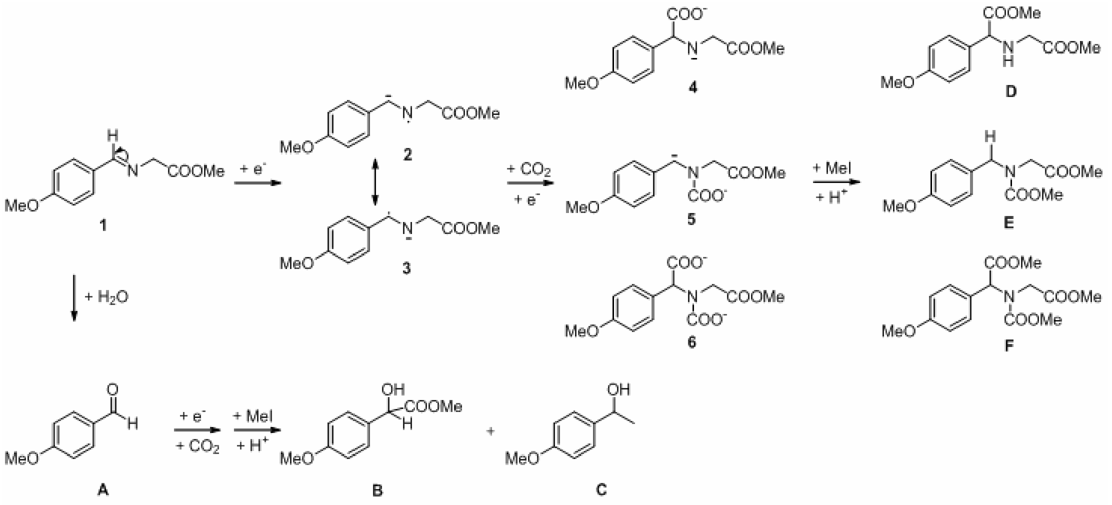


Figure 3. Cyclic voltammograms of 5.7 mmol L^{-1} [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester in DMF-0.1 mol L^{-1} $TEABF_4$ solution on the GC electrode at various scan rates (V s^{-1}): 0.05 → 0.1 → 0.2 → 0.3 → 0.4 → 0.5. Insert: Relationships between cathodic current peaks and the square root of scan rate.

3.3.Reaction pathway

Accounting for all these electrosynthesis data available and cyclic voltammograms, a possible reaction mechanism could be put forward (Scheme 4) [27]. Although there is not a affirmatory conclusion yet that whether the electrocarboxylation of the imine proceed through ECEC or EECC path such as consecutive electrochemical (E) and chemical (C) reaction, it is clear that in the initial step of the reaction the imine substrate **1** obtained one electron from the electrode to become two resonated anodic radicals **2** and **3**. As the solvent was dried and saturated with CO_2, most of the reactive species underwent a nucleophilic attack on CO_2 via carbon or nitrogen atom to give the corresponding adducts **4** and **5**.

Through the workup procedure of esterification and hydrolyzation, the aimed **D** and **E** were obtained as a result. Another related sequence involves adding a second CO_2 molecule to form C, N-carboxylated product **F**. In addition, once the imine substrate hydrolyzed, electrocarboxylation and hydrogenation of resulted *p*-methoxybenzaldehyde **A** would certainly happen to generate **B** and **C**, respectively.



Scheme 4.

4. CONCLUSIONS

To sum up, a novel electrosynthetic system for incorporation of carbon dioxide into one kind of aryl alkyl imine, [(4-methoxy-benzylidene)-amino]-acetic acid methyl ester, under very mild conditions was realized. This new electrocarboxylation widens the research field in the application of clean electrochemical technology to synthesize organic chemicals including aryl alkyl amino acid derivate via utilization of CO_2.

We have shown that the electrocarboxylation of the imine was easily affected by various conditions, such as the solvent, supporting electrolyte, cathode material, current density, charge passed and temperature. The electrochemical behavior of the imine was also investigated by cyclic voltammetry on glassy carbon electrode and a possible mechanism has been proposed, which suggested the radical anion of the imine existed as a resonance hybrid and its reaction with electrophilic carbon dioxide showed some diversity to give diverse carboxylated products.

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