Efficient Electrocarboxylation of *p*-Methylpropiophenone in the Presence of Carbon Dioxide

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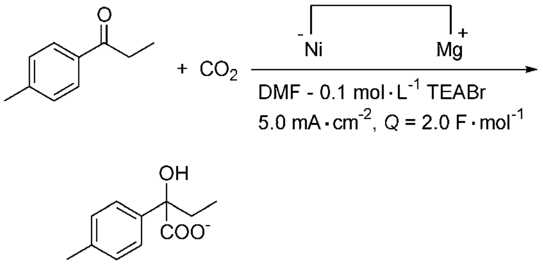
In the one compartment electrochemical cell 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester was electrosynthesized by electrochemical carboxylation of *p*-methylpropiophenone in the presence of carbon dioxide. Under galvanostatic conditions, the electrocarboxylation was influenced by supporting electrolytes, cathode materials, the current density, passed charge and temperatures. Application scope of the eletrocarboxylation system was then examined, and an excellent yield of 97% was obtained when the electrolysis was carried out in DMF-0.1 mol•L^{-1} TEABr solution using cheap and environmentally benign nickel as the cathode under a controlled current density of 5.0 mA•cm^{-2} until 2.8 F•mol^{-1} charge passed through the cell at −10 ℃. The electrochemical behavior of *p*-methoxylacetophenone has been studied on the glassy carbon electrode by cyclic voltammetry and the probable mechanism was proposed accordingly.

Keywords *p*-methylpropiophenone, electrocarboxylation, carbon dioxide, galvanostatic electrolysis

Introduction

Electrocarboxylation via electrochemical fixation of carbon dioxide as a central, low-cost, widely available C1-organic building block is a powerful tool for the construction of carbon-carbon bond.[1-3] Since the pioneering work of Wagenknecht in 1986,[4] electrochemical carboxylation of aromatic ketones has attracted a considerable interest as a method of obtaining various *α*-hydroxy acids (AHAs), which were extensively used in cosmetic dermatology to cure skin disorders including acne, warts, and psoriasis and to correct photoaged skin.[5-7] Among these successful examples, the critical cathode utilized in many applications employed toxic lead foil[8] or highly expensive platinum[9] to form 2-aryllactic acids and 2-hydroxy-2-alkylphenyl propanoic acids, respectively. Despite these successes, the development of the efficient and appropriate cathode materials is still a challenge and has become a much attempting research endeavor.

In this paper, we report data on the electrolytic synthesis of 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester by electrocarboxylation of *p*-methylpropiophenone in the presence of carbon dioxide in good to excellent yields by employing environmentally benign and much cheaper nickel cathode (Eq. 1). Nevertheless, the only conventional method of synthesis on which most industrial processes are based consists of several dangerous or toxic reagents such as very strong bases, Grignard reagents, *etc*.[10] Therefore, electrochemical technology can provide a valuable and desirable alternative for synthesis of some important *α*-hydroxy acids within the domain of green chemistry. Thanks to the electron transfer between the electrode and the substrate molecules, carbon dioxide with its intrinsic thermodynamic stability can be readily activated by coupling with anions or radical anions to ensure introduction of a carboxylic function onto an organic center upon conserving intact the original carbon skeleton. Hence, electrocarboxylation offers an effective means of fixation and utilization of the largest contributor to the greenhouse effect under neutral and mild conditions, which makes our work even more significant and meaningful.



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The mechanism of electrocarboxylation of aromatic ketones has not been investigated in detail. Ikeda and

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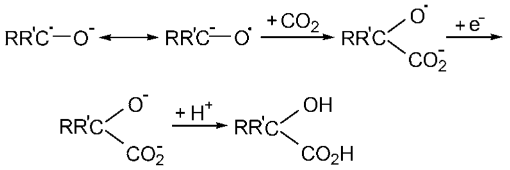
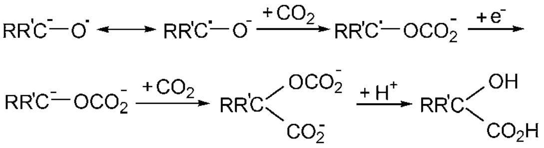
Manda[11] once invoked the resonance structure of the ketyl radical anion of a series of benzophenones to explain the influence of the substituted groups on the experimental results. As shown in Scheme 1, the authors proposed the structure with the negative charge localized on the carbon atom was likely to be predominant and hence the carboxylation is very efficient when the electron-withdrawing groups were present in the phenyl rings. However, both resonance structures were important with the molecule bearing electron-donating substituents. Then the carboxylation yield may decrease and dimers or tars became crucial.

Scheme 1



More recently, a slightly different mechanism involving two carbon dioxide molecules, illustrated in Scheme 2 has been more favored.[12] The ketyl radical anion reacts with CO_2 via the oxygen atom to give a species which undergoes immediate reduction and then incorporates a second CO_2 molecule. It is worth noting that the actual carboxylation product is not the dicarboxylation anion but an α-hydroxy acid. The latter is assumed to form by hydrolysis in the workup procedure. In this paper, the results of mechanistic investigation of electrocarboxylation are also described according to the cyclic voltammogram of *p*-methylpropiophenone.

Scheme 2



Experimental

General procedure for electrochemical analysis

Voltammetric measurements were carried out by using a CHI650C electrochemical station. Potential scan was performed in a dry DMF solution containing tetraethylammonium tetrafluoroborate ($TEABF_4$) 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 a Ag/AgI/*n*-TBAI (0.1 $mol\cdot L^{-1}$) in DMF as the reference electrode. All experiments were performed at 25 ℃ under an atmospheric pressure.

General procedure for electrosynthesis

The preparative galvanostatic and potentiostatic electrolysis was carried out in a mixture of *p*-methylpropiophenone (0.1 $mol\cdot L^{-1}$) and TEABr (0.1 $mol\cdot L^{-1}$) in 10 mL of dry DMF in a one-compartment electrochemical cell equipped with a magnesium rod as the sacrificial anode and a nickel cathode (area$\approx$8 cm^2) until 2.0 $F\cdot mol^{-1}$ of charge was passed. During the whole electrocarboxylation the electrolyte was saturated with carbon dioxide, with the latter being passed through vigorously for the duration of the entire synthesis. At the end of the electrolysis, MeI as an alkylating agent was added in 5-fold molar excess and the electrolyte was allowed to reflux at 50—60 ℃ for 5 h under stirring. The esterification completed, the solvent was distilled off under reduced pressure, and the residue was acidified with aqueous HCl (20 mL) and extracted with diethyl ether (20 mL×3). The combined organic layers were then washed with saturated brine and dried over $MgSO_4$. After evaporating an almost pure 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester was isolated by column chromatography using petroleum ether/ethyl acetate mixture as an eluent. The main features of the aimed methyl ester identified by GC-MS, ^1H NMR, and ^{13}C NMR analyses were described in the following and the yields were determined by GC with respect to the starting material using *n*-decane/1,4-dioxane as an internal standard. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.01 (t, $J=7.4$ Hz, 3H), 2.07—2.14 (m, 1H), 2.27—2.34 (m, 1H), 2.38 (s, 1H), 3.77 (s, 3H), 4.06 (s, 1H), 7.20 (d, $J=8.1$ Hz, 2H), 7.56 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 7.69 (s, 1C), 29.54 (s, 1C), 32.29 (s, 1C), 52.55 (s, 1C), 78.39 (s, 1C), 125.16 (s, 2C), 128.54 (s, 2C), 136.82 (s, 1C), 138.67 (s, 1C), 175.53 (s, 1C); GC-MS *m/z* (%): 208 (1.4), 179 (0.6), 149 (100.0), 131 (1.9), 119 (21.0), 105 (1.8), 91 (14.5), 77 (2.3), 57 (33.7), 43 (1.7).

Results and discussion

Cyclic voltammetry of *p*-methylpropiophenone and reaction pathway

In cyclic voltammetry, there was not any redox peak from -1.4 to -2.8 V before addition of the substrate under N_2 in DMF containing 0.1 $mol\cdot L^{-1}$ $TEABF_4$ at glassy carbon electrode (Figure 1, curve a). In comparison, 0.01 $mol\cdot L^{-1}$ *p*-methylpropiophenone gave rise to three successive reduction peaks at the scan rate of 0.1 $V\cdot s^{-1}$ in the employed scan region with the intensity of the first peak being noticeably higher than those of the others (Figure 1, curve b). The first partially reversible cathodic peak with $E_{p1}=-1.91$ V corresponded to one electron reduction of *p*-methylpropiophenone to the corresponding anion radical. The second irreversible peak at -2.30 V could be relevant to the transfer of the second electron, resulting in the aromatic ketone dianion formation. It was worth noting that the third reduction peak with $E_{p3}=-2.57$ V was newly found compared to some previously studied electroreduction behavior of aromatic ketones,[12,13] which could be supposed to involve the third electron uptake of the whole phenyl ring[1] since some unexpected ring carboxylation of aromatic ketones has been reported.[14,15] Studying the electrochemical activation of *p*-methylpropiophenone at higher sweep rate of 0.5 V•s^{-1} showed an appreciable I_p increase and negative E_p shift for all three reduction waves (Figure 1, curve c). On the base of the evaluation of I_a/I_c for the first cathodic peak, we estimated the radical anion of *p*-methylpropiophenone forming at 0.5 V•s^{-1} (I_a/I_c=0.36) was more stable than that forming at 0.1 V•s^{-1} (I_a/I_c=0.30) to undergo the second electron uptake.

When the cyclic voltammograms were recorded after the solution was saturated with CO_2, there was an obvious growth of the first cathodic peak (presumably by 1.72 times) and its shift into more anodic region as well as the complete disappearance of the other two cathodic peaks and the anodic peak attributed to the first electron transfer (Figure 1, curve d). The observed changes were indicative of a fast chemical reaction of *p*-methylpropiophenone radical anion with carbon dioxide followed by a second electron reduction[16] since CO_2 was a stronger electrophile than *p*-methylpropiophenone. The first cathodic peak shifted into the more positive potential region could be caused by subsequent chemical reactions between the anion radicals and carbon dioxide and by the formation of aromatic ketone complexs with CO_2 molecule which were more reducible than the starting material. Similar association of CO_2 with ketones has been revealed recently.[15]

Based on the understanding of the generalized mechanism depicted in the previously reported electrocarboxylation of the aromatic ketones,[17,18] proposed reaction pathways involving two CO_2 molecules for the present carborxylation are revealed in Scheme 3. In the initial step of the reaction the ketone **1** took up an electron from the cathode to become an anionic radical **2**. As the solvent was dried and saturated with CO_2 most of **2** underwent a nucleophilic attack on CO_2 via the oxygen atom to give an adduct **3**, which was more easily reducible than the starting ketone. Then further one-electron reduction followed by incorporating a second CO_2 molecule led to the formation of **4**. Through the work-up procedure of acidification, in which a CO_2 was lost, **4** reacted to produce the aimed product **5**. In the electrolysis, the magnesium ions dissolved from a magnesium anode could readily capture carboxylate ions **4** to form the corresponding magnesium carboxylates,[19] upon which the esterified carboxylation product was more favored than the hydride or dimer.

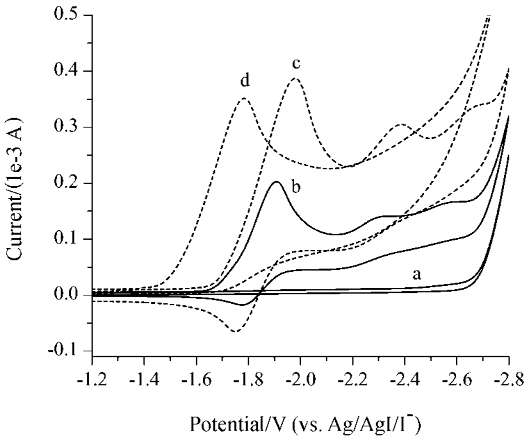


Figure 1 Cyclic voltammograms of *p*-methylpropiophenone in DMF solution containing 0.1 mol•L^{-1} $TEABF_4$ at glassy carbon electrode. (a) without *p*-methylpropiophenone; (b), (c) with 0.01 mol•L^{-1} *p*-methylpropiophenone in the presence of N_2 at v=0.1 V•s^{-1} and v=0.5 V•s^{-1}, respectively; (d) as b in the presence of saturated CO_2, T=25 ℃.

Electrochemical carboxylation of *p*-methylpropiophenone

Influence of supporting electrolytes The potentiostatical electrocarboxylation of *p*-methylpropiophenone with CO_2 to 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester in DMF solution employing stainless steel as the cathode was conducted using various supporting electrolytes as presented in Table 1. The potential was chosen at the second reduction peak potential of −2.3 V. As a result, for the studied supporting electrolytes, the carboxylation yield decreased in an order of TEABr> TBABr>TBAI>$TEABF_4$>TEAI>TEACl. The influence of supporting electrolytes composed of different cations and anions was distinct under the same other

Scheme 3

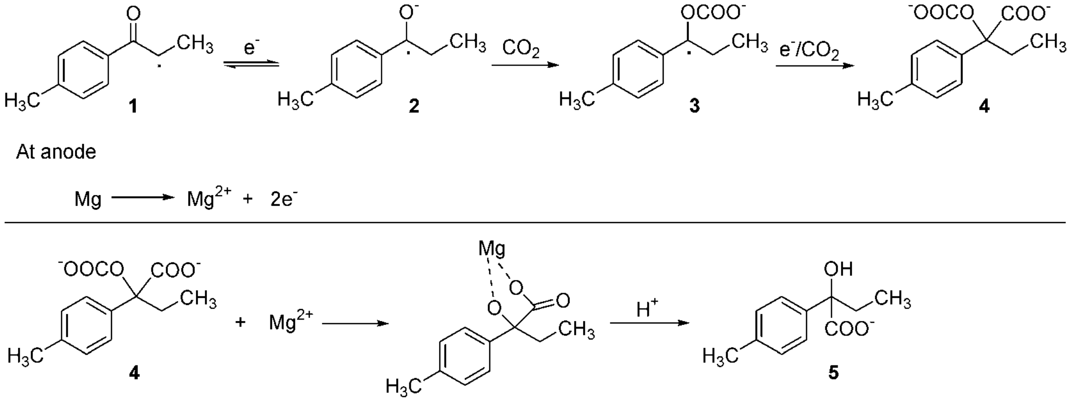


Table 1 Influence of supporting electrolytes on the potentiostatical electrocarboxylation of *p*-methylpropiophenone[a]

Entry	Supporting electrolyte	Cathode	Yield[b]/%
1	TEABr	−2.3	38
2	TEAI	−2.3	14
3	TBAI	−2.3	23
4	$TEABF_4$	−2.3	15
5	TBABr	−2.3	25
6	TEACl	−2.3	12
7	TEABr	−1.9	—

[a] The electrolysis was carried out in DMF using the stainless steel as the cathode until 2.0 F•mol^{-1} charge was passed at 25 ℃; *p*-methylpropiophenone, 0.1 mol•L^{-1}, $p(CO_2) = 1 \times 10^5$ Pa; [b] yields of the 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester were determined by GC with respect to the starting material.

Table 2 Galvanostatical electrocarboxylation of *p*-methylpropiophenone under various conditions[a]

Entry	Cathode	j/(mA•cm^{-2})	Q/(F•mol^{-1})	T/℃	Yield[b]/%
1	Ss	5.0	2.0	25	33
2	Cu	5.0	2.0	25	52
3	Ni	5.0	2.0	25	79
4	Ti	5.0	2.0	25	10
5	Ag	5.0	2.0	25	70
6	C	5.0	2.0	25	7
7	Ni	4.0	2.0	25	58
8	Ni	4.5	2.0	25	66
9	Ni	5.5	2.0	25	57
10	Ni	6.0	2.0	25	41
11	Ni	5.0	1.2	25	41
12	Ni	5.0	1.6	25	61
13	Ni	5.0	2.4	25	81
14	Ni	5.0	2.8	25	83
15	Ni	5.0	2.8	0	93
16	Ni	5.0	2.8	−10	97

[a] DMF, 10 mL; TEABr, 0.1 mol•L^{-1}; *p*-methylpropiophenone, 0.1 mol•L^{-1}; [b] as depicted in Table 1.

operative parameters. The relative higher yield of 38% was obtained with TEABr. From the view of practice, the currents of controlled-potential electrolysis were very small. Then much more unnecessary byproducts were probably engendered. When the potential was changed to the potential of the first reduction peak (−1.9 V), no aimed product could be identified regrettably with an even smaller current (Entry 7).

Influence of the nature of the electrode Since the constant potential electrolysis was not so effective as expected, the following electrocarboxylation of *p*-methylpropiophenone was performed under the controlled current densities. The nature of the cathodic material had an important influence on the carboxylation yield of the electrolysis.[20] Among common cathode materials, the nickel (Ni) was much better than the others and 79% of 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester was obtained. The employment of a silver cathode (Ag) decreased the yield a little to 70%. However, other cathode materials such as copper (Cu) and stainless steel (Ss) were much inferior and gave lower yields of the desired product. The cathodes of graphite (C) and titanium (Ti) were even worse. A comparison of the effect of these cathodes under similar conditions was summarized in Table 2 (Entries 1—6).

Influence of the current density Appreciable difference in the yield of the product was found at the end of the electrosynthesis under various current densities (Table 2, Entries 7—10). The best current density was 5.0 mA•cm^{-2} on the electrodes of Mg-Ti and the electrolysis at a higher or a lower current density resulted in both lower yields (Figure 2). On one hand, the larger the current density was, the more negative the electrode potential would be. Therefore there would be other unneeded reactions on the electrode surface, such as the reduction of CO_2 or dissolved Mg^{2+}, which would decrease the carboxylation yield. On the other hand, the lower the current density was, the more positive the electrode potential would be. So the proportion of the Faradaic current would be declined, which decreased the carboxylation yield too.[21]

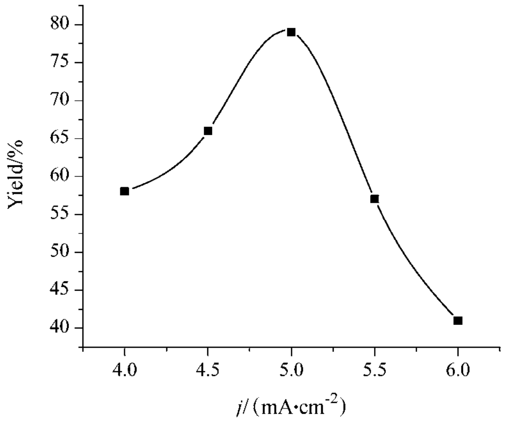


Figure 2 Effect of the current density on electrocarboxylation of *p*-methoxylacetophenone.

Influence of the passed charge The electrocarboxylation of *p*-methylpropiophenone is a two-electron reduction reaction, which means the theoretic charge of this reaction is 2.0 F•mol^{-1}. As the presence of the non-Faradaic current, the Faradaic efficiency can not achieve 100%. Consequently more over the theoretic charge is usually needed to improve the yield. The electrocarboxylation under various passed charges was then examined (Table 2, Entries 3 and 11—14). As shown in Figure 3, the best yield of 83 % was obtained when the passed charge reached 2.8 F•mol^{-1}. Before the point of 2.0 F•mol^{-1}, the yield increased rapidly with the increment of the passed charge. Increasing electricity from 2.0 to 2.8 F•mol^{-1} was slightly effective for improving

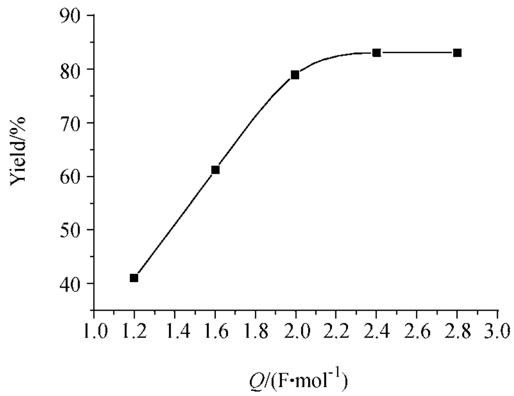


Figure 3 Effect of the charge passed on electrocarboxylation of *p*-methoxylacetophenone.

the yield.

Influence of the temperature To investigate the effect of the temperature, the electrocarboxylation was carried out at 25, 0 and −10 ℃ respectively (Table 2, Entries 14—16). An enhancement in yield was obtained by decreasing the temperature, that is to say, by increasing the CO_2 concentration.[22] An almost excellent yield of 97% was achieved finally at −10 ℃. It showed that the lower temperatures could quite favor the electrocarboxylation process.

Conclusion

In conclusion, we have developed a simple and efficient electrochemical route with nickel cathode for electrocarboxylation of *p*-methylpropiophenone to 2-hydroxy-2-*p*-tolyl-butyric acid methyl ester in CO_2-saturated DMF solution. We have shown that various conditions, such as the supporting electrolyte, cathode material, current density, charge passed and temperature, can affect the yield of carboxylic acid ester. After optimizing the synthetic parameters, the highest yield of 97% was achieved on Mg-Ni electrodes under a constant current density of 5 $\mathrm{mA \cdot cm^{-2}}$ until 2.8 $\mathrm{F \cdot mol^{-1}}$ of charge passed through the cell at −10 ℃. The electrochemical behavior of *p*-methylpropiophenone was investigated by cyclic voltammetry and the mechanism has been proposed on the basis of the results, which suggested a typical ECEC (one electron reduction-chemical reaction-another electron reduction-another chemical reaction) process.

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