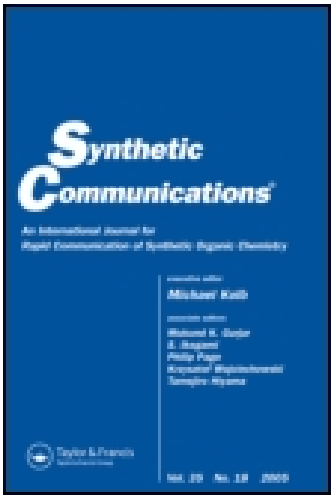

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Electrochemical Synthesis of α-Hydroxycarboxylic Acids From Acetophenones

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Abstract: α-Hydroxy carboxylic acids are synthesized in 80–86% isolated yields by electrochemical carboxylation of methyl aryl ketones in the presence of carbon dioxide (1 atm.) using a platinum cathode and a sacrificial magnesium anode at a constant current density of $10\,mA/cm^2$. Reversibility of the carbonyl group reduction and generation of anionic radical were shown by cyclic voltammetry.

Keywords: Cyclic voltammetry, electrochemical carboxylation, α-hydroxy carboxylic acids, methyl aryl ketones, sacrificial anode

INTRODUCTION

α-Hydroxy acids (AHAs) are used extensively in cosmetic dermatology to cure skin disorders including acne, warts, and psoriasis and to correct photoaged skin.[1–3] Howard et al.[4] reported the possible role of AHAs in photocarcinogenesis. The preparation of AHAs from the corresponding cyanohydrins using hydrogen cyanide is unattractive because of the use of highly toxic cyanides.[5] Wawzoneck[6] and Hori[7] reported electrochemical carboxylation of acetophenones in low yields. By using oxalates and formates as counterelectrodes, Engels et al.[8] improved the yields of

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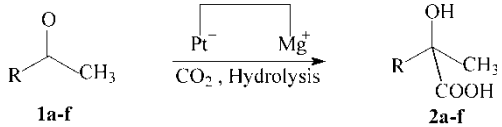
electrocarboxylation of acetophenones. Electrochemical synthesis of AHAs using a mercury cathode in a divided cell (reported by Ikeda et al.[9]) in spite of good yields was not efficient because of the inability of the system to be developed into a commercially useful process. Also, the use of highly toxic mercury was environmentally unacceptable, and the use of a divided cell substantially increases the cost of production. Later Silvestri et al.[10] used a sacrificial Al anode in the electrocarboxylation of acetophenones. Wagenknecht et al.[11,12] developed the process for the electrocarboxylation on a pilot scale. In electrocarboxylation, magnesium is used as the most efficient sacrificial anode,[13,14] which solves the problem of cathodic reaction. The dissolved ions also function as added supporting electrolytes, and in many cases the magnesium ions play an important role in forming the product during the reaction.[15] To develop a convenient and commercially useful synthesis, it is desirable to develop a high-yield system with an undivided cell and a sacrificial anode.

Electrochemical methods are frequently referred to as one of the prototypical green technologies of the future.[16] In this communication, we describe the synthesis and mechanism of electrochemical carboxylation of α-hydroxy acids by employing waste-free technologies such as electrochemical carboxylation and avoiding the use of toxic reagents such as cyanides.



1a-f **2a-f**

a. R = Ph **d**. R = p-CN Ph
b. R = p-OH Ph **e**. R = p-NO_2 Ph
c. R – p-MeO Ph **f**. R = 

EXPERIMENTAL

Electrolyses were carried out using Potentiostat (model PS 605). Melting points were determined on Mel-Temp apparatus and are uncorrected. ^{1}H NMR were recorded on a Varian EM-360. IR spectra were recorded on a Perkin-Elmer 1600. Cyclic voltammetric measurements were carried out with a Metrohm unit 757VA Comptrance. Solvent DMF and MeCN were distilled by standard Vogel's procedure and supporting electrolytes, TBAI and TBAB, were analytical grade. Carbon dioxide used was 99% pure.

Electrochemical Carboxylation

A mixture of acetophenone (**1a**; 1.16 mL) and TBAI (3.69 g) in DMF (50 mL) was added into an undivided cell equipped with a platinum cathode and

magnesium anode. Before electrolysis, the O_2 in the system was removed by passing N_2 gas through this solution. The mechanically stirred homogeneous solution was electrolyzed at about 25°C at constant current density of 10 mA/cm^2 under a constant pressure (1 atm.) of carbon dioxide until 2 F/mol of electricity was passed. After electrolysis, the power supply was shut off, and the solution was transferred to a round-bottom flask. The DMF solvent was stripped in a rotary evaporator until a viscous residue was obtained. The residue was stirred well in 50 mL of toluene for about 5 h for removal of uncorrected starting material. The mixture was filtered, and the solid was stirred well in 50 mL of 5% aqueous hydrochloric acid for 5 h. The product was extracted with diethylether (90 mL) and dried over $MgSO_4$. Evaporation of solvent afforded 1.41 g of 2-hydroxy-2-phenylpropanoic acid (**2a**) in 85% yield; mp 113–114°C [lit.[17] mp 115–116°C]. IR (neat): $\nu = 3485$ (OH) cm^{-1}, 1732 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.34$ (bs, 1H, –COOH), 9.32 (bs, 1H, OH), 7.11–7.32 (m, 5H, Ar-H), 1.92 (s, 3H, CH_3). Anal. calcd for $C_9H_{10}O_3$ (166.18): C, 65.05; H, 6.07. Found: C, 65.14; H, 6.02.

2-Hydroxy-2-(4-hydroxyphenyl)propanoic acid (***2b***): Yield 83%; mp 218–220°C [lit.[18] mp 220–223°C]. IR (neat): $\nu = 3481$ (OH) cm^{-1}, 1726 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.45$ (bs, 1H, –COOH), 9.12 (bs, OH), 4.53 (s, 1H, Ar-OH), 7.08–7.23 (m, 4H, Ar-H), 1.91 (s, 3H, CH_3). Anal. calcd. for $C_9H_{10}O_4$ (182.17): C, 59.34; H, 5.53. Found: C, 59.09; H, 5.61.

2-Hydroxy-2-(4-methoxyphenyl)propanoic acid (***2c***): Yield 82%; mp 145–147°C [lit.[19] mp 146–147°C]. IR (neat): $\nu = 3472$ (OH) cm^{-1}, 1728 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.48$ (bs, 1H, –COOH), 9.25 (bs, 1H, OH), 7.01–7.19 (m, 4H, Ar-H), 3.81 (s, 1H, $-OCH_3$), 1.99 (s, 3H, CH_3). Anal. calcd. for $C_{10}H_{12}O_4$ (196.20): C, 61.22; H, 6.16. Found: C, 61.08; H, 6.19.

2-(4-cyanophenyl)-2-Hydroxypropanoic acid (***2d***): Yield 85%, mp 196–198°C [lit.[18] mp 199–201°C]. IR (neat): $\nu = 2234$ (CN) cm^{-1}, 3462 (OH) cm^{-1}, 1733 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.39$ (bs, 1H, –COOH), 9.27 (bs, 1H, OH), 7.15–7.29 (m, 4H, Ar-H), 1.81 (s, 3H, CH_3). Anal. calcd. for $C_{10}H_9NO_3$ (191.18): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.71; N, 7.18.

2-Hydroxy-2-(4-nitrophenyl)propanoic acid (***2e***): Yield 86%; mp 219–220°C. IR (neat): $\nu = 3468$ (OH) cm^{-1}, 1725 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.51$ (bs, 1H, –COOH), 9.29 (bs, 1H, OH), 7.24–7.41 (m, 4H, Ar-H), 1.77 (s, 3H, CH_3). Anal. calcd for $C_9H_9NO_5$ (211.18): C, 51.19; H, 4.30; N, 6.63. Found: C, 51.28; H, 4.23; N, 6.59.

2-Hydroxy-2-thiophene-2-yl-propanoic acid (***2f***): Yield 80%; mp 108–110°C, [lit.[20] mp 111–113°C]. IR (neat): $\nu = 3468$ (OH) cm^{-1}, 1724 (C═O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 11.42$ (bs, 1H, –COOH), 9.16 (bs, 1H, OH), 6.51–6.94 (m, 3H, thio H), 1.61 (s, 3H, CH_3). Anal. calcd. for $C_7H_8O_3S$ (172.2): C, 48.82; H, 4.68; N, 27.87. Found: C, 48.79; H, 4.71; N, 27.81.

Table 1. Electrochemical carboxylation of methyl aryl ketones[a]

No.	Supporting electrolyte	Solvent	Yields (%)[b]					
			2a	**2b**	**2c**	**2d**	**2e**	**2f**
1	TBAI	DME	84	83	82	85	86	80
2	—	MeCN	77	71	71	74	76	72
3	TBABr	DMF	83	82	80	83	84	79
4	—	MeCN	75	71	70	74	76	70

[a]Electrolysis was carried in the presence of carbon dioxide (1 atm.) with a platinum cathode and magnesium anode at 10 mA/cm^2.
[b]Isolated yields.

RESULTS AND DISCUSSION

Electrochemical carboxylation of methyl aryl ketones, **1a**–**f** readily takes place to give α-hydroxy carboxylic acids **2a**–**f** as carboxylation products in 80–86% yields. Table 1 shows that yields of **2a**–**f** are quite sensitive to the reaction media and the reaction conditions. The yields are less in acetonitrile than DMF because of the lower polarity of acetonitrile. In less polar solvents such as acetonitrile, the carboxylation product precipitated on the electrodes during the reaction and caused by-product formation. The major by-product was pinacol-type dimer.

Cyclic voltammogram of p-Cyanoacetophenone (**1d**) (Fig. 1) shows a reduction peak at -1.60 V vs. Ag/AgCl in DMF containing 0.1 M Bu_4NI at 0.2 V/s at glassy carbon disk electrode (GCDE) of area 0.0706 cm^2, which

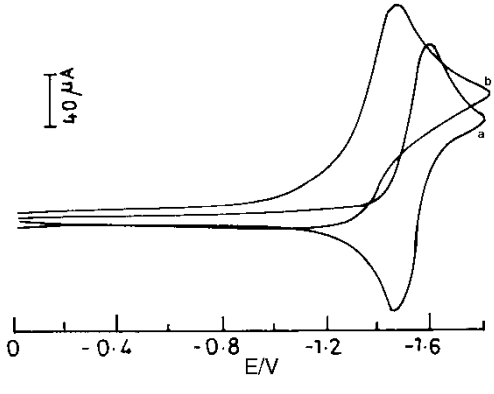


Figure 1. Cyclic voltammogram of p-cyanoacetophenone in DMF containing 0.1 M TBABr at scan rate of 0.2 V/s and Ag/AgCl as reference electrode: (a) absence of CO_2 and (b) presence of CO_2.

is due to a reduction of the carbonyl group in a reversible process. Addition of carbon dioxide to the solution causes an increase in cathodic current, an anodic shift in peak potential, and elimination of the reverse anodic current. This indicates a very fast reduction of the anion radical of methyl aryl ketone.

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