Electrochemical Carboxylation of Aliphatic Ketones: Synthesis of β -Keto Carboxylic Acids

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A constant current electrolysis of saturated aliphatic ketones in a CH_3CN or DMF solution containing $0.1 \text{ mol dm}^{-3} \text{ Bu}_4\text{NBF}_4$ with a platinum cathode and a magnesium anode under an atmospheric pressure of CO_2 resulted in an efficient fixation of CO_2 at α -position of carbonyl group in the ketones to give the corresponding β -keto carboxylic acids in moderate to good yields.

Key Words : Electrochemical Carboxylation, Fixation of Carbon Dioxide, β -Keto Carboxylic Acids, Reactive Metal Anode

1 Introduction

Electrochemical carboxylation (EC) is one of useful and attractive methods for fixation of carbon dioxide to organic molecules. Carboxylic acids can be readily obtained in high yields under neutral and mild conditions even in an atmospheric pressure of CO_2 when a reactive metal, such as magnesium and aluminum, is used as an anode in the electrolysis.^{1, 2)} Previously, we successfully carried out EC of various organic molecules to obtain carboxylic acids in good yields.^{3–12)} It was also reported that EC of aryl aldehydes and ketones gave α -hydroxyphenylacetic acids^{13–18)} and the reaction was applied to the synthesis of 2-hydroxy-2-phenylpropanoic acids, which are known to be useful precursors for non-steroidal anti-inflammatory agents.^{15–18)} On the other hand, little attention has been paid for a similar carboxylation of saturated aliphatic ketones. To the best of our knowledge, EC of benzyl methyl ketone is the only example,¹⁴⁾ and no further investigation has been reported from viewpoint of organic synthesis.¹⁹⁾ As one of our continuous studies on electrochemical fixation of CO_2 to organic molecules, we tried EC of saturated aliphatic ketones and found that the corresponding β -keto carboxylic acids could be obtained in moderate to good yields. Herein, we would like to report our recent results on EC of aliphatic ketones **1** to give β -keto carboxylic acids **2** (Scheme 1).

2 Experimental

Commercially available ketones **1a–h** were used without further purification. Anhydrous CH_3CN and anhy-

drous DMF were purchased from Kanto Chemical Co. and Aldrich, respectively.

Ketone **1** (2.0 mmol) in 20 cm^3 of CH_3CN or DMF containing $0.1 \text{ mol dm}^{-3} \text{ Bu}_4\text{NBF}_4$ was electrolyzed at 0°C with a constant current (15 mA cm^{-2}) under an atmospheric pressure of carbon dioxide with bubbling. A one-compartment cell equipped with a Pt plate cathode ($2 \times 2 \text{ cm}^2$) and an Mg rod anode ($\phi 6 \text{ mm}$) was used for electrolysis. The electricity passed was $10 \text{ Faradays mol}^{-1}$ of ketone **1**.²⁰⁾ After electrolysis, the electrolyzed solution was poured into $1 \text{ mol dm}^{-3} \text{ HCl}$ (100 cm^3) and extracted with diethyl ether ($30 \text{ cm}^3 \times 3$). The combined ethereal solution was washed with saturated NaHCO_3 ($40 \text{ cm}^3 \times 3$). The resulting aqueous solution was acidified with $3 \text{ mol dm}^{-3} \text{ HCl}$, and then extracted with diethyl ether ($30 \text{ cm}^3 \times 3$). The combined ethereal solution was washed with saturated brine and dried over MgSO_4 . Evaporation of the solvent gave an almost pure β -keto carboxylic acid **2**.

Spectral data of the products are identical with reported data of **2a**,⁸⁾ **2b**,²¹⁾ **2c**,⁸⁾ **2d**,⁸⁾ **2f**,²¹⁾ **2g**,²²⁾ and **2h**,⁸⁾ respectively. **2e**: m.p. $88\text{--}91^\circ\text{C}$ (petroleum ether); δ_{H} (400 MHz, CDCl_3 , keto form) 1.15–1.5 (14H, m), 1.7–1.8 (2H, m), 1.8–1.9 (1H, m), 2.1–2.2 (1H, m), 2.58 (1H, dt, $J = 6.3$ and 16.9 Hz), 2.79 (1H, dt, $J = 5.9$ and 16.9 Hz), 3.70 (1H, t, $J = 6.3$ and 3.7 Hz); δ_{C} (100 MHz, CDCl_3 , keto form) 21.8, 22.1, 22.4, 23.6, 23.9, 24.0, 25.2, 25.4, 27.3, 38.8, 55.9, 174.2, 209.0; IR 3700–2700, 1688, 1638, 1473, 1276, 1133, 933 cm^{-1} ; EIMS m/z 226 (M^+ , 3), 208 (2), 182 (14), 139 (9), 125 (14), 111 (29), 98 (100); Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_3$ 226.1569. Found M^+ 226.1572.

3 Results and Discussions

As a first attempt, EC of cyclohexanone (**1a**) was examined under various conditions. Two representative supporting electrolytes (SE) used in our previous EC^{9, 11)} were tested in DMF and CH_3CN . It was found that the product yields strongly depend on SE. Thus, when Et_4NClO_4 was used, 2-oxocyclohexanecarboxylic acid (**2a**)

Scheme 1 EC of aliphatic ketones **1**.

Scheme 2 EC of Cyclohexanone (**1a**).

was obtained in only poor yields (8% in DMF and 9% in CH₃CN). On the other hand, EC of **1a** proceeded more efficiently when Bu₄NBF₄ was used instead of Et₄NClO₄. Under the optimized reaction conditions, EC of **1a** in CH₃CN containing 0.1 mol dm⁻³ Bu₄NBF₄ at 0 °C with a constant current (15 mA cm⁻²) gave β-keto carboxylic acid **2a** in 53% yields (Scheme 2).

The results of the present EC using various saturated aliphatic ketones **1** were summarized in Table 1. Although EC of cyclopentanone (**1b**), known to be reactive in aldol reactions, gave 2-oxocyclopentanecarboxylic acid (**2b**) in 28%, EC of cycloheptanone (**1c**) and cyclooctanone (**1d**) could proceed more efficiently to give keto acids **2c** and **2d** in better yields, 47 and 53%, respectively (entries 2 and 3). When cyclododecanone (**1e**) was subjected to the present EC, 2-oxocyclododecanecarboxylic acid (**2e**) was obtained in 92% yield. On the other hand, EC of acyclic ketones took place less efficiently than that

of cyclic ketones (entries 5-7). Thus, EC of 4-heptanone (**1f**) gave 2-ethyl-3-oxohexanoic acid (**2f**) in 34% yield. A similar carboxylation of 3,3-dimethyl-2-butanone (**1g**) afforded 4,4-dimethyl-3-oxopentanoic acid (**2g**) in 30% yield. When 2-octanone (**1h**), an unsymmetric ketone, was subjected to the present EC, carboxylation took place regioselectively at a terminal carbon to give a 9:1 mixture of 3-oxononanoic acid (**2h**) and 2-acetylheptanoic acid (**2i**) in 32% yield.

Although there are some possible pathways to produce **2** in the present EC, the most likely pathway to β-keto carboxylic acids **2** would involve enolate **A** as an intermediate. Thus, enolate **A** generated *in situ* reacts with CO₂ to give carboxylate **B**. Magnesium ion, which is generated by dissolution of anode metal, readily captures **B** to form stable magnesium salt **C** and/or **D** which upon an acid treatment gives carboxylic acid **2** (Scheme 3).

For the generation of **A** from ketone **1**, abstraction of α-proton of ketone **1** should be necessary. In the present EC, some species could be considered to act this important role, like a base, for generation of enolate **A**. Although decomposition of Bu₄NBF₄ during the electrolysis would generate Bu₃N which can act as a base, it could not be detected by ¹H NMR and GC analyses.²³⁾ On the other hand, electrogenerated anion radical of ketone **1** could also play such a role; however, no reduc-

Table 1 EC of aliphatic ketones **1**^a.

Entry	Substrate	Product and yield ^b	Entry	Substrate	Product and yield ^b
1		 2b 28%	5		 2f 34%
2		 2c 47%	6		 2g 30%
3		 2d 53%	7 ^c		 2h + 2i 32%
4		 2e 92%			2h : 2i = 9 : 1

^aEC was carried out in CH₃CN under the conditions described in experimental.

^bIsolated yield.

^cIsomer ratio was determined by ¹H NMR.

Scheme 3 Probable reaction pathways.

tion peak was observed at > -3.0 V vs Ag/Ag^+ in cyclic voltammetry of **1a**. In addition, on the basis of this hypothesis, it is difficult to explain the result of the EC affording **2e** in 92% yield.²⁴⁾ From these results, one possible pathway could be proposed that anion radical of CO_2 would work as a base to abstract α -proton of ketone **1** to generate enolate **A**.²⁵⁾

4 Conclusion

We tried and achieved EC of saturated aliphatic ketones. The reaction could take place readily with a constant current electrolysis in a one-compartment cell under an atmospheric CO_2 by using a magnesium anode and a platinum cathode to give β -keto carboxylic acids in moderate to good yields. Probable reaction pathway has been also proposed.

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- 24) If the generation of enolate **A** would proceed only through deprotonation by anion radical of **1** resulting in the formation of hydromonomer and/or hydrodimer of ketone **1**, the yield of carboxylic acid **2** should be theoretically less than 67% yield.
- 25) CO_2 has more positive reduction peak potential than that of **1a**. See ref. 8 and 11.