June, 1985] © *1985 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn., 58, 1723—1726 (1985)* 1723

Syntheses of Benzilic Acids through Electrochemical Reductive Carboxylation of Benzophenones in the Presence of Carbon Dioxide

Yoshikazu IKEDA* and Eiichiro MANDA
National Chemical Laboratory for Industry, Tsukuba 305

(Received December 14, 1984)

Reaction conditions for the electrochemical synthesis of benzilic acid (**2a**) under the atmosphere of carbon dioxide was investigated from the preparative points of view. The highest yield of **2a** (86%) was obtained under the following conditions; cathode: mercury, electricity passed: 2.3 F/mol, constant current density: 2.5 mA/cm^2, benzophenone (**1a**) (8.2×10^{-3}mol), electrolyte(KI, 1.7×10^{-2}mol) in DMF (50 ml). This method and conditions were applied to the syntheses of twelve benzilic acids (**2b—2m**) and yielded acids in the range of 10—92%. The yields were strongly depended on the electronic effect of substituents and benzilic acids were not obtained when the ring substituent was NO_2, OH, or Br group.

There are many reports on the production of carboxylic acids by bubbling CO_2 during reduction processes through catholytes containing organic materials. Among these, Wawzoneck *et al.*$^{1)}$ have shown that benzophenone(**1a**) and acetophenone could be carboxylated to form benzilic acid (**2a**) and 2-hydroxy-2-phenylpropionic acid, respectively, during the course of mechanistic investigation on the reduction process of aromatic ketones. The yields of these acids were 54 and 6%, but the synthetic aspects of this reaction were not investigated.

We recently reported$^{2)}$ that the electrochemical carboxylation reaction of 4-isobutylacetophenone in *N,N*-dimethylformamide (DMF) gave significant amounts of 2-hydroxy-2-(4-isobutylphenyl)propionic acid by a modification of the method of Wawzoneck for the synthetic application of organic electrochemistry. As an extension of this work, we report here a preparative electrochemical syntheses of benzilic acids from benzophenones in high yields under controlled conditions.

Experimental

All the melting points were measured on a Yanagimoto micromelting point apparatus and were uncorrected. IR spectra were recorded on a JASCO A-302 grating spectrometer in KBr. NMR spectra were measured on a Hitachi R-24 high resolution spectrometer (90 MHz) in $CDCl_3$ using TMS as an internal standard. Elemental analyses were performed by Microanalysis Laboratory of the Physical and Chemical Research Institute.

Materials. DMF was dried over anhydrous potassium carbonate for several days and distilled prior to use. Acetonitrile was refluxed and distilled from phosphorus pentaoxide and calcium hydride. Reagent grade lithium, sodium, potassium, rubidium, cesium and tetrabutylammonium iodide were used as supporting electrolytes without further purification. Benzophenones used were also reagent grade and were recrystallized from ethanol. Carbon dioxide used was 99.99% pure.

Electrolysis Apparatus. Preparative electrolysis experiments were carried out by using a Hokuto Denko HA-105 potentio-galvanostat equipped with a Hokuto Denko HF-201 coulometer. The electrolysis cell was a 200 ml H type vessel divided (3.6 cm dia.) with a sintered glass diaphragm. The cathode compartment was fitted with a glass bubbler tube placed very close to the cathode surface for introduction of CO_2.

General Electrolysis Procedure. All compounds listed in Table 2 were synthesized and isolated by using the procedures described in detail for the typical example below. A typical electrolysis procedure is as follows.

*Preparative Scale Electroreduction of Benzophenones in the Presence of CO_2, the Synthesis of **2a**.* A mercury pool (surface area 10.2 cm^2) was used as the cathode and the anode was a platinum plate (4.0 cm^2). 50 ml of DMF containing 14.2 g of KI was placed in each compartment. **1a** (1.5 g, 8.2×10^{-3} mol) was then added to the cathode compartment and CO_2 was passed through the catholyte for 60 min before the beginning of electrolysis. Catholyte was stirred magnetically and electrolysis was carried out under a fine stream of CO_2. The catholyte slowly turned opaque pale grayish with the progress of the electrolysis. After 2.3 F/mol of electricity was passed with a constant current of 2.5 mA/cm^2, the contents of the catholyte was poured into a separatory funnel. The mercury was taken off and DMF was removed under reduced pressure by a rotary evaporator. The residue was taken up in 150 ml of ether and the residue remaining after removal of the ether was dissolved in 100 ml of water and filtered. The filtrate was acidified with concentrated hydrochloric acid to yield white precipitates, which were collected by filtration, washed thoroughly with water, and dried *in vacuo*. Recrystallization from ethanol gave a pure compound of **2a**. Yield and physical properties are listed in Table 2.

Results and Discussion

At first, the synthesis of **2a** by electrochemical reduction of **1a** in the presence of CO_2 was investigated. Mercury pool cathode in DMF containing 8.6×10^{-3} mol of KI was used in a divided cell. Electricity passed was 2.0 F/mol of **1a** at a constant current of 2.5 mA/cm^2. The products and yields obtained in this system were essentially identical with those obtained previously.$^{1)}$ **2a** was not obtained under the same conditions using undivided cell.

In order to optimize the yield of **2a**, the following experiments were carried out to investigate the influence of supporting electrolyte, solvent, concentrations of substrate and supporting electrolyte, amount of

TABLE 1. EFFECT OF SUPPORTING ELECTROLYTES AND SOLVENTS ON THE ELECTROCHEMICAL CARBOXYLATION OF **1a**[a]

Entry	Supporting electrolyte	Solvent	Yield of **2a**[b] %
1	LiI	DMF	4
2		CH_3CN	c)
3	NaI	DMF	29
4		CH_3CN	8
5	KI	DMF	49
6		CH_3CN	9
7	RbI	DMF	34
8		CH_3CN	c)
9	CsI	DMF	46
10		CH_3CN	c)
11	Bu_4NI	DMF	33
12		CH_3CN	30

a) Catholyte: **1a**(4.7 mmol) in 50 ml of DMF containing of 16 mmol of supporting electrolyte. Mercury pool was used as a cathode. Constant current density, 2.5 mA/cm^2. Electricity, 2.0 F/mol. Temperature, *ca.* 20 °C. b) Isolated yield, based on **1a**. c) It can not be determined, because supporting electrolyte did not solved entirely in CH_3CN.

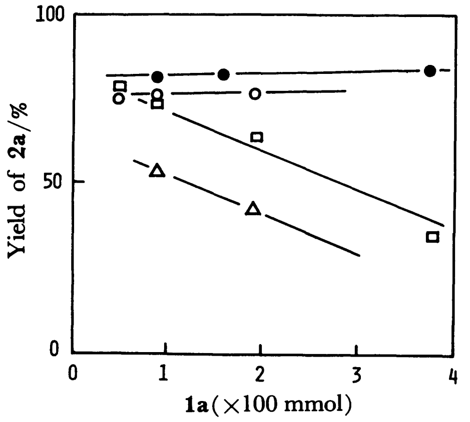

Fig. 1. The influence of the concentration of **1a** on the yield of **2a** under various concentration of KI as a supporting electrolyte.
Concentration of KI: -●-: 85.5 mmol, -○-: 47.0 mmol, -□-: 16.0 mmol, -Δ-: 8.0 mmol.
Divided cell, mercury cathode, 2.0 F/mol, constant current density (2.5 mA/cm^2), solvent dry DMF (50 ml).

electricity, and cathode material. The influence of supporting electrolyte and solvent is shown in Table 1. Under similar experimental conditions, the maximum yield was obtained with KI–DMF system and effect of solvent was larger for alkali metal supporting electrolyte than for tetraalkylanmonium salt such as *n*-Bu_4NI, but remarkable improvement of the yield was not realized under these conditions.

The most significant effect was observed with the concentration of KI and the molar ratio of substrate to KI in KI–DMF system as shown in Fig. 1. The best yield (80%) was obtained when 10 moles of KI per mole of **1a** was used at high concentration of electrolyte, but further increase of the molar ratio showed no effect. In addition, the amount of electricity affected the yield of **2a**. The yield rose upon increasing the amount of electricity up to about 2.5 F/mol and then gradually decreased with excess faraday per mole of **1a**. However, an increase of the amount of polymeric materials as by-products, which were reported in earlier studies,[1] was not observed in the reaction products from the electrolysis of the excess faraday. These observations seem to suggest that good yields are attained by the inhibition of the migration *via* diffusion of a substrate caused by a high potential gradient at low concentration of supporting electrolyte (KI) and prolonged reaction time during the passage of larger amount of electricity.

The influence of cathode materials was found to be none under the same conditions. The employment of graphite plate cathode instead of mercury decreased the yield of **2a** to 14%. In the case of cadmium, platinum, nickel, copper and zinc cathode, a similar electrolysis of **1a** resulted in the formation of tarry materials predominantly and **2a** could not be isolated. On the basis of these experimental results, the current density of 2.5 mA/cm^2, 2.3 F/mol of electricity, DMF as solvent, KI as supporting electrolyte and highly concentrated solution of KI which KI is 10 times or more to the concentration of **1a** were selected as the most suitable synthetic conditions for the electrochemical carboxylation of **1a**. The carboxylic acid, **2a**, could be isolated in 86% yield under the above conditions.

On the other hand, **2a** has been synthesized *via* the reductive carboxylation of **1a** by using alkali metal[3] or radical anion of arylpyridine sodium,[4] benzilic acid rearrangement,[5] solvolytic reaction of diphenylketene,[6] and the reaction of benzoyl cyanide and imines.[7] The reported yields are in the range from 55 to 88% and these methods are very tedious compared with the present method.

This method is proved to be useful by the syntheses of substituted benzilic acids which cannot be easily synthesized by conventional methods.[8–11] The synthesis of twelve benzilic acids (**2b**—**2m**), affording relatively high yield, were carried out under the optimum conditions for the preparative synthesis of **2a**. The application to the syntheses of 4-bromo-, 4-nitro-, 4-hydroxy- and 4-(dimethylamino)benzilic acids were unsuccessful in the reaction system under the conditions employed by us. Resulting benzilic acids are summarized in Table 2 together with some previously reported data for comparison. Present method also indicates superiority in isolated yield over the previously reported one on the synthesis of substituted benzilic acids, as shown in the case of **2i**. All the methylated compounds (**2b**—**2g**) showed high yields in the range of 81—83% yield except the case of **2g**. Methoxy compounds (**2h**—**2i**) were obtained in the range of 64—75% yield. In a series of halogen compounds (**2j**—**2l**), **2k** was obtained in the yield of 92%. It is noteworthy that C–Cl bond cleavage[12] which resulted in a normal

Table 2. Yield, Elemental Analyses and Physical Data b) of Substituted Benzilic Acid a)

Entry	Substituted benzilic acid c)	Isolated yield d) %	Found (Calcd) % C	H	X	IR (KBr) ν/cm^{-1}	Mp(θ_m/°C) Obsd (lit)
13	(**2a**) Unsubstituted	86 (55,60,67,88)	73.21 (73.67)	5.23 (5.30)		3420, 1720	151—152 (150) g)
14	(**2b**) 2-Methyl	83 f)	74.48 (74.36)	5.79 (5.82)		3530, 1710	116—117 (114—115.4) h)
15	(**2c**) 3-Methyl	83 f)	74.49 (74.36)	5.79 (5.82)		3460, 1730	115—118 (118—119) h)
16	(**2d**) 4-Methyl	83 (35,70)	74.58 (74.36)	5.82 (5.82)		3440, 1725	132 (132—133.2) i)
17	(**2e**) 2,4-Dimethyl	81 f)	74.85 (74.98)	6.24 (6.29)		3590, 1700	131—131.5 (129.5—131.5) h)
18	(**2f**) 4,4′-Dimethyl	81 f)	75.14 (74.98)	6.29 (6.29)		3440, 1720	126 (132—133.8) h)
19	(**2g**) 2,4′,5-Trimethyl	10 f)	75.67 (75.53)	6.73 (6.71)		3450, 1725	155—156
20	(**2h**) 4-Methoxy	75 (6,48)	69.57 (69.76)	5.40 (5.46)		3410, 1723	142—144 (147—147.5) j)
21	(**2i**) 4,4′-Dimethoxy	64 (0)	66.84 (66.66)	5.57 (5.60)		3240, 1742	161—163 (165—167) k)
22	(**2j**) 4-Fluoro	88 f)	68.50 (68.29)	4.46 (4.50)		3490, 1725	117—117.5
23	(**2k**) 4-Chloro	92 f)	64.11 (64.01)	4.18 (4.22)	13.47 (13.50)	3460, 1732	129—130 (131) l)
24	(**2l**) 4,4′-Dichloro	73 e) f)	56.62 (56.59)	3.26 (3.39)	23.81 (23.86)	3400, 1710	115—117 (114—115)
25	(**2m**) 4-Phenyl	92 (53, 91)	78.98 (78.93)	5.35 (5.30)		3420, 1725	164—167 (167.2—168.6) m)

a) Catholyte: benzophenones(8.2 mmol) in 50 ml of DMF containing 85.5 mmol of KI, Hg pool cathode, A constant current(2.5 mA/cm^2, 2.3 F/mol) was applied. b) Although NMR signals of OH and COOH in benzilic acids were not ascertained clearly, other signals of phenyl and alkyl displayed proper assignment. The proportions of integration of protons were consistent with the structure of benzilic acids when were integrated as involving two protons of OH and COOH in the phenyl signal. c) The products obtained were identified by a comparison of their physical and IR-spectral data with the literature data. d) Value in parentheses refers to yield of literature data. e) Electrolyzed were carried out with 2.4 mmol of 4,4′-dichlorobenzophenone and 85.5 mmol of KI in 50 ml of DMF. f) Yield has not been described. g) In Ref. 3, 4, 6, and 7. h) In Ref. 8. i) In Ref. 3 and 8. j) In Ref. 3 and 9. k) In Ref. 3, 8, and 10. l) In Ref. 10. m) In Ref. 4, 8, and 11.

electrochemical reduction of 4-chlorobenzophenone in DMF did not occur in our reaction system. In contrast, 4-bromobenzophenone gave **2a** in 30% yield, which resulted from the reductive cleavage of C–Br bond.[12] Also, **2j** was obtained in 88% yield. A synthetically useful intermediate for tick insecticide, **21**, was obtained in the yield of 73% when the reaction was carried out at low concentration of 4,4′-dichlorobenzophenone becauce of its low solubility in DMF. Likewise, **2m** was obtained in 92% yield. These results show that the yields are generally affected by electric effects of substituents. Steric effect is not observed for **2b**—**2d** in a series of methylated compounds. In the case of 4-nitrobenzophenone, the reduction of nitro group took place and the isolated product was 4,4′-dibenzoylazobenzene[13] (60%). 4-Dimethylamino- and 4-hydroxybenzophenone mainly provided tarry products.

The reduction potentials of the first reduction wave of methoxy-, unsubstituted and 4,4′-dichlorobenzophenones were −1.68, −1.63, and −1.52 V *vs.* Ag/AgCl by polarographic measurements in the presence of CO_2. The relationship between Hammett's substituent con-

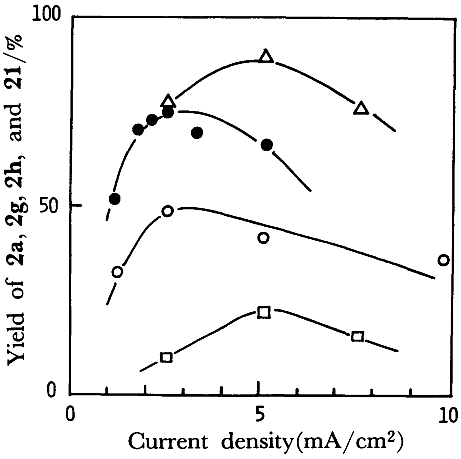

Fig. 2. The relation of the yields of benzilic acids with the current density in the electrochemical carboxylation of substituted benzophenones containing KI (85.5 mmol) in 50 ml DMF using a Hg pool cathode.

-○-: **2a**; **1a** (9.3 mmol), 2.0 F/mol, KI (16.0 mol), -△-: **2h**; 4-methoxybenzophenone (8.2 mmol), 2.3 F/mol, -●-: **21**; 4,4′-dichlorobenzophenone (2.4 mmol), 2.3 F/mol, -□-: **2g**; 2,4′,5-trimethylbenzophenone (8.2 mmol), 2.3 F/mol.

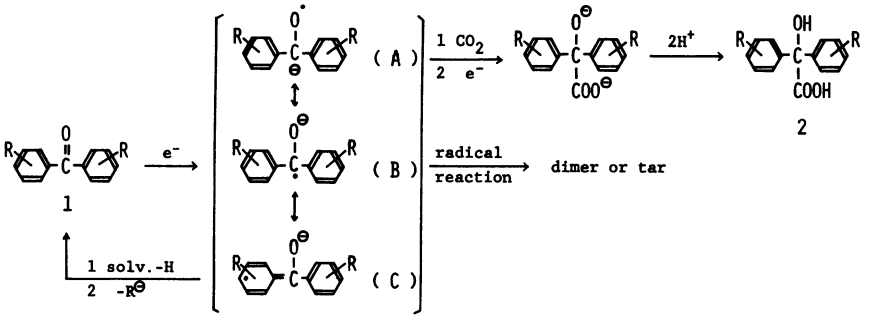

Fig. 3. Reaction scheme.

stants and the reduction potentials is in accord with the result reported with benzophenones.[14] On the assumption that the reduction potentials correspond to the current density, we tried to improve the yield of **2h**, **2g**, and **2l** by changing the current density as shown in Fig. 2. The yield of **2h** increased from 73% to 95% by increasing a current density from 2.5 mA/cm^2 to 5.0 mA/cm^2. In a similar manner the yield of **2g** also increased to 25% but, this value was not so good as expected. The yield of **2l**, which is expected to increase at lower current density, could not be improved by changing the current density above or even below 2.5 mA/cm^2. In addition, similar treatment for the syntheses of 4-bromo- and 4-hydroxybenzilic acid could not produce benzilic acids. Thus it became evident that the influence of the working reduction potential on the product yields is relatively small compared to that of the electronic effect of substituents.

Although it is not completely understood as yet whether the mechanism of the electrochemical carboxylation of aromatic carbonyl compounds proceed through ECEC or EECC path such as successive electrochemical(E) and chemical(C) reaction, it is obvious that the reaction begins with the formation of a ketyl radical by one-electron reduction of a substrate.[15] The electron distributions of a ketyl radical are shown in Fig. 3, and structure A may be predominant when R is electron-withdrawing and structure B may be predominant when R is electron-donating. Thus, benzilic acid may be obtained easily from the substrate having electron-withdrawing substituents *via* successive carboxylation, electrochemical reduction and protonation. In contrast, the substrates having electron-donating substituents have the possibility of radical reactions such as coupling or polymerization, and the yield of benzilic acids may go down. When the substituent moiety is more reactive than carbonyl moiety in the reaction system, the obtained products are not corresponding benzilic acids but some other products as are shown in 4-bromo, 4-nitro, 4-hydroxy, and 4-dimethylamino derivatives.

In conclusion, we found suitable reaction conditions for the synthesis of **2a** through the electrochemical reduction of **1a** in the presence of CO$_2$ in view of preparative points. This method and conditions were successfully applied to the syntheses of some substituted benzilic acids. The results also showed that the electrochemical carboxylation is easily affected by the electronic effects of substituent together with the reduction potential of substrate.

We wish to thank Dr. Chizuko Nishihara of our institute for the measurement of polarography.

References

1) S. Wawzoneck and A. Gundersen, *J. Electrochem. Soc.*, **107**, 537 (1960).
2) Y. Ikeda and E. Manda, *Chem. Lett.*, **1984**, 453.
3) S. Selman and T. F. Eastham, *J. Org. Chem.*, **30**, 3804 (1965).
4) B. Angelo, *Bull. Chem. Soc. Fr.*, **1969**, 1710.
5) D. A. Ballard and W. M. Dehn, *Org. Synth.*, Coll. Vol. I, 29 (1921).
6) I. Lillien, *J. Org. Chem.*, **29**, 1631 (1964).
7) A. Dornow and D. Lupfert, *Chem. Ber.*, **89**, 2718 (1956).
8) C. D. Shacklett and H. A. Smith, *J. Am. Chem. Soc.*, **75**, 2654 (1953).
9) E. R. Bockstahler and D. L. Wright, *J. Am. Chem. Soc.*, **71**, 3760 (1949).
10) A. H. Ford-Moore, *J. Chem. Soc.*, **1947**, 952.
11) F. F. Blicke and N. Grier, *J. Am. Chem. Soc.*, **65**, 1725 (1943).
12) L. Nadio and J. M. Saveant, *J. Electroanal. Chem.*, **30**, 41 (1971).
13) T. Posner, *Chem. Ber.*, **35**, 2343 (1902).
14) P. Zuman, O. Exner, R. F. Pekker, and W. Th. Nauta, *Collect. Czech. Chem. Commun.*, **33**, 3213 (1968).
15) P. H. Given, M. E. Peover, and J. Schoen, *J. Chem. Soc.*, **1958**, 2674; D. E. G. Austen, P. H. Given, D. J. E. Ingram, and M. E. Peover, *Nature*, **182**, 1784 (1958).