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AN ELECTROCHEMICAL SYNTHESIS OF 2-HYDROXY-2-(*p*-ISOBUTYLPHENYL)-PROPIONIC ACID

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The title compound, which is a good precursor of 2-(*p*-isobutylphenyl)propionic acid, was synthesized in 85% yield by the electrochemical reduction of *p*-isobutylacetophenone in DMF containing 0.5 M Bu_4NI on Hg pool cathode by passing 2.0 F/mol electricity with a constant current density of 48.2 mA/cm^2 in the presence of CO_2.

A simple, clean and high yield procedure for the synthesis of 2-hydroxy-2-(*p*-isobutylphenyl)propionic acid (2) would be of great synthetic value, because it is an important precursor for the preparation of 2-(*p*-isobutylphenyl)propionic acid (ibuprofene, an antiinflammatory agent).

The well known chemical method for the synthesis of 2 by the reaction of *p*-isobutylacetophenone (1)[1] with hydrogen cyanide[2] or dichlorocarbene[3] in somewhat troublesome in industrial view. Electrochemical carboxylation of acetophenones already reported[4] but the yield of 2-hydroxy-2-(*p*-substituted phenyl)-propionic acid are not satisfactory in a practical sense and that the reaction of 1 with CO_2 has not been reported. In this communication, we wish to report the high yield electrolytic synthesis of 2 from 1.

$$\underset{1}{p\text{-}i\text{-}C_4H_9C_6H_4COCH_3} \xrightarrow[CO_2]{2e^-} \underset{2}{p\text{-}i\text{-}C_4H_9C_6H_4\overset{CH_3}{\overset{|}{C}}(OH)COOH}$$

The following experimental procedure is typical. The electrolysis was carried out in a H-type glass cell equipped with a bubbler tube for introduction of CO_2 at the cathode compartment. The surface areas of Hg pool cathode and Pt anode were 9.6 cm^2 and 4.0 cm^2, respectively. Each 50 ml of DMF containing 9.2 g Bu_4NI was placed into the both compartments, and 1 (0.88 g, 5×10^{-3}mol) was added to the cathode compartment. Under a fine stream of CO_2 and vigorous stirring at the cathode, the solution of 1 was electrolyzed under a constant current density of 48.2 mA/cm^2 at 0 °C until 2.0 F/mol of electricity was passed. Removal of DMF from catholyte under reduced pressure was followed by the addition of water (30 ml), filtering off a supporting electrolyte, and the oily product was separated from the aqueous solution by acidifying it with hydrochloric acid. The oily product was extracted with ether (150 ml) and dried over magnesium sulfate. Evaporation of ether gave a crude pale yellow solid which was recrystallized from n-hexane to afford 0.94 g (85%) of 2 with satisfactory spectral characteristics.[5]

As shown in Table 1, the yield of 2 remarkably depends on the electrolysis conditions. Variation of temperature (0 to 25 °C), amount of electricity (2 to 3 F/mol), solvent (DMF to CH_3CN) and cathode material (Hg to C plate) always reduced

Table 1. Electrolytic conditions for the preparation of 2[a)]

Entry	Cathode material	Solvent	Supporting electrolyte	Temp °C	Electricity F/mol	Yield of 2[b)] %
1	Hg	DMF	KI	0	2.0	7
2	Hg	DMF	Bu_4NI	0	2.0	85
3	Hg	DMF	Bu_4NBr	0	2.0	84
4	Hg	DMF	Bu_4NCl	0	2.0	c)
5	Hg	DMF	Bu_4NBF_4	0	2.0	32
6	Hg	DMF	Bu_4NHSO_4	0	2.0	c)
7	Hg	DMF	Bu_4NI	25	2.0	73
8	Hg	DMF	Bu_4NI	0	3.0	18
9	Hg	CH_3CN	Bu_4NI	0	2.0	68
10	C	DMF	Bu_4NI	0	2.0	10

a) Catholyte; *p*-isobutylacetophenone (5×10^{-3}mol) and supporting electrolyte (2.5×10^{-2}mol) in 50 ml of solvent. The reaction was carried out at constant current density of 48.2 mA/cm^{-2}, which showed the maximum yield of 2 through control experiments.
b) Isolated yields are based on 1.
c) Uncrystallized viscous liquid was obtained, but not further investigated.

the yield in the range 7 - 73%. Among various kinds of supporting electrolyte, Bu_4NI was the most effective one on improving the yield of 2 in our system. However, it is interesting that, when Bu_4NCl or Bu_4NHSO_4 was used a supporting electrolyte, 1 mainly gave a considerable amount of a highly viscous liquid which could not be crystallized. Although the reason for the phenomenon is not clear at present, we are further investigating the scope and limitation of electrochemical carboxylation of aromatic ketones.[6)]

References

1) 1 was prepared from *p*-isobutylbenzene by the method of G. Baddeley et al.; G. Baddeley and E. Wrench, J. Chem. Soc., 1956, 4943.
2) Y. Yamada, Japan Kokai 95035(1976).
3) S. Kudo, Japan Kokai 111534(1978); 90237(1977); Y. Yamada, ibid., 34744(1978); Y. Ikeda and E. Manda, Nippon Kagaku kaishi, 1982, 830.
4) S. Wawzonek and A. Gunderson, J. Electrochem. Soc., 107, 537(1960). The reported yields of 2-hydroxy-2-phenylpropionic acid and 2-hydroxy-2-(*p*-methoxyphenyl)propionic acid were 3.6% and trace, respectively.
5) Physical properties of 2 is as follows; mp 110 - 111 °C, Found: C, 70.43; H, 8.09%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. IR(KBr) 3445 cm^{-1} (O-H), 1743 cm^{-1} (C=O), ^{1}H-NMR($CDCl_3$) δ 0.9 (6H, d, J=6 Hz), 1.5 - 2.2 (1H, m), 1.8 (3H, s), 2.4 (2H, d, J=7.5 Hz), 5.8 - 6.7 (2H, bs), 7.13 (2H, d, J=8 Hz), 7.4 (2H, d, J=8 Hz).
6) Y. Ikeda, E. Manda, and T. Shimura, Abstr. No.749, 48th National Meeting of the Chemical Society of Japan, Sapporo, August 1983.

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