A Novel Synthesis of 2-Aryllactic Acids via Electrocarboxylation of Methyl Aryl Ketones

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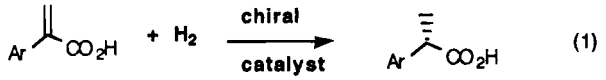
Received July 20, 1994

Introduction

In recent years there has been increased interest in the development of economical processes for the production of 2-arylacrylic acids which can be asymmetrically hydrogenated to the corresponding chiral 2-arylpropionic acids.[1–5]



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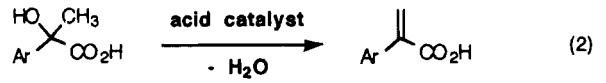
A handful of 2-arylpropionic acids including (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen) and 2-(*p*-isobutylphenyl)propionic acid (ibuprofen) constitute an important class of anti-inflammatory drugs.[6]

One of the most convenient methods of preparing 2-arylacrylic acids is via the acid-catalyzed dehydration of the corresponding 2-aryllactic acids.[2,7]



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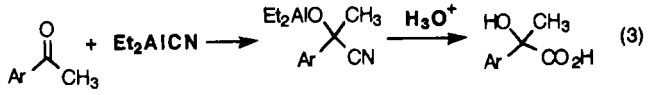
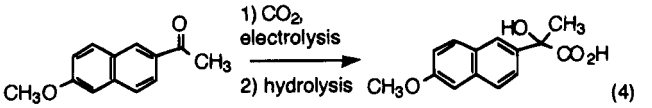
Traditionally 2-aryllactic acids can be prepared via the corresponding cyanohydrins.[7]



(3)

However, the need of using highly toxic cyanides makes this chemistry less attractive, particularly for the production of pharmaceutical materials which are for human consumption. Alternatively the 2-hydroxycarboxylic acid can be prepared via the electrocarboxylation of the corresponding methyl aryl ketones. In 1984 Ikeda *et al.* reported the electrocarboxylation of methyl aryl ketones with a mercury cathode, glass frit divided cell, and platinum anode.[8] While the reported yields were quite high, the system was impractical for its development into a commercially useful process. (The use of the highly toxic mercury cathode was environmentally unacceptable and the use of a divided cell substantially increased the cost of production.) These authors also reported that changing electrode materials substantially decreased the yields of the desired products. In order to make the chemistry practical and commercially useful, it is desirable to develop a high-yield system with an undivided cell. In this paper we report a highly effective synthesis of 2-aryllactic acids via the electrocarboxylation of methyl aryl ketones using an undivided cell with a sacrificial aluminum anode. The use of a sacrificial anode eliminates the problems of the cathodic reactions.[9–15] Our focus is to develop a convenient method for the preparation of 2-(6-methoxy-2-naphthyl)lactic acid (**1**) and 2-(*p*-isobutylphenyl)lactic acid (**2**), the useful intermediates for the preparation of naproxen and ibuprofen, respectively.



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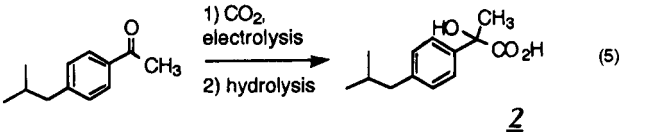

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Since the carboxyl functionality of the product comes from carbon dioxide instead of cyanide, this new process is safer and more economical than the traditional methods.

Results and Discussion

In a typical electrocarboxylation reaction we used a lead foil cathode and an aluminum foil anode. The sacrificial anode dissolved during the reaction, providing the aluminum cation for the carboxylate product. Carbon dioxide was bubbled into the system to maintain a CO_2-saturated solution. For more convenient, larger scale synthesis, we also used a flow-cell reactor which could be operated under higher CO_2 pressure. For the convenience of product analysis, the electrocarboxylation product (i.e., the aluminum salt of the 2-carbonato-2-arylcarboxylic acid) was hydrolyzed to the 2-aryllactic acid which was then analyzed by ^{1}H NMR and HPLC.

In our initial study of the electrocarboxylation of 2-acetyl-6-methoxynaphthalene, we found that the selectivity for the desired 2-(6-methoxy-2-naphthyl)lactic acid was quite sensitive to the reaction media and the reaction conditions. Among common solvents, *N*,*N*-dimethylformamide was found to be most effective for the reaction, probably due to the higher solubility of the

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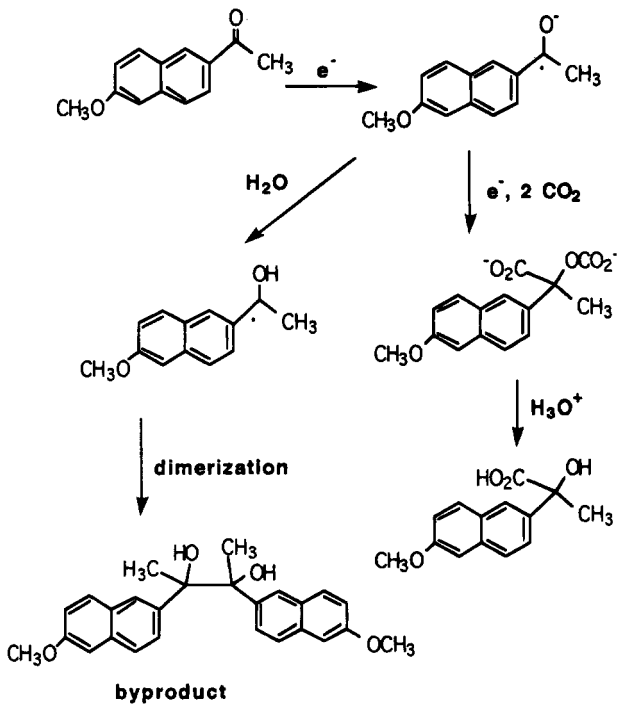
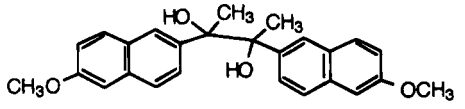


Figure 1. A proposed mechanism for the electrocarboxylation of methyl aryl ketone.

electrocarboxylation product in this solvent. In acetonitrile and less polar solvents, the carboxylation product precipitated on the electrodes during the reaction and caused severe byproduct formation. The most noticeable byproduct in this reaction was the pinacol type dimer (**3**).



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The percentage of this dimer in the final product mixture increased significantly in the presence of protic agents such as water and alcohols. The formation of the dimer was suppressed when a higher concentration of carbon dioxide was used. It was quite possible that competing reactions took place as depicted in Figure 1.

The increased dimerization in the presence of a protic agent could be explained as follows. In the initial step of the reaction the ketone took up an electron from the cathode to become an anionic radical which had less tendency to dimerize, owing to the effect of charge repulsion. In the presence of a protic agent, the anionic radicals were protonated to form neutral hydroxyl radicals which dimerized to form the pinacol type byproduct. For this reason it was important to use dry, nonprotic solvents for the electrocarboxylation of ketones. When a higher concentration of carbon dioxide was used, the radical intermediate was more rapidly trapped and converted to the desired product. The higher concentration of CO_2 was achieved by using lower reaction temperature and/or higher CO_2 pressure. Lower concentration of the substrate in the reactor also gave better selectivity for the desired product. This was consistent with the alleviation of the dimerization problem. From a practical standpoint, particularly for the industrial application of this technology, it was desirable to use reasonably high payload in the reaction. To achieve this goal and to alleviate the dimerization problem, we modified the method by using slow, continuous feeding of the substrate into the reaction system. With this modification, high productivity could be achieved even though the substrate concentration in the reactor was kept quite low during the reaction. Typical results of this reaction are summarized in Table 1.

Table 1. Electrocarboxylation of 2-Acetyl-6-methoxynaphthalene[a]

entry	conc (g/mL)	P_{CO_2} (psig)	temp (°C)	time (h)	conv (%)	yield (%)[b]
1	10	atm.	35	6	85	80
2	10	atm.	0	6	84	92
3[c]	10	atm.	0	6	80	82
4[d]	20	60	35	1.5	85	91
5[d]	80	60	25	6	84	80
6[d]	80[e]	60	25	6	82	91
7[d]	80[e]	60	35	6	83	90

[a] Aluminum anode; lead cathode; electrolyte = Bu_4NBr (0.1 M); volume of solvent = 400 mL for entry 1–3; volume of solvent = 900 for entry 4–7. [b] Analytical yield based on converted starting material. [c] Current = 0.6 A; current density = 10 mA/cm^2. [d] Current = 6 A; current density = 20 mA/cm^2. [e] Slow addition of substrate by syringe pump.

Table 2. A Comparison of the Effect of Electrolytes in the Electrocarboxylation of 2-Acetyl-6-methoxynaphthalene[a]

electrolyte	conversion (%)	yield of **1**[b]
Bu_4NBr	82	91
Et_4NBr	82	87
LiBr	72	87
KBr	40	38

[a] Aluminum anode; lead cathode; total amount of substrate = 80 g, slow addition by a syringe pump; concentration of electrolyte = 0.1 M; total volume = 900 mL; reaction temperature = 25 °C; pressure of carbon dioxide = 60 psig; current = 6 A; reaction time = 6 h. [b] Based on the converted starting material.

Table 3. Electrocarboxylation of *p*-Isobutylacetophenone[a]

entry no.	temp (°C)	P_{CO_2} (psig)	conv (%)	yield (%)[b]
1[c]	25	65	95	90
2[d]	25	65	94	99
3[d]	30	65	97	98
4[d]	35	75	98	98

[a] Aluminum anode; lead cathode; electrolyte = Bu_4NBr (0.1 M); solvent = DMF (900 mL); current = 6 A. [b] Based on the converted starting material. [c] All the substrate (100 g) was added at the beginning of the reaction; reaction time = 4 h. [d] The substrate was slowly added (over a period of 4 h) to the reactor by a syringe pump; total reaction time = 5 h.

The nature of the electrolyte had an important influence on the selectivity of the electrolysis. Among common electrolytes, tetrabutylammonium bromide gave the best results. Tetraethylammonium bromide and lithium bromide were slightly less effective; however, other metal halides such as potassium bromide and sodium bromide were much inferior and gave lower yields of the desired carboxylation product. A comparison of the effect of these electrolytes under similar conditions is summarized in Table 2.

The electrocarboxylation of methyl *p*-isobutylphenyl ketone was very similar to the electrocarboxylation of 2-acetyl-6-methoxynaphthalene. The yields of the desired product, 2-(*p*-isobutylphenyl)lactic acid (after hydrolysis), were even higher (Table 3). (Analytical yields greater than 95% based on the converted starting material were routinely obtained.)

On the basis of these experimental results, we believe that the electrocarboxylation of alkyl aryl ketones can be used conveniently either in laboratory or in large-scale production of 2-hydroxy-2-arylcarboxylic acids.

Experimental Section

Synthesis of 2-(6-Methoxy-2-naphthyl)lactic Acid with a Simple Stirred Reactor. A typical procedure for electrocarboxylation was as follows. A 60 cm^2 aluminum foil anode and a 60 cm^2 lead foil cathode were placed in a 1 L glass kettle into which was added 10 g of 2-acetyl-6-methoxynaphthalene, 13 g of tetrabutylammonium bromide (electrolyte), and 400 mL of DMF (anhydrous grade). A stream of dry CO_2 was continuously introduced into the mechanically stirred homogeneous solution which was maintained at about 0 °C. A constant current of 0.6 A was maintained during the reaction (current density = 10 mA/cm^2). After 6 h of reaction, the power supply was turned off and the solution was transferred to a 2-L round-bottomed flask. A small solution sample was hydrolyzed with concentrated hydrochloric acid and the ^1H NMR spectra of the hydrolyzed product showed 84% conversion of the starting 2-methoxynaphthalene with 92% selectivity to 2-(6-methoxy-2-naphthyl)lactic acid. The DMF solvent was stripped in a rotary evaporator until a viscous residue was obtained. The residue was stirred well in 500 mL of toluene for about 5 h. (Most of the unconverted starting material was found in the organic solution.) The mixture was filtered and the solid was stirred well in 500 mL of 5% aqueous hydrochloric acid for 5 h. The white powder was filtered and washed three times with 100 mL water. The white solid was then air-dried to give 8.7 g of 2-(6-methoxy-2-naphthyl)lactic acid.

Acknowledgment. We thank John Matthew and William Stultz of Monsanto Corporate Research for their excellent assistance in the construction of the flow-cell reaction system. A generous gift of *p*-isobutylacetophenone from Boots Chemicals is greatly appreciated. A. S. C. Chan also thanks the National Science Council, R. O. C., for a grant which supports his collaborative research in Taiwan.

JO941242I