Electrochemical synthesis of precursors of non-steroidal anti-inflammatory agents

J Damodar, R Ramesh Raja & S Jayarama Reddy*7

Electrochemical Research Laboratories, Department of Chemistry, S.V.University, Tirupati 517 502, India
E-mail: jreddy_s@yahoo.com

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In recent years, there has been increased interest in the development of economical processes for the production of α-hydroxyarylpropionic acids from α-hydroxy acids. α-Aryl-2-propionic acids including 2-(p-isobutylyphenyl)propanoic acid (Ibuprofen) and 6-methoxy-2-naphthylpropionic acid (Naproxen) constitute an important class of non-steroidal anti-inflammatory drugs which can be synthesised from α-hydroxy acids. The earliest studies of electrocatalysis of alkyl aryl ketones reported a low yield of carboxylated products from acetophenones and later it was shown that acetophenone could be electrochemically carboxylated with considerable yields in an undivided cell using an oxalate electrode.

Traditionally 2-hydroxy-2-arylpropionic acids can be prepared via the corresponding cyanhydrins using hydrogen cyanide. However, need of using highly toxic cyanides makes this process less attractive and somewhat troublesome from the point of view of industry, particularly for the production of pharmaceutical materials which are for human consumption. Alternatively, the 2-hydroxypropionic acids can be prepared via the electrocarboxylation of the corresponding alkyl aryl ketones with a mercury cathode in a divided cell. In this process, use of mercury was highly toxic and the use of a divided cell substantially increased the cost of production and decreased the yields of desired products. In order to develop a convenient and commercially useful synthetic method of drugs, it is desirable to develop a high yield system with an undivided cell, performing electrochemical carboxylations.

The influence of the reaction conditions on product yields of the electrocarboxylation of alkyl aryl ketones have been the objective of present investigation. In this communication, we report the synthesis of 2-hydroxy-2-arylpropionic acids via electrochemical carboxylation of alkyl aryl ketones using an undivided cell with a platinum cathode and magnesium anode in DMF as supporting electrolyte using DMF as solvent.

Materials and Methods

Apparatus

For the preparative electrolysis, the electrochemical cell of capacity 100 mL volume was equipped with a platinum cathode (20 cm²) and magnesium anode (20 cm²) arranged with the carbon dioxide inlet, outlet tubes. The two electrodes were separated by 1 cm and connected to a DC power supply. The electrolysis measurements were carried out using potentiostat (Model: PS-603). Cyclic voltammetric measurements were carried out using 757 VA computrace (Herisau, Switzerland) controlled by computer running electrochemical analysis software, output was a Hewlett-Packard 2240 low terminal. The voltammetric cell assembly was teflon coated small volume cell with hanging mercury drop electrode (HMDE) as working electrode, Ag/AgCl as reference electrode and Pt wire as auxiliary electrode. 0.01 M substrate and 0.1 M supporting...
electrolyte (TBAI) were prepared with DMF and cyclic voltammograms were taken at scan rate of 50 mV s\(^{-1}\). G.C analysis was performed with a Shimadzu 14B gas chromatograph (flame-ionisation detector) equipped with SE-30 columns.

**Electrochemical carboxylation**

A DMF (50 mL) solution of \( p \)-isobutylacetophenone (1 g) containing TBAI (4.6 g) was placed in the electrolysis cell equipped with a platinum cathode and magnesium anode. Atmospheric pressure of carbon dioxide gas was introduced into the mechanically stirred homogeneous solution which was maintained at 5° C and was electrolysed at constant current density of 10 mA cm\(^{-2}\) until 2 F mol\(^{-1}\) of electricity was passed.

A one-electron reduction of aryl alkyl ketone gave radical anion. This radical anion attacks carbon dioxide followed by the addition of second electron to give carboxylate anion. The capture of carboxylate anion by magnesium ions, which are generated by dissolving of the anode, would give stable magnesium complex. Acid hydrolysis of the complex followed by ether extraction gave the crude acid (Chart 1).

The electrolysed solution was taken into a round bottom flask and DMF was removed under reduced pressure by a rotatory evaporator followed by the addition of water, filtering off a supporting electrolyte. The product was isolated from the aqueous solution by acidifying it with hydrochloric acid. The product was extracted with ether and dried over anhyd. magnesium sulfate. Evaporation of the ether gave yellow solid, which was recrystallised from pet. ether to afford a 0.84g of 2-hydroxy-2-(\( p \)-isobutylphenyl) propanoic acid and a similar procedure was applied for electrochemical synthesis of 2-hydroxy-2-(6-methoxynaphthyl)propanoic acid with 89% yield with following physical and spectral characteristics:

**2-Hydroxy-(\( p \)-isobutylphenyl)propanoic acid.**

m.p. 112-13°C; \(^1\)H NMR (CDCl\(_3\)) : \( \delta \) 0.9 (d, 6H, CH\(_3\)X2), 1.5 -2.35 (m, 1H, -CH), 1.75 (s, 3H, -CH\(_3\)), 2.5 (d, 2H, -CH\(_2\)), 7.1 -7.42 (m, 4H, H\(_{arom}\)), 9.2 (s, 1H, -OH), 11.6 (s, 1H, -COOH).

**2-hydroxy-2-(6-methoxynaphthyl)propanoic acid.**

m.p. 169-70°C; \(^1\)H NMR (CDCl\(_3\)) : \( \delta \) 2.1 (s, 3H, -CH\(_3\)), 3.8 (s, 3H, -OCH\(_3\)), 7.05 -7.75 (m, 6H, H\(_{arom}\)), 9.5 (s, 1H, -OH), 11.5 (s, 1H, -COOH).

The chemical structure and reaction sequences, which is the subject of this study, are shown in Scheme I.

**Analysis**

In this study, G.C analysis was mainly performed to identify any by-products present in the electrolysed solution. For this, the resulting electrolysis solution was poured into an aq. sodium bicarbonate solution, neutralised with conc. hydrochloric acid and extracted with ether. The organic layer was washed with water, dried over sodium sulfate and subjected to G.C analysis. However, for G.C analysis only peaks corresponds to product and reactant are observed, no other by-products were found and the identification of the products was based on the G.C retention time.

**Results and Discussion**

In a typical electrochemical carboxylation reaction, platinum cathode and magnesium anode were used,
carbon dioxide was bubbled into the system to maintain a CO₂ saturated solution. In our study of the electrochemical carboxylation of p-isobutylacetophenone and 2-acetyl-6-methoxynaphthalene, selectivity of the desired products i.e 2-hydroxy-2-(p-isobutylphenyl)propanoic acid and 2-hydroxy-(6-methoxy-2-naphthyl)propanoic acid were found to be quite sensitive to the nature of the solvents, supporting electrolyte and the cathode material.

Among common solvents, DMF is found to be most effective for the reaction, probably due to the higher solubility of the carboxylation product in this solvent. In acetonitrile (CH₃CN) or less polar solvents, the carboxylation product precipitated on the electrode during the reaction and there is a possibility of by-product formation like pinacol type dimer. This is because the starting alkyl aryl ketone takes one electron from the cathode to become an anion radical in the presence of protic solvents; the anion radicals get protonated to form neutral hydroxyl radical which dimerises to form the pinacol type by-products. This decreases the product yields and that can be minimised when high pressure of CO₂ is used. For this reason, it is important to use dry, non-protic solvents for the electrocarboxylation of alkyl aryl ketones. Lower concentration of the substrate also gave better reactivity for the desired product. This was consistent with the alleviation of the dimerisation problem. Among the common electrolytes, TBAI gave good results. TEAI is slightly less effective; however NaI and KI were much inferior and gave lower yields of the carboxylated product. Pt was found to be more suited as cathode compared to Cu. The use of alternate cathode material lead to poorer yields except for Pt. This suggests that the other by-products must be significantly reduced when Pt cathode is used. A comparison of the effect of these solvents, supporting electrolytes and cathode material on electrocarboxylation is summarised in Table I.

Table I represents the list of results that clearly demonstrates the wide scope of synthetic applications of the process and describes the influence of the solvent, supporting electrolyte and cathode. The results show that this electrocarboxylation can be successfully applied to various classes of ketones. The proc-

<table>
<thead>
<tr>
<th>Supporting Electrolyte</th>
<th>Cathode</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>DMF</td>
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<tr>
<td></td>
<td></td>
<td>CH₃CN</td>
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<td>CH₃CN</td>
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<td></td>
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</tbody>
</table>

* Isolated yields
ess appears to be particularly convenient to prepare some products of industrial interest, such as pharmaceuticals having anti-inflammatory activity.

**Cyclic voltammetry**

Cyclic voltammetric determination of $p$-isobutylacetophenone in DMF containing TBAI was carried out at HMDE. The reduction peak occurs at -1.50V vs. Ag/AgCl and the reduction is reversible indicating that the reduction product of $p$-isobutylacetophenone is stable radical anion. The difference in cathodic and anodic peak potential i.e. $E_{pa} - E_{pc} = 0.6V$. Addition of CO$_2$ to the solution causes increase in cathodic current, an anodic shift in peak potential and elimination of the reversible anodic current (as evidenced by the absence of a corresponding anodic peak). This is due to the second charge transfer step arising by the reduction of the radical anion to the dianion. This indicates a fast reaction of $p$-isobutylacetophenone radical anion with carbon dioxide followed by the addition of second electron (Figure 1).

The electron distribution of alkyl aryl ketyl radical anion in the presence of CO$_2$ is as follows:

\[
\text{Ar-C-CH}_3 + e^- \rightarrow \text{Ar-C-CH}_3 \quad \text{(i) CO}_2 \\
\text{Ar-C-CH}_3 \quad \text{(ii) } e^+ \quad \text{CO}_2
\]

**Conclusions**

It has been shown that the electrochemical carboxylation of $p$-isobutylacetophenone and 2-acetyl-6-methoxynaphthalene to precursors of Ibuprofen and Naproxen were found to give good yields at suitable reaction conditions in the presence of CO$_2$. This reaction may be carried out with good yields at fairly high current densities by changing the variables including cathode material, electrolyte, solvent, temperature, pressure and payload. This study may give an idea to develop commercial process. Since the carboxyl functionality of the product comes from carbon dioxide instead of cyanide, this process is safer, pollution free, environment friendly and more economical than the traditional methods.

**References**