Synthesis of aryl-2-propionic acids by electrocarboxylation of methyl aryl bromides

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Abstract
Electrochemical carboxylation of methyl aryl bromides in the presence of carbon dioxide at atmospheric pressure using a platinum cathode and a magnesium anode at a constant current density of 10 mA/cm^2 gave the corresponding aryl-2-propionic acids in 80-84% isolated yields.

Keywords: Aryl-2-propionic acids, methyl aryl bromides, electrocarboxylation, carbon dioxide

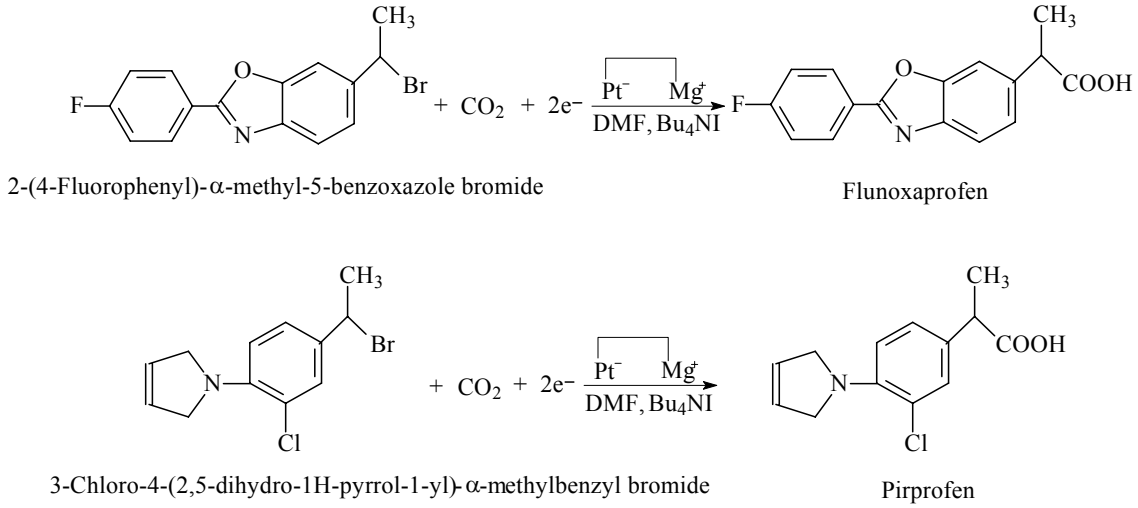
Introduction

Electrochemical carboxylation is one of the most useful methods for the fixation of carbon dioxide into organic substrates. Electrochemical carboxylation takes efficiently place using a reactive metal anode such as magnesium.[1] Aryl-2-propionic acids including flunoxaprofen and pirprofen constitute an important class of non-steroidal, anti-inflammatory drugs.[2] These are used to cure cold, fever and inflammation in various musculoskeletal disorders, menstrual cramps, and body pains.[3-9] The conventional synthesis of these drugs reported in the literature,[10,11] has certain drawbacks such as the formation of hazardous chemicals like cyanides, and low yields due to high temperatures required, which make these methods inefficient. In this paper, we report the synthesis using an electrochemical approach.

Results and Discussion

The electrochemical carboxylation of organic halides is a promising procedure for the synthesis of carboxylic acids, in the field of carbon-carbon bond formation involving carbon dioxide with a platinum cathode and a magnesium anode.[12,13] Thus, an organic halide can be reduced to the corresponding anion, which then nucleophilically adds to carbon dioxide resulting in carbon-

carbon bond formation.[14-16] The reaction sequence and mechanism of this study is shown in Scheme 1.



Scheme 1

In this mechanism, the reaction starts with the formation of an intermediate carbanion by two-electron reduction of methyl aryl bromides, which attacks carbon dioxide to give the carboxylate anion. Capture of the anion by metal ions generated by the dissolution of the anodic metal gives a metal carboxylate. Finally, treatment of the metal carboxylate with acid gives aryl-2-propionic acids. The conditions that favour good yields of the products are low concentrations of the substrate and a proper selection of the cathode material. For the electrosynthesis, a high concentration of the substrate was not successful. Because, the product started to deposit at the

cathode, the voltage between anode and cathode increased dramatically. A lower concentration allowed the electrosynthesis to proceed at a constant current with a good yield without any deposit at the cathode. This process appears to be particularly convenient to prepare products of industrial interest, such as pharmaceuticals having anti-inflammatory activity.

Experimental Section

General Procedures. Precursors of flunoxaprofen (2-(4-fluorophenyl)-α-methyl-5-benzoxazole bromide) and pirprofen (3-chloro-4-(2,5-dihydro-1H-pyrrol-1-yl)-α-methyl benzyl bromide) were prepared according to the published procedure.[17,18] Electrochemical carboxylation was carried out in an undivided cell equipped with a platinum cathode and magnesium anode. The cell was charged with 50 mL of dimethylformamide (DMF) solution containing reagent grade 0.04 M tetrabutylammonium iodide (Bu_4NI) and 2-(4-fluorophenyl)-α-methyl-5-benzoxazole bromide (20 mmol) was added to the cell. Then the cell was immersed in cold water to dissipate the heat evolved by the electrolysis and to keep the temperature near 5 ^{0}C. Before electrolysis, the oxygen in the system was removed by passing nitrogen gas through the solution. After that, the stirred mixture was saturated by bubbling carbon dioxide through the solution. In this saturated solution, the system was electrolyzed by supplying regulated DC power at 10 mA/cm^2 until 2 F/mole has been passed through the cell under 5 ^{0}C. Usual work up of the electrolyzed solution afforded flunoxaprofen in 80% yield.

The synthesis of pirprofen was also achieved in 84% yield by the similar method.

The carboxylated products are characterized by ^{1}H NMR and IR.

Flunoxaprofen. M.p. 162-164 ^{0}C, ^{1}H NMR ($CDCl_3$): δ = 1.45 (d, 3H, J=6.2Hz), 3.52-3.65 (q, 1H, J=6.2Hz), 7.12-7.74 (m, 7H, Ar-H), 11.74 (brs, 1H); IR (neat): ν = 1715 cm^{-1} (see ref. 11).
Pirprofen. M.p. 96-98 ^{0}C, ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, 3H, J=5.9Hz), 3.97-4.12 (q, 1H, J=5.9Hz), 4.36-4.68 (m, 4H), 6.34-6.68 (m, 5H, Ar-H), 11.73 (brs, 1H); IR (neat): ν = 1720 cm^{-1} (see ref. 18).

The electrochemical carboxylation was carried out using a platinum cathode in a DMF solution containing a supporting electrolyte (Bu_4NI) with different substrate concentrations. The experimental results presented in table 1, demonstrate the variation in the yields of product due to changes in the initial concentrations of the substrate.

Table 1. Electrochemical carboxylation of methyl aryl bromides [a,b,c]

Expt. No.	Temp. (^{0}C)	Substrate concentration (g/dm^3)	Yield (%)[d]	
			Flunoxaprofen	Pirprofen
1	5	2.0	82	84
2	5	4.0	80	82
3	5	6.0	76	79
4	5	8.0	68	73

[a] Pco_2 = 1 atm, [b] Current density = 10 mA/cm^2, [c]Charge passed = 2 F/mol, [d] Isolated yields.

Conclusions

The electrochemical carboxylation of methyl aryl bromides gives aryl-2-propionic acids with good yields when the electrolysis is performed in an undivided cell with constant current density of 10 mA/cm^2 using platinum cathode and sacrificial magnesium anode. This process is safer, pollution free, environment friendly and more economical than the traditional methods.

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