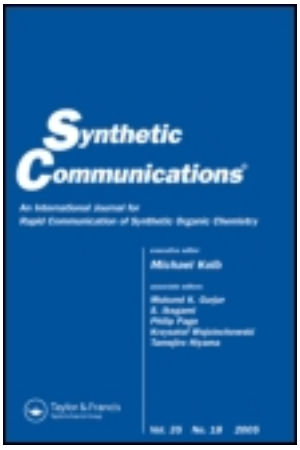

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Electrosynthesis of 2-Arylpropionic Acids from α-Methylbenzyl Chlorides and Carbon Dioxide by [Co(Salen)]

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Abstract: The electrochemical synthesis of the 2-arylpropionic acid group of nonsteroidal anti-inflammatory agents such as ibuprofen, naproxen, indoprofen, biprofen, cicloprofen, and fenoprofen has been carried out in dimethylformamide (DMF) containing tetra-n-butylammonium perchlorate (nBu_4NClO_4) by electrochemical carboxylation of α-methylbenzyl chlorides catalyzed by a schiff-base complex [Co(salen)] in an undivided cell equipped with a platinum cathode and magnesium anode under constant current density of $10\,mA/cm^2$ in good yields. Cyclic voltammetric studies have also been carried out to investigate the mechanism by which [Co(salen)] catalyzes the cathodic reaction of α-methylbenzyl chlorides in presence of CO_2 by taking α-phenylethylchloride as the model compound.

Keywords: Benzyl chloride, carbon dioxide, carboxylic acid, cobalt complex, cyclic voltammetry

INTRODUCTION

Electroreductive carboxylation of organic halides with CO_2 is an interesting method for the synthesis of carboxylic acids.[1–6] Catalytic systems based

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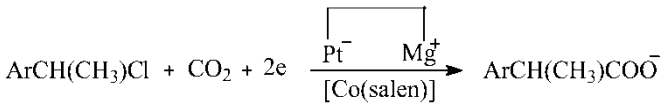
on transition-metal complexes have been proposed to improve the yield of electrocarboxylations. The electrochemistry of the cobalt complexes has been extensively studied and it has been shown that the cobalt(I) complexes have strong nucleophilic properties with a stable cobalt–carbon bond commonly resulting from the reactions with electrophiles and it is well known that nucleophilic cobalt(I) complexes readily react with organic halides to give the corresponding organometallic complexes.[7] Electrochemical reaction of these complexes has been investigated by several groups and the electrochemical carboxylation of organic halides including benzylic and allylic chlorides has been shown to be catalyzed by [Co(salen)] (salen = N,N′-bis[salicylidenethane-1,2-diamine).[8–11] The use of low-valent-metal complexes as catalysts makes the reduction of organic halide easier. The electrochemical studies have shown that Co(salen) in its reduced form, cobalt(I), permits the catalytic reduction of organic halides. Fauvarque et al.[12–14] reported the syntheses of the 2-arylpropionic acid class of nonsteroidal anti-inflammatory agents through electrocarboxylation of α-methylbenzyl chlorides by using nickel complexes. As part of our continuing studies on the electrochemical carboxylation of k-methylbenzyl chlorides using transition-metal catalysts,[15] to improve the yield of electrocarboxylations, we carried out the electrocarboxylation of k-methylbenzyl chlorides using the schiff base Co(salen) catalyst. In this communication we describe the synthesis and mechanism of electrochemical carboxylation of k-methylbenzyl halides in DMF catalyzed by Co(salen) in a CO_2 saturated solution in an undivided cell equipped with a platinum cathode and a magnesium anode under a constant current density of $10\,mA/cm^2$.



EXPERIMENTAL

Electrolyses were carried out using Potentiostat (model PS 605). Melting points were determined on Mel-Temp apparatus and are uncorrected. ^{1}H NMR was recorded on a Varian EM-360. IR spectra were recorded on a Perkin-Elmer 1600. Cyclic voltammetric measurements were carried out with a Metrohm unit 757VA Computrace at hanging mercury drop electrode (HMDE) of area 0.15 mm and Ag/AgCl as the reference electrode. Solvent DMF was distilled over CaH_2. nBu_4NClO_4 (Fluka) was recrystallized from ethanol. The model compound α-phenylethyl chloride[16] and the precursors of ibuprofen,[17] naproxen,[17] indoprofen,[18] biprofen,[17,19] cicloprofen,[20] and fenoprofen[17] as α-methylbenzyl

chlorides were prepared according to the literature. The complex [Co(salen)] was prepared as described in the literature.[21]

Electrochemical Carboxylation

Electrolysis was carried out in an undivided cell equipped with a Pt cathode and a Mg anode. The cell was first charged with 50 ml of solvent DMF containing nBu_4NClO_4 (4 mmol) as the supporting electrolyte. Then, the starting halide 1-chloro-1-(4-isobutylphenyl)ethane (a precursor of ibuprofen) (20 mmol) was added to the cell, followed by a catalyst [Co(salen)] (1 mmol). Before electrolysis, the O_2 in the system was removed by passing N_2 gas through this solution. After that, the solution was saturated by bubbling CO_2 for 1 h. In this saturated state, the system was electrolyzed at a constant current density of $10\,mA\,cm^{-2}$ until $2\,F\,mol^{-1}$ had been passed through the cell at 5°C. Usual workup of the electrolyzed solution afforded 2-(4-isobutylphenyl)-propionic acid (ibuprofen) in 83% isolated yield.

2-(4-Isobutylphenyl)propionic acid (ibuprofen): mp 75–76°C (lit.[22] mp 70–72°C); IR (neat): $\nu = 1700\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.1$ (d, 6H, J = 4.8), 1.5 (d, 3H), 1.75–1.95 (dd, 1H), 2.45 (d, 2H), 3.68 (q, 1H, J = 4.8), 7.0–7.3 (m, 4H), 11.56 (s, 1H).

2-(6-Methoxy-2-naphthyl)propionic acid (naproxen): mp 156–157°C (lit.[23] mp 160–161°C); IR (neat): $\nu = 1720\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.6$ (d, 3H, J = 4.7), 3.86 (q, 1H, J = 4.7), 3.92 (s, 3H), 7.02–7.7 (m, 6H), 11.57 (s, 1H).

2-[4-(1-Oxo-2-isoindolinyl)phenyl]propionic acid (indoprofen): mp 212–213°C (lit.[18] mp 213–214°C); IR (neat): $\nu = 1690\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.37$ (d, 3H, J = 7.0), 3.68 (q, 1H, J = 7.0), 5.0 (s, 2H), 7.2–8.0 (m, 8H), 11.65 (s, 1H).

2-(2-Biphenyl)propionic acid (biprofen): mp 145–146°C (lit.[24] mp 147–148°C); IR (neat): $\nu = 1700\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.46$ (d, 3H), 3.65 (q, 1H), 6.97–7.44 (m, 9H), 11.52 (s, 1H).

2-(2-Fluorene)propionic acid (cicloprofen): mp 184–185°C (lit.[25] mp 181–183°C); IR (neat): $\nu = 1710\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.43$ (d, 3H), 3.2 (s, 2H), 3.74 (q, 1H), 7.14–7.63 (m, 7H), 11.54 (s, 1H).

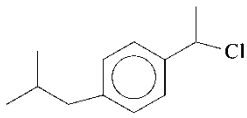
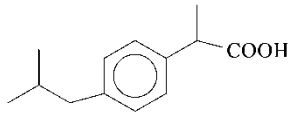
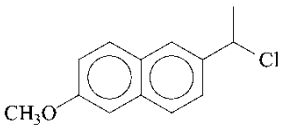
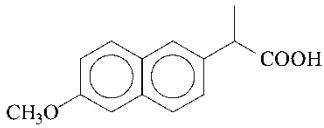
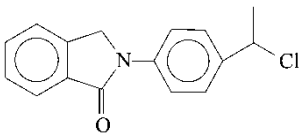
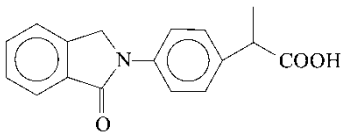
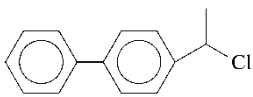
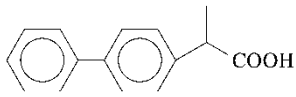
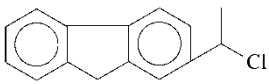
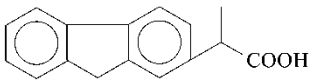
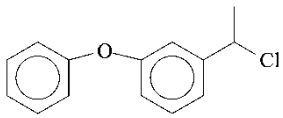
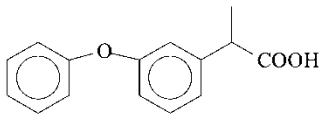
2-(3-Phenoxyphenyl)propionic acid (fenoprofen): bp 168–169°C (lit.[26] bp 168–171°C); IR (neat): $\nu = 1720\,cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.50$ (d, 3H), 3.71 (q, 1H), 6.92–7.50 (m, 9H), 11.54 (s, 1H).

RESULTS AND DISCUSSION

The electrochemical carboxylation of precursors of ibuprofen, naproxen, indoprofen, biprofen, cicloprofen, and fenoprofen were examined under various

electrolytic conditions. The proper choice of cathode material was found to have a large effect on the electrocarboxylation on the α-methylbenzyl chlorides at higher concentrations. Although the acids were obtained in very low yields when an Ni, Cu, or C cathode was used, the product started to deposit at the cathode except for Pt. For example, ibuprofen was obtained in lower yields with Ni (75%), Cu (67%), and C (60%) compared with Pt (83%) as cathodes. A current density of $10\,mA/cm^2$ was accessible and consumption of $2\,F/mol$ of halide was required for efficient carboxylation. For efficient electrolysis, DMF is considered to be a good solvent because of the

Table 1. Electrochemical synthesis of 2-arylpropionic acids[a]

$ArCH(CH_3)Cl$	$ArCH(CH_3)COOH$	Yield (%)[b]
		83
		80
		86
		85
		84
		78

[a] $ArCH(CH_3)Cl = 20\,mmol$, $Co(salen) = 1\,mmol$, $nBu_4NClO_4 = 4\,mmol$, $DMF = 50\,ml$, current density $= 10\,mA\,cm^{-2}$, electricity $= 2\,F\,mol^{-1}$, $PCO_2 = 1\,atm$. cathode = Pt, anode = Mg.

[b] Isolated yields.

$$[Co(II)L] + e^- \longrightarrow [Co(I)L]^-$$

$$[Co(I)L] + RX \longrightarrow [RCo(III)L] + X$$

$$[RCo(III)L] + e^- \longrightarrow [RCo(II)L]^-$$

$$[RCo(II)L]^- + CO_2 \longrightarrow RCO_2^- + [Co(II)L]$$

Scheme 1.

higher solubility of the acid in this solvent. Less concentrated solutions allowed the electrolysis to proceed with a good yield without deposition at the cathode. The presence of the catalyst influenced the chemical yield. Table 1 gives the results of electrocarboxylation of α-methylbenzyl chlorides catalyzed by Co(salen) at the Pt cathode and Mg anode. The increase in the yield of 2-arylpropionic acids in presence of Co(salen) when compared with using $PdCl_2(PPh_3)_2$[15] may be due to the strong nucleophilic properties of Co(I) complexes.

This electroreaction of arylalkylhalide with CO_2 catalyzed by [CoL] has a different mechanism and the probable reaction pathways of the present electrochemical carboxylation are shown in Scheme 1. In electrolysis, the central cobalt of [CoL] was electroreduced from [Co(II)L] to $[Co(I)L]^-$,

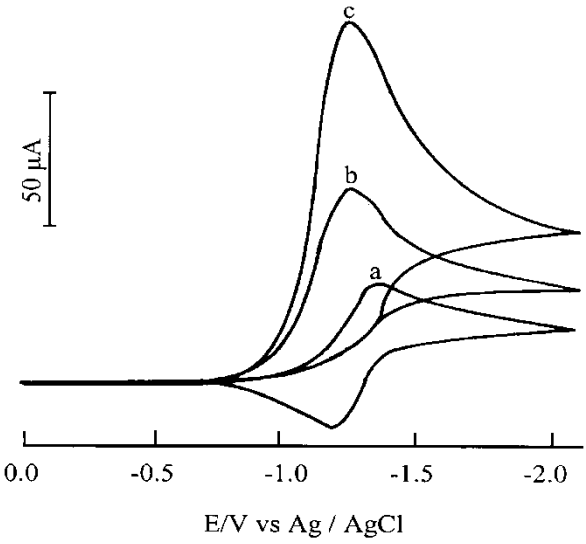


Figure 1. Cyclic voltammograms of (a) 1 mmol [Co(salen)], (b) as (a) +10 mmol $PhCH(CH_3)Cl$, (c) as (b) in presence of CO_2 in DMF + 10 mmol nBu_4NClO_4 at HMDE at 0.2 V/s.

which is the actual catalyst of the reaction. The formed $[Co(I)L]^-$ anion possesses strong nucleophilicity. The first step of the electrocatalytic reaction of arylalkylhalide (RX) is the oxidative addition of electrogenerated $[Co(I)L]^-$ to form organometallic complex [RCo(III)L]. One electron reduction of organometallic complex [RCo(III)L] gives the unstable species $[RCo(II)L]^-$. The decomposition of $[RCo(II)L]^-$ in the presence of CO_2 was the key step in the reaction. This step may consist of a direct attack of CO_2 on $[RCo(II)L]^-$ followed by bond breaking to give carboxylate and [Co(II)L].

Cyclic Voltammetry

The cyclic voltammetry of [CoL] in DMF containing nBu_4NClO_4 as the supporting electrolyte shows a reversible peak at $E_p = -1.28$ V vs Ag, or AgCl at 0.2 V/s. Addition of $PhCH(CH_3)Cl$ to this strongly modifies the voltammetric pattern of the complex. The cathodic peak shifted to less negative potentials and its anodic peak completely disappears. This indicates that the chemical reaction occurs between $[Co(I)L]^-$ and $PhCH(CH_3)Cl$. When CO_2 is passed to the solution, the reduction peak of the organocobalt complex is substantially enhanced. Figure 1 shows cyclic voltammogram of [CoL] in the presence of $PhCH(CH_3)Cl$ under CO_2.

CONCLUSIONS

It can be observed that, when carried out in the presence of CO_2, the electrochemical reduction of α-methylbenzyl chlorides catalyzed by [CoL] leads to the corresponding 2-arylpropionic acids in good yields.

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