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Nickel catalysed electrosynthesis of anti-inflammatory agents. Part I — Synthesis of aryl-2 propionic acids, under galvanostatic conditions

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Aryl-2 propionic acids such as fenoprofen and ibuprofen, which are anti-inflammatory agents, are synthesized by electrolysing a solution of $ArCH(CH_3)Cl$ in the presence of carbon dioxide and a nickel catalyst. The electrolyses are carried out galvanostatically in an undivided cell at a large scale of 50 mmol in 100 ml of solvent (e.g. tetramethylurea). Conversion rates close to 80% and chemical yields up to 85% are achieved. Electrolyses can be performed without catalyst.

1. Introduction

Aryl-2 propionic acids, $ArCH(CH_3)CO_2H$ are non-steroidal anti-inflammatory agents [1–3]. We have already reported an electrochemical synthesis of such compounds, starting from $ArCH(CH_3)Cl$ and carbon dioxide, catalysed by an electrogenerated zerovalent nickel complex, according to the reaction [4, 5]

$$ArCH(CH_3)Cl + CO_2 + 2e^- \xrightarrow[10\%]{NiCl_2(dppp) + COD} ArCH(CH_3)COO^- + Cl^-$$

The best catalyst was $NiCl_2(dppp)$ (dppp = $PPh_2CH_2CH_2CH_2PPh_2$) associated to one equivalent of a labile coligand COD (1,5-cyclo-octadiene). The electrolyses were carried out in a laboratory divided cell, on a small scale, 10 mmol (0.1 M), at a controlled potential. The solvent was a mixture of THF and HMPA (hexamethylphosphorotriamide). The anodic reaction was the oxidation of lithium oxalate: $Li_2C_2O_4 \longrightarrow 2Li^+ + 2CO_2 + 2e^-$.

Since aryl-2 propionic acids are interesting drugs we attempted to develop such electrosyntheses on a large scale more suited to industrial production. Thus, the electrosyntheses had to be carried out in an undivided cell (separators are expensive and lead to significant ohmic drop and consequently to important Joule heating effects), with a constant current instead of a controlled potential which needs expensive potentiostats. The electrolyses had to be performed in concentrated solutions (0.5 to 1 M) using cheap and non-toxic solvents instead of HMPA. The electrodes had to be as large as possible in order to work with high currents, as close as possible to decrease ohmic drop, and made of an easily fabricated and cheap material. Furthermore, the amount of catalyst had to be minimized.

We report here results concerning electrosyntheses of aryl-2 propionic acids under galvanostatic conditions. In every case, oxidation of lithium oxalate is the anodic reaction. Other procedures using sacrificial anodes have also been described [6–8].

2. Experimental details

Electrolyses were carried out using a stabilized power supply Sodilec PB Autorange (1.5 A 60V). Analytical HPLC were performed on a LKB apparatus equipped with a UV detector set at 254 nm. More details on these HPLC analyses will be published [9]. H^1 NMR were recorded on a JEOL PM60. IR spectra were recorded on a PERKIN ELMER IR 450.

Electrolyses were carried out under anhydrous conditions. Solvents were distilled just prior to the electrolyses. HMPA was distilled over $LiAlH_4$, NMP, DMF, DMA and TMU over CaH_2 [10], and THF over sodium-benzophenone.

$NiCl_2(dppp)$ was synthesized according to the literature [11]. Precursors of naproxen [12–14], ibuprofen [14], cicloprofen [14–16], biprofen [16, 17], indoprofen [18] were synthesized according to published work. The fenoprofen precursor was synthesized by a Grignard reaction of CH_3MgBr on commercial *m*PhO-Ph-CHO (Janssen) and then conversion of the resulting alcohol to chloride using concentrated HCl [14].

Electrolyses were carried out in the cell described in Fig. 1. The cell was first charged with 100 ml of solvent containing nBu_4NBF_4 0.04 M as supporting electrolyte [19]. The solution was saturated by bubbling

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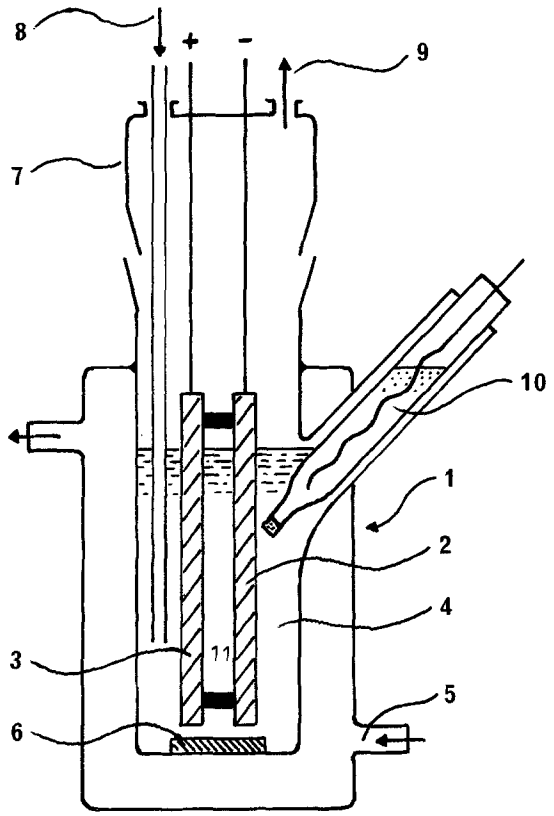


Fig. 1. (1) Cell; (2) cathode, graphite plate or nickel foam plate (20 cm^2); (3) anode, graphite plate (20 cm^2); (4) solution to be electrolysed, 100 ml; (5) cooling liquid; (6) magnet stirrer; (7) cap; (8) CO_2 bubbling; (9) gas exit; (10) reference, Ag($AgClO_4$ 0.1 M in THF); (11) distance between the two electrodes = 0.9 cm.

carbon dioxide. Then the starting halide was added to the cell, followed by the catalyst, the coligand and lithium oxalate. After cooling the cell to 0° C, the chosen current was applied and the electrolysis was conducted at a suitable constant current until (when possible) 3 Faradays per mol had been passed through the cell. The potential between the cathode and the anode was recorded. This was generally constant except when a deposit appeared at the cathode. A millivoltmeter between the cathode and the reference electrode (Ag/$AgClO_4$ 0.1 M in THF) permitted a check that the value of the cathodic potential was not more negative than −2.7 V.

Products were generally isolated for analyses. Treatment of the solution with an aqueous basic solution (NaOH 1 M) and extraction with ether, separated the aryl-2 propionic acid from the starting material and non-polar by-products, which were in the ethereal phase. After evaporation of ether, $ArCH(CH_3)Cl$ and $ArCH_2CH_3$ were identified by H^1 NMR. The basic solution containing the aryl-2 propionic acid as the sodium carboxylate was acidified by aqueous HCl (6 M). The aryl-2 propionic acid was extracted with ether. After evaporation of ether, we obtained the pure aryl-2 propionic acid which was characterized by the usual methods, IR, H^1 NMR and mass spectra. Spectra of fenoprofen [2], ibuprofen [2, 14], naproxen [2], cicloprofen [20], biprofen [20] and indoprofen [18], were consistent with the literature.

When TMU was employed as solvent, it was better to evaporate the solvent before treatment with aqueous NaOH.

3. Results and discussion

3.1. *Electrosynthesis of phenyl-2 propionic acid*

Preliminary tests were performed on $PhCH(CH_3)Cl$.

$$PhCH(CH_3)Cl + CO_2 + 2e^- \xrightarrow[10\%]{NiCl_2(dppp) + COD} PhCH(CH_3)COO^- + Cl^-$$

We attempted to carry out the electrolysis in an undivided cell, first at a controlled potential and then at a constant current. Results in Table 1 are compared to those obtained in a divided cell (entry 1) as previously described [5].

These experiments demonstrate the possibility of synthesizing phenyl-2 propionic acid in an undivided cell working with a constant current, controlled by a simple power supply. The chemical yield is good. The current efficiency is not as good as in a divided cell, due to the oxidoreduction of intermediate nickel complexes or, maybe, to the reduction of carbon dioxide (we checked that, in the mixture THF + HMPA, carbon dioxide was electroreducible at −2.8 V against Ag/Ag^+).

Each electrosynthesis reported hereafter was carried out in an undivided cell with a constant current. For this purpose, a new cell was built as shown in Fig. 1.

The anode and the cathode were two plates of equal area (20 cm^2). The distance between them was constant and was chosen to be as short as possible in order to minimize the ohmic drop. The cell could be fitted with a reference electrode only to insure that, when working with a constant current, the cathodic potential was not too high and close to −2.6 V which is the reductive potential of $PhCH(CH_3)NiCl(dppp)$ suggested as an intermediate [5].

Electrolyses were performed on larger scales (Table 2). The value of the applied current was chosen in order to have a cathodic potential of −2.7 V. The electrolysis was stopped when 3 Faradays per mol of starting material had been passed through the cell.

When carrying out the electrolysis on 20 mmol

Table 1. Results in divided and undivided cells

Entry	*Cell*	*Controlled potential* V	*Constant current* mA	F mol^{-1}	RCOOH (*isolated*) τ %	Rc %	R_F %
1	A	−2.6	–	1.92	100	89	93
2	B	−2.6	–	2.54	100	80	63
3	B	–	200	2.6	85	90	59

(A) divided cell; (B) undivided cell; (τ) conversion rate; (Rc) chemical yield (isolated acid); (R_F) current efficiency.
Solvents: THF and HMPA (2-1) 70 ml containing nBu_4NBF_4 0.1 M. PCO_2 = 1 atm. T = 0° C. $Li_2C_2O_4$ = 10 mmol. $PhCH(CH_3)Cl$ = 10 mmol. $NiCl_2(dppp)$ = 1 mmol. COD = 1 mmol; *Cathode*: carbon fibre; *Anode*: graphite plate, 20 cm^2.

Table 2. Larger scale electrolysis

Entry no.	RCl mmol	Catalyst mmol	I mA	F mol^{-1}	RCOOH (isolated) τ %	Rc %	R_F %
4	3 × 20	1	500	3	90	75	45
5	100	1	500	3	100	77	51
6	100	0	500	3	100	77	51
7	20	0	180	2	72	76	55

Solvent: THF + HMPA (2-1), 100 ml nBu$_4$NBF$_4$ = 0.1 M; *Cathode*: graphite; *Anode*: graphite; R = PhCH(CH$_3$)-. [$Li_2C_2O_4$] = 1.5[RCl]. PCO_2 = 1 atm. T = 0° C.

(entry 4), we checked by voltammetry at a gold microelectrode that, at the end of the electrolysis, nickel catalyst was still present and electroreducible. It was effectively possible to charge the cell twice more with 20 mmol of PhCH(CH$_3$)Cl and $Li_2C_2O_4$ and to carry out the electrolysis again. The electrolysis in entry 5 was performed on a larger scale (100 mmol in 100 ml of solvent) with only 1% of catalyst. A concentration of the starting material of 1 M could be profitably used in industrial reactors.

Surprisingly we found that it was also possible to electrosynthesize PhCH(CH$_3$)CO$_2$H with a good chemical yield without catalyst, when running the electrolysis at large concentration, 1 M (entry 6). When working with a smaller concentration 0.2 M (entry 7), we also obtained the acid without catalyst, but in that case we could only apply a current of 180 mA instead of 500 mA in the presence of catalyst (entry 4). In order to explain this phenomenon, we ran voltammetry at the graphite macroelectrode of the cell, on solutions containing PhCH(CH$_3$)Cl alone and in the presence of the catalyst $NiCl_2$(dppp) + COD. When the catalyst was added to the solution, we first electrogenerated the zerovalent nickel complex which is the actual catalyst of the reaction:

$$NiCl_2(dppp) + COD + 2e^- \longrightarrow (COD)Ni(dppp) + 2Cl^-$$

After that, voltammetry was performed.

As already described, this complex can react with PhCH(CH$_3$)Cl [5]:

$$(COD)Ni^0(dppp) + PhCH(CH_3)Cl \longrightarrow PhCH(CH_3)NiCl(dppp) + COD$$

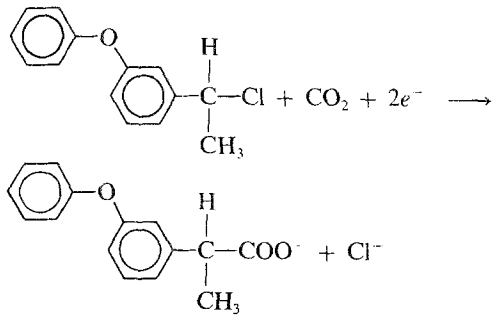
This intermediate is electroreducible and then reacts with carbon dioxide to give phenyl-2 propionic acid

$$PhCH(CH_3)NiCl(dppp) + CO_2 + 2e^- \longrightarrow PhCH(CH_3)CO_2^- + Cl^- + Ni^0(dppp)$$

The voltammograms are shown on Fig. 2. Curves a and b show that, for a high concentration of PhCH(CH$_3$)Cl, 1 M, currents at −2.7 V are about the same with or without catalyst. When the concentration of PhCH(CH$_3$)Cl is smaller (0.2 M), the current at −2.7 V is higher in the presence of the catalyst (curves c and d). Curves a and c show the beginning of the reduction wave of PhCH(CH$_3$)Cl at a macroelectrode, the magnitude of which is dependent on the PhCH(CH$_3$)Cl concentration, at a given potential. In the presence of a catalyst (1 mmol in both cases), we get the reduction waves of PhCH(CH$_3$)NiCl(dppp) (curves b and d). These two waves have about the same magnitude because of their dependence on the nickel concentration. When the concentration of PhCH(CH$_3$)Cl is low, the current at −2.7 V is higher in the presence of the catalyst and the electrolysis can be carried out within a shorter time. So the role of the catalyst is to accelerate an electrochemical reaction possible without it, i.e. to reduce the time necessary for an efficient electrosynthesis.

We have shown that it is possible to electrosynthesize PhCH(CH$_3$)CO$_2$H in an undivided cell with a constant current. Electrolyses can be carried out with highly concentrated solutions with or without catalyst. These experimental conditions were then applied to synthesize fenoprofen and ibuprofen which are commonly used anti-inflammatory agents.

3.2. *Electrosynthesis of fenoprofen*



Preliminary experiments on the electrosynthesis of fenoprofen, conducted in an undivided cell with a

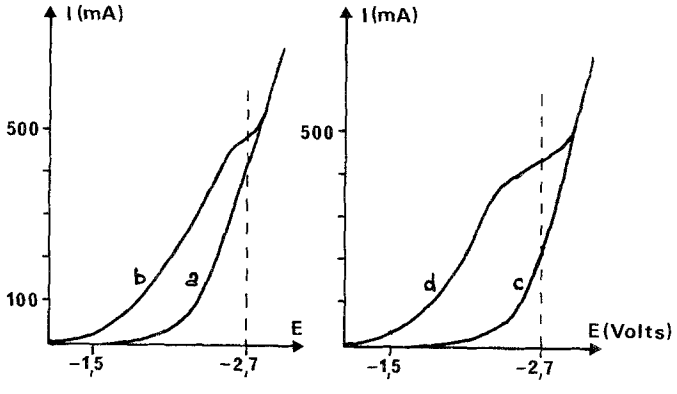


Fig. 2. Voltammograms at a graphite macroelectrode (S = 20 cm^2) at a sweep rate of 250 mV min^{-1} on a stirred solution of: (a) 100 mmol of PhCH(CH$_3$)Cl; (b) (a) + 1 mmol of $NiCl_2$(dppp) + COD; (c) 20 mmol of PhCH(CH$_3$)Cl; (d) (c) + 1 mmol of $NiCl_2$(dppp) + COD; 100 ml of THF + HMPA (2-1). nBu$_4$NBF$_4$ 0.1 M. Reference: Ag/AgClO$_4$, 0.1 M in THF.

Table 3. The difference in the use of a nickel foam cathode and of graphite

Entry	RCl mmol	*Catalyst* %	*Cathode* 20 cm^2	*I* mA	F mol^{-1}	*Fenoprofen (isolated)*		
						τ %	Rc %	R_F %
8	100	0	Graphite	340 ↘	2.3	76	75	50
9	50	0	Graphite	200	2.6	100	72	55
10	50	2	Graphite	400	2.6	83	69	44
11	50	0	Nickel	500	2.6	92	90	64

Anode: graphite plate; *Solvent*: 100 ml of THF + HMPA (2-1); $n$$Bu_4NBF_4$ = 0.04 M; ↘ = deposit at the cathode.

constant current, as described for the synthesis of $PhCH(CH_3)CO_2H$, showed that it was possible to decrease the amount of the supporting electrolyte $n$$Bu_4NBF_4$ from 0.1 M to 0.04 M without negative influence on the yields of the reaction.

3.2.1. Influence of the cathode. For industrial purposes, it is important to convert the starting reagent as quickly as possible which implies, conducting the electrolysis with the highest possible current density, compatible with a good current efficiency and reasonable polarization at the cathode. Table 3 shows that a nickel foam cathode can be used instead of graphite and permits an electrosynthesis of fenoprofen with an excellent conversion rate and chemical yield (entry 11) even without catalyst. In this case the apparent current density had been multiplied by 2.5 (entries 9 and 11) for the same cathodic potential of −2.7 V, and the current efficiency is better. Of course the current efficiency is not as high as achievable when conducting the electrolysis at very low current density.

An electrolysis conducted with a highly concentrated solution of mPhO–Ph–$CH(CH_3)Cl$, 1 M, was not very successful (entry 8). Fenoprofen started to deposit at the cathode and consequently, the voltage between the anode and the cathode increased dramatically. When the power supply limit was reached (60 V), the current decreased. But less concentrated solutions, 0.5 M, allowed the electrosyntheses to proceed with a constant current and gave fenoprofen with a good conversion rate and chemical yield without any deposit at the cathode.

3.2.2. Influence of the solvent. HMPA is not considered as a good industrial solvent, so we attempted to perform these electrolyses in other solvents. When conducting the electrolyses at a nickel foam cathode in solvents such as acetonitrile, acetone, 2-butanone and ethylacetate, fenoprofen was formed with only a poor conversion rate and a low chemical yield with or without catalyst. In most cases, fenoprofen deposited at the cathode.

Comparison of results obtained when using aprotic dipolar solvents are given in Table 4.

Aprotic dipolar solvents such as DMF, DMA, NMP are not suitable for our purpose. Fenoprofen deposits at the cathode. But TMU, tetramethylurea can be used, when pure, without a cosolvent (entries 17–19). Yields are not as good as in the mixture THF + HMPA but nevertheless, this non-toxic solvent permits the synthesis of fenoprofen with a good chemical yield (entry 18) without any deposit at the cathode. In that case, mPhO–Ph–CH_2CH_3 was detected as a by-product.

The voltage between the anode and the cathode was recorded and was constant during the electrolyses, its value depending on the intensity and the solvent (I = 400 mA, V = 35 volts in THF + HMPA; V = 23 volts in TMU).

Table 4. Results when using aprotic dipolar solvents

Entry	*Solvent*	*I* mA	F mol^{-1}	*Fenoprofen (isolated)*		
				τ %	Rc %	R_F %
11	THF-HMPA*	500	2.6	92	90	64
12	DMF	500 ↘	1.2	62	53	55
13	THF-DMF*	500 ↘	1.3	66	50	51
14	THF-DMA*	500 ↘	–	43	63	–
15	NMP	400 ↘	1.5	59	75	59
16	THF + TMU*	400 ↘	2.7	76	55	31
17	TMU	300	2.6	76	71	42
18	TMU	400	2.8	78	82	46
19	TMU	500	2.4	67	81	45

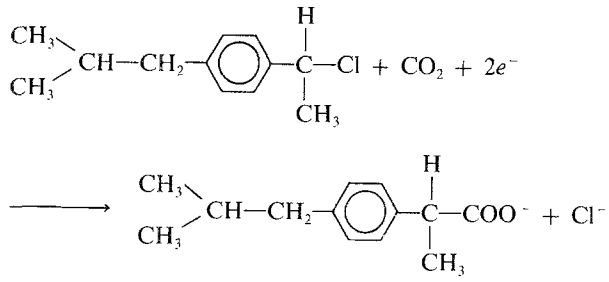
* Mixture (2-1) in volume; ↘ deposit at the cathode; mPhO–Ph–$CH(CH_3)Cl$ = 50 mmol; $Li_2C_2O_4$ = 65 mmol; *Solvent*: 100 ml $n$$Bu_4NBF_4$ = 0.04 M; *Cathode*: nickel foam; *Anode*: graphite.
DMF = dimethylformamide. DMA = dimethylacetamide. NMP = N-methylpyrrolidone. TMU = tetramethylurea.

Table 5. Influence of the solvent and the cathode

Entry no.	*Solvent*	*Cathode*	*I* mA	F mol^{-1}	*Ibuprofen (isolated)*		
					τ %	Rc %	R_F %
20	THF-HMPA	nickel	400	3	87	57	33
21	TMU	nickel	400	3	87	50	28
22	TMU	carbon felt	400	3	74	61.5	30
23	TMU	graphite	300	3	76	72	35

*p-i*Bu–Ph–$CH(CH_3)Cl$ = 50 mmol; $Li_2C_2O_4$ = 75 mmol; *Solvent*: 100 ml nBu_4NBF_4 = 0.04 M; *Anode*: graphite; Yields are determined by HPLC; Reaction without catalyst. PCO_2 = 1 atm. T = 0° C. The cathodic potential was −2.7 V against Ag/Ag^+.

3.3. *Electrosynthesis of ibuprofen*

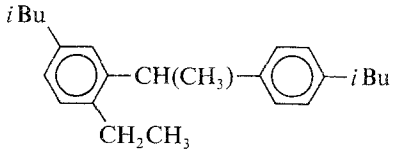


The electrosyntheses of ibuprofen were first conducted under the experimental conditions found to be the best for the synthesis of fenoprofen (entry 18, Table 4).

3.3.1. Influence of the solvent and the cathode. Results in the mixture THF + HMPA and in TMU were similar and in every case, chemical yields of ibuprofen were always lower than those of fenoprofen, because of the formation of by-products. HPLC analyses showed the presence of *p-i*Bu–Ph–CH_2CH_3 from 3 to 8% and three other by-products very close on the HPLC chromatogram. One of them was identified as *p-i* Bu–Ph–$CH(CH_3)$–$CH(CH_3)$–Ph-*p-i* Bu. One diastereoisomer was obtained by the reaction:

*p-i*Bu–Ph–$CH(CH_3)Cl$ + Mg
⟶ *p-i*Bu–Ph–$CH(CH_3)MgCl$
+ *p-i*Bu–Ph–$CH(CH_3)$–$CH(CH_3)$–Ph-*p-i*Bu

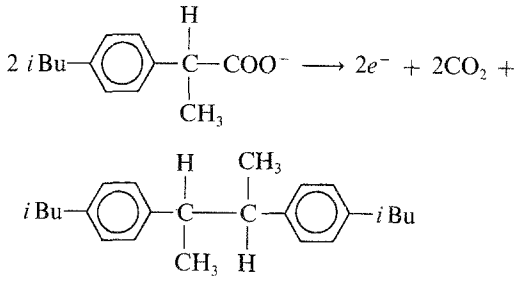
when conducted at room temperature. The other by-products were supposed to be the second diastereoisomer and the dimer



as suggested by Casanova [10].

3.3.2. Formation of the dimers [*p-i*Bu–Ph–$CH(CH_3)$]$_2$. These by-products may come from two different electrochemical reactions:

Kolbe anodic decarboxylation. Since the electrolyses were conducted in an undivided cell, the dimers may be produced at the end of the electrolysis by a decarboxylation at the anode:



To check this hypothesis, an electrolysis was performed until 8 Faradays per mol had been passed through the cell. Ibuprofen was always the main product present in the solution and the yield of the dimers had not increased.

An oxidation of pure *p-i*Bu–Ph–$CH(CH_3)CO_2Li$ did not produce any dimers after 1.5 Faradays per mol had been passed through the cell. So, dimers were not formed by a Kolbe anodic reaction.

Table 6. Influence of p-iBu-Ph-CH(CH_3)Cl concentration

Entry no.	RCl mmol	*I* mA	F mol^{-1}	*Ibuprofen (isolated)*			*Dimers*	RH %
				τ %	Rc %	R_F		
24	50	250	3	80	46	24	yes	
25	50	400	3	87	50	28	yes	
26	50	400[a]	3	76	68	34	yes	
27	20	300	3	56	87	33	no	6
28	20	400	3	66	85	37	no	5

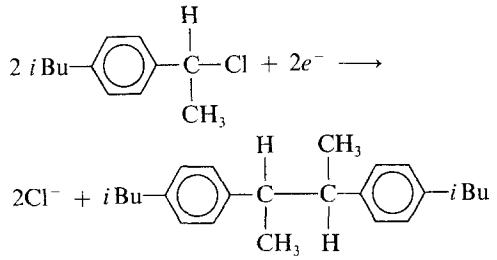
RCl = *p-i*Bu–Ph–$CH(CH_3)Cl$; *Solvent*: TMU; nBu_4NBF_4 = 0.04 M; *Cathode*: nickel foam; *Anode*: graphite, PCO_2 = 1 atm. T = 0° C, except (a) where T = −5° C. Reactions without catalyst.

Table 7. Influence of the catalyst

Entry	RCl mmol	*Catalyst* %	*Ibuprofen (isolated)*			*Dimers*	RH %
			τ %	Rc %	R_F		
25	50	0	87	50	28	yes	
29	50	2	83.5	62	34	yes	
28	20	0	65	85	37	no	5
30	20	5	51	90	31	no	2

3 F mol^{-1}. I = 400 mA; Catalyst: 1 mmol of $NiCl_2$(dppp) and 1 mmol of COD; PCO_2 = 1 atm. T = 0° C; *Solvent*: TMU, 100 ml; *Cathode*: nickel foam: *Anode*: graphite.

Cathodic reaction. The dimers may arise from a reductive dimerization of the starting halide.



When electrolysing a solution of *p-i* Bu–Ph–$CH(CH_3)Cl$ in the absence of carbon dioxide, we obtain the dimers with a total yield of 85%. These results agree with Casanova's work [10].

This secondary reaction could possible be avoided by working with less concentrated solutions, by adding a catalyst which is thought to favour the carboxylation or by increasing the carbon dioxide pressure.

3.3.3. Influence of p-iBu–Ph–$CH(CH_3)Cl$ concentration. Entry 26 shows the beneficial effect of lower temperature on the chemical yield, but we are limited by the freezing point of tetramethylurea. When working on concentrated solutions of *p-i* Bu–Ph–$CH(CH_3)Cl$, 0.5 M, the chemical yield is not good because of the formation of dimers. With less concentrated solutions, 0.2 M (entries 27, 28), chemical yields are better and the formation of the dimers has been completely eliminated.

3.3.4. Influence of the catalyst. Since the formation of the dimers is not catalysed by nickel complexes [5], the presence of the catalyst should favour the carboxylation. The presence of a catalyst is effectively beneficial on the chemical yield, for high concentrated solutions 0.5 M, but better yields are obtained when conducting the experiments at lower concentrations (entries 28, 30, Table 7).

3.3.5. Influence of carbon dioxide pressure. The electrolyses under carbon dioxide pressure were performed in a special undivided cell of 300 ml, at the SNPE research laboratory at Le Bouchet. The graphite electrode area was 40 cm^2 and the electrolyses were carried out with a constant current of 800 mA, with the same current density (2 A dm^{-2}) as in our experiments (Table 7, entry 30). No catalyst was used. Results in Table 8 show that electrolysis under carbon dioxide pressure enhances the chemical yield of ibuprofen. It was possible to work with more concentrated solutions, 0.5 M, and no dimers were formed. Results of entries 34 and 35 show that in these conditions, ibuprofen can be synthesized with yields comparable to fenoprofen. In that case, dimethylformamide can be used as well as tetramethylurea.

3.4. *Electrosynthesis of various anti-inflammatory agents*

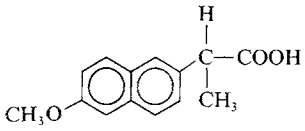
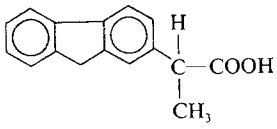
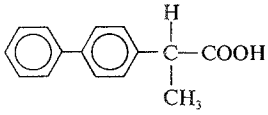
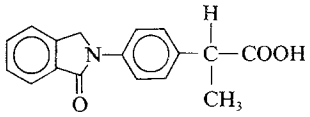
Optimal conditions for the synthesis of ibuprofen were applied in the synthesis of naproxen, cicloprofen, biprofen and indoprofen. Electrosyntheses were not optimized and in particular yields should be improved by increasing carbon dioxide pressure. Nevertheless, results of Table 9 show that this electrosynthesis of aryl-2 propionic acid is a quite general reaction.

Table 8. Influence of carbon dioxide pressure

Entry	RCl M l^{-1}	PCO_2 bar	*Solvent*	*Ibuprofen (isolated)*		
				τ %	Rc %	R_F %
31	0.2	1	TMU	60	95	38
32	0.2	4	TMU	72	90	43
33	0.5	1	TMU	74	68*	33
34	0.5	4	TMU	74	88	43
35	0.5	4	DMF	82	85	47

* Formation of dimers.

Table 9. Electrosynthesis of aryl-2 propionic acid

ArCH(CH$_3$)COOH	τ %	Rc* %	R_F %
NAPROXEN 	85	74	42
CICLOPROFEN 	73	86	41
BIPROFEN 	77	82	42
INDOPROFEN 	60	86	34

ArCH(CH$_3$)Cl: 20 mmol, $Li_2C_2O_4$: 20 mmol; *Solvent*: TMU, 100 ml; nBu$_4$NBF$_4$ = 0.04 M; *Cathode*: graphite; *Anode*: graphite, 20 cm^2; I = 400 mA; 3 F mol^{-1}; T = 0° C; PCO_2 = 1 atm.
Reactions without catalyst.
* Isolated acid.

4. Conclusion

Electrocarboxylation of *m*PhO–Ph–CH(CH$_3$)Cl, 0.5 M, gives fenoprofen with good yields (τ = 78%, Rc = 82%) when the electrolysis is performed in an undivided cell, with a constant current (density of 2.5 A dm^{-2}), with a nickel foam as cathode and TMU as solvent.

Ibuprofen can be synthesized by electrocarboxylation of *p-i*Bu–Ph–CH(CH$_3$)Cl. Best results are obtained in an undivided cell, upon electrolysing at a constant current in solvents such as TMU or DMF. When working under carbon dioxide pressure, highly concentrated solutions, 0.5 M, can be electrolysed without formation of by-products. Conversion rates are close to 80% and chemical yields are better than 85%.

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