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Sustainable and efficient Electrosynthesis of Naproxen using Carbon Dioxide and Ionic Liquids.

Silvia Mena, Sara Santiago, Iluminada Gallardo and Gonzalo Guirado*

Departament de Química, Universitat Autònoma de Barcelona,
08193-Bellaterra, Barcelona, Spain

ORCIDiDs:

Silvia Mena; <https://orcid.org/0000-0002-2800-2388>

Sara Santiago; <https://orcid.org/0000-0002-1206-1455>

Iluminada Gallardo; <https://orcid.org/0000-0003-3962-4745>

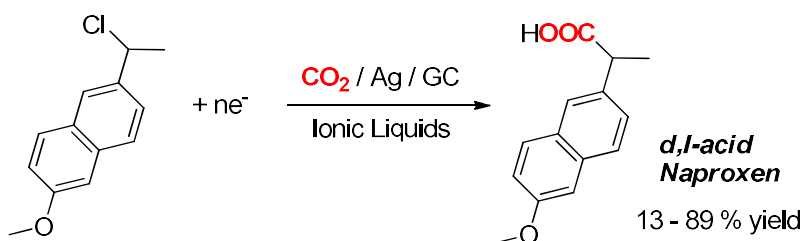
Gonzalo Guirado; <https://orcid.org/0000-0003-2128-7007>

Abstract

The use of CO₂ as a C1 carbon source for synthesis is raising increasing attention both as a strategy to bring value to carbon dioxide capture technologies and a sustainable approach towards chemicals and energy. Unfortunately, CO₂ activation is often hampered by its high thermodynamic and kinetic stability. The presented results focus on the application of electrochemical methods to incorporate CO₂ into organic compounds using ionic liquids as electrolytes, which provides a green alternative to the formation of C–C bonds. In this sense, the results presented show that Naproxen (6-Methoxy- α -methyl-2-naphthaleneacetic acid) can be synthesized in high yield (89%) and conversion rates (90%) through an electrocarboxylation process using CO₂ and ionic liquids. The role of the cathode and solvent, which can potentially enhance the synthesis, is also discussed. The “green” route described in the current work would open a new sustainable strategy for the electrochemical production of pharmaceutical compounds.

Keywords: Ionic Liquids; Electrochemistry; Carbon Dioxide, Naproxen

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Highlights:

- Electrocarboxylation of 2-(1-chloroethyl)-6-methoxynaphthalene using CO_2 as building block and Ionic Liquids for synthesizing useful chemicals.
- Electrochemical reactivity of CO_2 in function of the nature of the cathode and the electrolyte.
- Electrochemical Synthesis of Naproxen with high yields (89 %) and conversion rates (90 %).
- New “greener” route for the synthesis of Naproxen.

1. Introduction

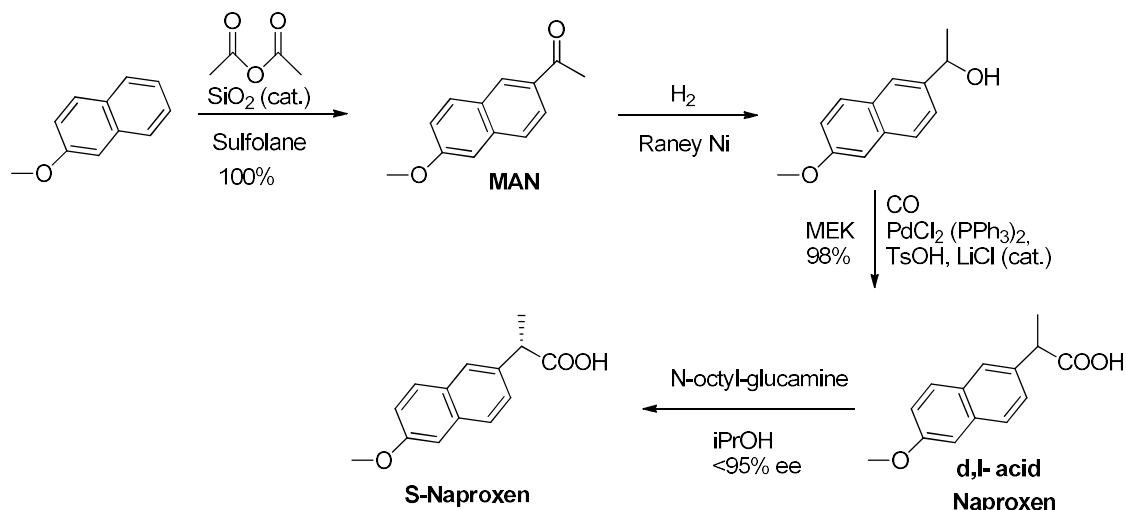
Nonsteroidal anti-inflammatory drugs (NSAID)(Ruelius et al., 1987), such as Ibuprofen or Naproxen that are the 2-arylpropionic acid (profen) derivatives, are commonly used to treat pain, menstrual cramps, inflammatory diseases such as rheumatoid arthritis, and fever (Adelman J.U, Alexander W.J, Barrett P.S, Brandes J.L, Kudrow D, Lener S.E. , O'Carroll C.P., O'Donnell F.J, Spruill S.E, 2007; H.J. et al., 2008; Uziel et al., 2000). Naproxen was firstly commercialized by Syntex in 1976 (Harrington and Lodewijk, 1997), its manufacture started from β -naphthol and produced 500 kg in 1970 (Harrison et al., 1970). However, this process involved several undesirable associated reagents: nitroaromatic compounds (used in acylation), ammonium sulfide (for performing the Willgerodt reaction), sodium hydride, as well as methyl iodide ((Figure S1. Route A).

These disadvantages were overcome with a new procedure to obtain naproxen that was also created at Syntex in 1972-1975 (Figure S1. Route B1). In this manufacturing process, there were also significant associated problems associated to this second synthetic strategy; First, a stoichiometric amount of zinc chloride was used for the naphthylzinc coupling reaction, hence large amounts of zinc hydroxide by-product were also produced. Second, this coupling reaction not only showed poor yields but also led to undesirable side products such as 2-methoxynaphthalene, which is volatile, and large amounts of binaphthyl, a highly insoluble “dimer” by product.

Focusing on the major problems resulting from the naphthylzinc coupling reaction, an alternative coupling was introduced to this second manufacturing process (Figure S1. Route B2). Besides, from 1984 to 1993 the yield increased, from less than 50% to a 90%, after a series of process improvements introduced to the above-mentioned synthetic approach. At this point it is important to highlight that overall atom economy for the previously described modern Syntex process described (Figure S1. Route B2) was a **24%**. Considering that 98% of N-alkylglucamine was recoverable by cycle, the atom economy raised to **34%**. However, it is important not to forget that the bromination and the coupling reactions still produce high amounts of waste.

In order to ameliorate the manufacture processes of Naproxen new approaches have been explored and discussed in the last years. Nate Shaw and Steve Schlitzer (Shaw and Schlitzer, 2015) introducing the use of safer solvents and auxiliaries (Scheme 1); sulfolane, as well as gaseous reagents (H_2 and CO in steps 2 and 3). Moreover, catalysts (SiO_2 , Raney Niquel, Palladium catalyst, tosylic acid, LiCl, virtually all recoverable) were

employed. So, its atom economy is higher (39.4%, which rises to 77.7% when considering recoverability of resolving agent) than in the case of Syntex and reduces the use of halogens and alkali metals as much as possible. On the other hand, this adapted synthesis required the use of a sophisticated catalyst and CO, which are well-known pollutants.



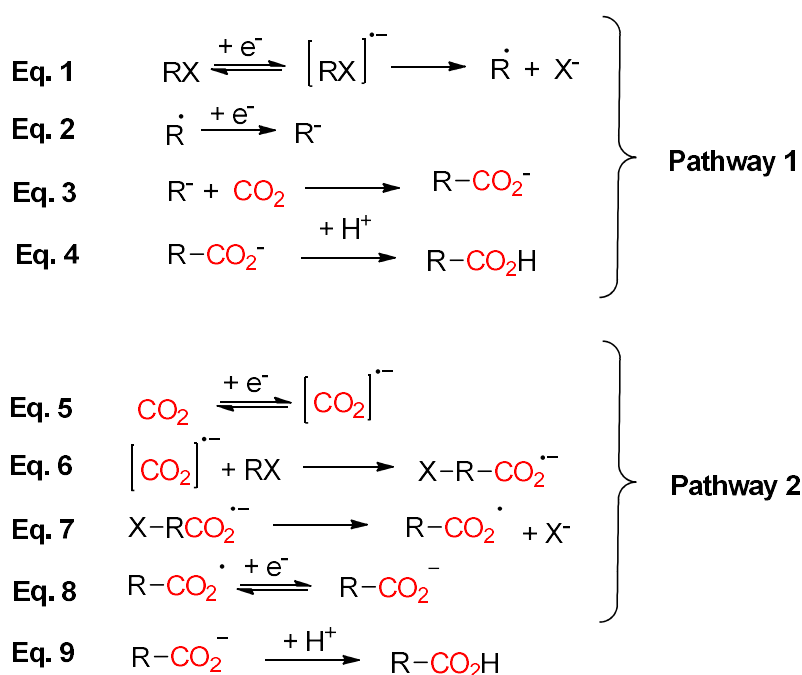
Scheme 1. Schlitzer/Shaw adapted synthesis

Carbon dioxide (CO_2) can be described as a carbon source for chemical synthesis. In this sense, the use of electrochemical methods for triggering the formation of C–C bonds by coupling CO_2 to organic compounds is a very attractive “green” alternative (Matthessen et al., 2014; Senboku and Katayama, 2017; Tokuda, 2006). Hence, the use of CO_2 as a feedstock is perceived as a promising attractive strategy for obtaining carboxylic acids *via* electrochemical fixation of CO_2 (Frontana-Urbe et al., 2010). One of the most important examples of its application can be found in NSAIDs such as Ibuprofen or Naproxen (Fauvarque et al., 1988a, 1988b; Mena et al., 2019b). The CO_2 incorporation to organic skeleton can be easily reached at low CO_2 pressure and under mild conditions with the use of a suitable of electrodes, electrolytes and catalysts in the electrolysis. In terms of green and sustainable chemistry, this approach is essentially environmentally benign and carbon dioxide is an eco-friendly C1 source (Yamauchi et al., 2010, 2008; Yoo et al., 2019).

Electrocarboxylation reactions of organic compounds using CO_2 is achieved via two different reaction pathways. The first one is depicted in Scheme 2, Eq. 1-4, and this

involves the generation of organic anionic intermediates. The carbanions electrochemically formed upon the passage of two electron undergo a nucleophilic attack on carbon dioxide to yield the corresponding carboxylic acids. This mechanism takes place when the reduction potentials of the organic substrates are less negative than that of carbon dioxide (Amatore and Savéant, 1981; Costentin et al., 2013; Gennaro et al., 1996b).

In turn, reaction pathway 2 occurs when the reduction potentials of the organic substrates are more negative than those of carbon dioxide (Scheme 2, Eq. 5-9). Via this mechanism, the electrogenerated anion radical of carbon dioxide reacts with organic substrates leading to the corresponding carboxylic acids (Damodar et al., 2001; Isse et al., 2005; Liu et al., 2015).



Scheme 2. Electrochemical carboxylation of organic compounds with CO₂.

Both strategies are associated to several advantages compared with the classical carboxylation process. However, electrochemical carboxylation processes usually uses organic aprotic solvents that are toxic and flammable (Alvarez-Guerra et al., 2015). Hence, our strategy for electrochemically synthesizing CO₂ will be based on the replacement of those organic solvents with ionic liquids (ILs).

In the last decade the use of ILs has been considered a sustainable solvent choice for several organic transformations, including the preparation of pharmaceutical drugs (Marrucho et al., 2014). Chemical and electrochemical reactions in ILs usually do not require special apparatus or methodologies. Focusing on electrochemical synthesis in ILs, a large array of different cations and anions available today in the IL toolbox. Wide electrochemical windows and good conductivities are obtained by combining unsymmetrical bulky organic cations combined and hydrophobic anions such as $[\text{BF}_4]^-$ or $[\text{NTf}_2]^-$. For electrocarboxylation process, the use of ILs offers the possibility to recycle the solvent at the end of the reaction (Chen et al., 2016; Lim and Kim, 2017; Pappenfus et al., 2009; Sun et al., 2014; Tateno et al., 2015; Zhou et al., 2015).

In this sense, our strategy for electrochemically synthesizing NSAIDs involve the use of CO_2 as reagent, which is valorised through an electro carboxylation process, that would allow the synthesis of Naproxen. We also introduce electrochemistry as a technology to enhance the synthesis with the use of milder conditions, easy control and monitoring of the process, selectivity and the use of electrodes as cheap, green catalysts. Hence, this manuscript reports a sustainable, green and new approach to synthesise 2-(6-methoxy-2-naphthyl)propanoic acid (Naproxen) using electrochemical methods, ILs, and CO_2 feedstock.

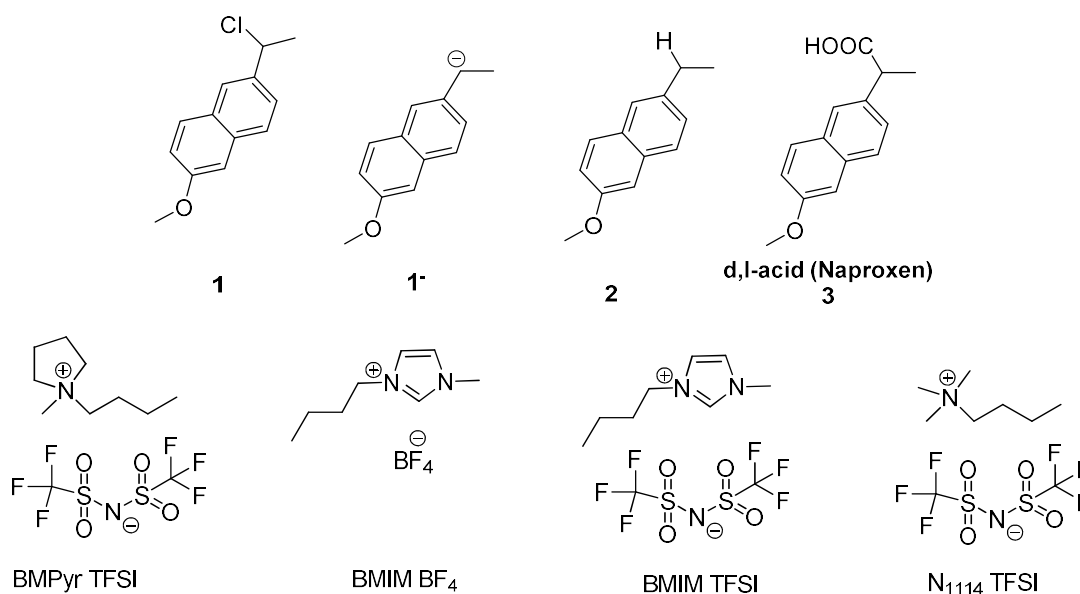
2. Experimental Section

2.1. Chemicals

Reagents: Carbon dioxide, CO_2 , and nitrogen, N_2 , were obtained from Carburos Metálicos S.A. (purity of 99.9999%). 2-(1-chloroethyl)-6-methoxynaphthalene (**1**) was obtained from SigmaAldrich and employed without further purification.

Solvents and Electrolytes: *N,N*-dimethylformamide anhydrous (DMF), 99.8%, was obtained from SigmaAldrich. Ionic Liquids were purchased from Solvionic (N-Butyl-N-methylpyrrolidonium bis(trifluoromethanesulfonyl)imide (BMPyr TFSI, purity 99.5%, $\text{H}_2\text{O} \leq 0.02\%$), 1-Butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (BMIM TFSI, purity 99%, $\text{H}_2\text{O} \leq 0.5\%$), 1-Butyl-3-methylimidazolium tetrafluoroborate (BMIM BF_4 , purity 99%, $\text{H}_2\text{O} \leq 0.5\%$), N-trimethyl-N-butylammonium bis(trifluoromethanesulfonyl)imide (N_{1114} TFSI, purity 99.5%, $\text{H}_2\text{O} \leq 0.02\%$) (Scheme 3). Tetrabutylammonium tetrafluoroborate (TBA BF_4), 99%, was obtained from SigmaAldrich and employed without further purification. After received all the solvents

and electrolytes prepared, they were dried under vacuum using activated molecular sieves for 48h in order to make sure that the amount of water was always less than $\text{H}_2\text{O} \leq 0.001\%$ (Williams and Lawton, 2010). The physical chemical parameters of the electrolytes used in the current work in terms of viscosity, density and water content are conveniently summarised in Table 1.



Scheme 3. Diagram of the structures

2.2. Experimental Procedures and Instrumentation

Electrochemical measurements were performed in a one-compartment cell using the three-electrode configuration. All experiments have been carried out at room temperature. Cyclic voltammetry experiments were recorded using a potentiostat equipped with positive feedback compensation and current measurer previously described (Cruz et al., 2011, 2008; Gallardo and Soler, 2017; Mena et al., 2019a, 2019b, 2018; Reche et al., 2015, 2014a, 2014b). The working electrode was a 1 mm diameter glassy carbon or 3 mm diameter silver electrode disk carefully polished with 1 μm diamond paste (DP-Paste, P) and rinsed with ethanol. The counter electrode was a 2 mm platinum electrode disk and the reference electrode a Saturated Calomel Electrode (SCE) separated from the solution by a sintered-glass disk. All potentials were reported versus this reference.

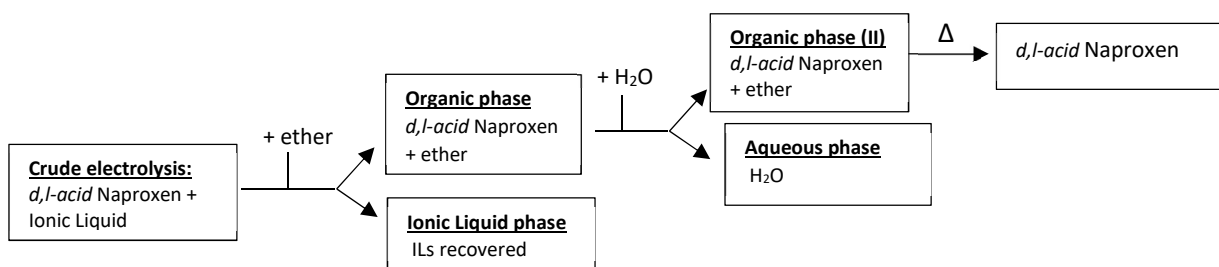
It is worthy to remark the current values obtained for the cyclic voltammograms in the different electrolytes were first normalized by the concentration and the scan rate ($I_p/cv^{1/2}$) due to the moderate conductivity and larger viscosity of the ionic liquids. Under these experimental conditions the diffusion coefficient of the electroactive compounds was determined and normalized taking into account their relationship. Hence, the normalization coefficients expressed as a ratio were the following: 4.1, 8.1, 6.0, and 2.7 for DMF + 0.1 M TBABF₄/[BMIM]TFSI, DMF + 0.1 M TBABF₄/[BMIM]BF₄, DMF + 0.1 M TBABF₄/[N₁₁₁₄] TFSI, and DMF + 0.1 M TBABF₄/[BMPyr]TFSI, respectively.

Table 1. Physical-Chemical properties and recyclability of selected Ionic Liquids

Ionic Liquid	Viscosity* (mPa·s)	Conductivity* (mS·cm ⁻¹)	Density* (g·cm ⁻³)	H ₂ O content before drying (%)	H ₂ O content after drying (%)	Recyclability (%)
BMIM TFSI	68.8	3.23	1.44	≤ 0.5	≤ 0.001	93
BMIM BF₄	103	3.15	1.20	≤ 0.5	≤ 0.001	76
N₁₁₁₄ TFSI	138	1.60	1.40	≤ 0.02	≤ 0.001	57
BMPyr TFSI	998	2.21	1.39	≤ 0.02	≤ 0.001	61

* Obtained from MSDS of Solvionic webpage: <https://en.solvionic.com/family/ionic-liquids>

Controlled potential electrolysis were carried out using a potentiostat EG&G PRINCETON APPLIED RESEARCH model 273A following a previous described methodology (Cruz et al., 2011, 2008; Gallardo and Soler, 2017; Mena et al., 2019a, 2019b). The working electrode was a graphite bar or a silver foil; the counter electrode, a platinum bar separated from the solution by a sintered-glass disk; and the reference, the SCE electrode. Electrocarboxylation reactions were performed under CO₂ atmosphere using a Mass Flow Meter to control the CO₂ concentrations and flows. These experiments were also monitored using Cyclic Voltammetry. When the electrolysis was completed, Naproxen was extracted from the IL using diethylether (Scheme 4). Later, the organic phase was washed with water and dried with anhydrous sulphate sodium and removed under high vacuum. The residue was dissolved in dichloromethane and characterized by gas chromatography, gas chromatography–mass spectrometry, and Proton Nuclear Magnetic Resonance (¹H-RMN). Finally, it is important to highlight that, in all the cases, more than a half of the IL used as electrolyte (Table 1), can be recovered, recycle and reused after a purification process for a new set of electrochemical experiments.

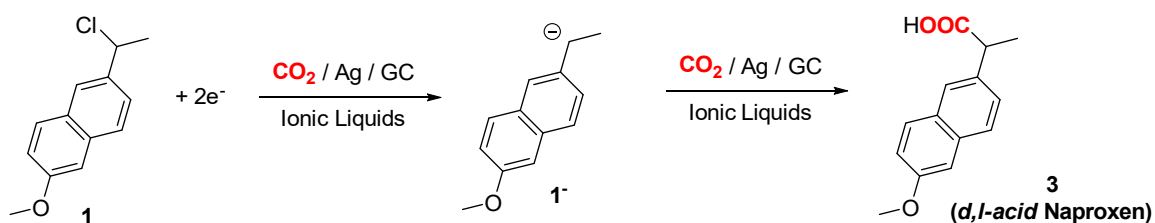


Scheme 4. Schematic process for Naproxen purification and Ionic Liquid recovery after electrocarboxylation reaction.

The ^1H NMR spectra were recorded on a Bruker DPX250 operating at 250,13 MHz. Gas chromatography (GC) were performed with a Clarus 500 from Perkin Elmer (vector gas: Helium, column: Elite 5, $l = 30$ m, $d = 0.25$ mm). Apparatus for gas phase chromatography coupled with mass spectrometry was a Hewlett Packard 6890 and the detector were Hewlett Packard 5973.

3. Results and discussion

2-(6-methoxy-2-naphthyl)propanoic acid (**3**, Naproxen) was obtained by taking a new environmentally friendly approach that combines electrochemical techniques and ionic liquids as green solvents to valorise CO_2 with an electrocarboxylation process (Scheme 5).



Scheme 5. Electrocarboxylation of **1** under CO_2 atmosphere

For this reason, compound **1** must be electrochemically characterised in an inert and CO_2 saturated atmosphere to find out whether its relative anion, 1^\bullet , is stable enough to catch CO_2 .

3.1. Electrochemical reduction of 2-(1-chloroethyl)-6-methoxynaphthalene (**1**) in inert atmosphere

Compound **1** was characterised with cyclic voltammetry (CV) at several scan rates (and in different solvents (DMF + 0.1 M TBA BF₄, BMIM TFSI, BMIM BF₄, N₁₁₁₄ TFSI, and a BMPyr TFSI) using either glassy carbon (GC) or silver (Ag) cathodes in N₂ atmosphere (Figure 1a and S2). In all the cases, compound **1** shows a two-electron irreversible reduction peak followed by a one-electron reversible one. The analysis of the peak current and potential values as well as their dependence on the concentration and the scan rate reveals that the chemical reaction coupled to the electron transfer is a first order reaction. The shape of CVs, peak width value (ΔE_p), is always more than 100 mV (at 0.5 V/s, Table 1), which means that compound **1** involves slow electron transfer with charge transfer coefficient (α) between 0.2-0.4.

Finally, the second reversible one-electron transfer can be assigned to the reduction of **2**. Figure 1b shows a cyclic voltammogram of pure samples of **1** and **2**, the second electrochemical reduction wave of **1** and the first reduction wave of **2**, which have the same shape and cathodic peak potential value for both electrodes.

In order to confirm this hypothesis, control potential electrolysis at -2.0 V vs SCE in ILs and at -2.2 V vs SCE in DMF under N₂ atmosphere was carried out. After the passage of 2F, for all the electrolytes investigated, compound **2** was obtained as a unique quantitative product (100%) (Figure S3). The use altogether of electrochemical techniques (such as CV and Controlled potential electrolysis) allows to establish an ECE mechanism for the electrochemical reduction of **1** (Scheme 6). A radical anion is firstly formed (Eq. 1, electrochemical reaction, E). After that, a chemical reaction coupled to this electron transfer leads to the corresponding organic radical, **1**[•], and halide anion (Eq. 2, chemical reaction step, C). Finally, the organic radical formed is reduced at the electrode surface yielding the corresponding anion (Eq. 3, electrochemical reaction, E), which evolves to compound **2** after a protonation reaction (Eq. 4).

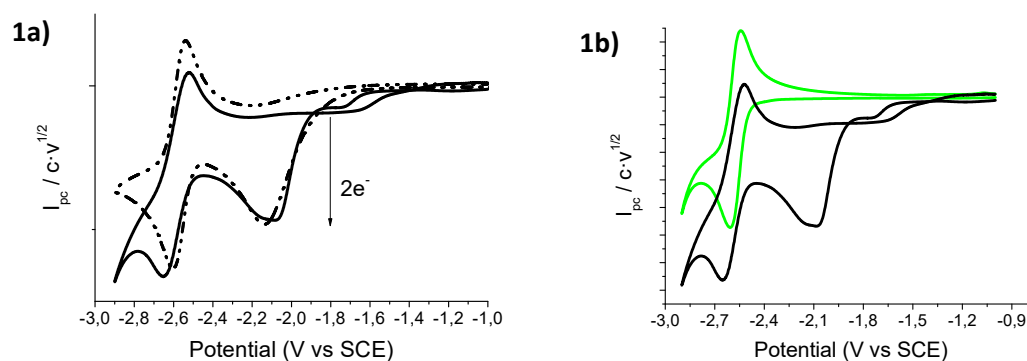


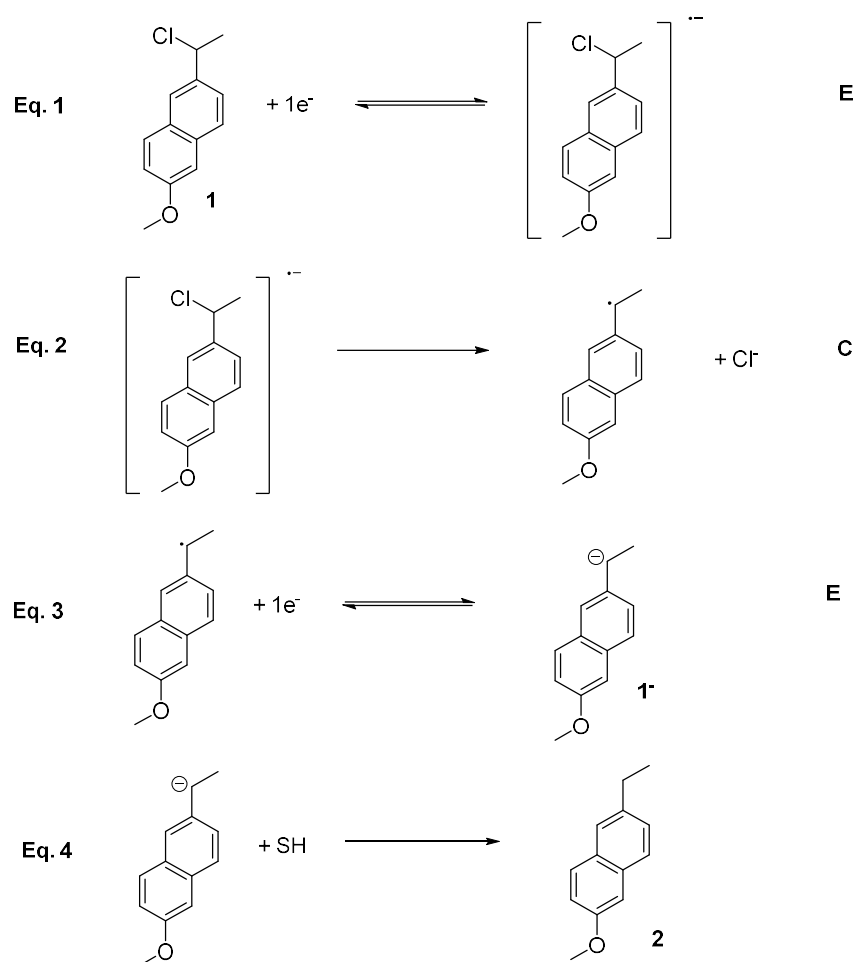
Figure 1. Cyclic voltammograms in DMF + TBABF₄ (scan rate 0.5 V s⁻¹) at 25 °C a) of **1** on a GC (dotted line) and Silver (solid line) electrodes b) **1** (black line) and **2** (green line) on a GC in inert atmosphere

Table 2. Cathodic Peak Potential (E_{pc} in V), $\Delta E_p = |E_{pc} - E_{pc/2}|$ (in mV), Charge transfer coefficient (α), scan rate: 0.5 V s⁻¹ for solutions of **1** c.a. 5-10 mM **1** in different electrolytes at 25 °C under N₂ atmosphere.

Entry	Electrode	Solvent	E_{pc} (V)	ΔE_p (mV)	α	Number of electrons
1	Carbon	DMF + EF ^[a]	-2.14	160	0.33	2.1 ₅
2	Carbon	BMIM TFSI	-1.97	200	0.24	2.1 ₈
3	Carbon	BMPyr TFSI	-1.95	210	0.22	2.2 ₀
4	Carbon	N ₁₁₁₄ TFSI	-1.90	190	0.25	2.2 ₀
5	Silver	DMF + EF ^[a]	-2.09	130	0.37	2.0 ₁
6	Silver	BMIM BF ₄	-1.76	110	0.43	2.1 ₅
7	Silver	BMPyr TFSI	-1.94	100	0.45	1.9 ₉
8	Silver	N ₁₁₁₄ TFSI	-1.83	110	0.40	2.0 ₆

[a] DMF + 0.1 M of *N*-tetrabutylammonium tetrafluoroborate (TBABF₄)

Note that the E_{pc} values obtained in all the ILs for both electrodes are positively shifted (Figure S2a), which means that the cation of the IL may have a role as a co-catalyst (as was previously pointed out by ourselves and some other authors). The reduction potential can be lowered to more than 0.24 V ($5.5 \text{ kcal}\cdot\text{mol}^{-1}$) and 0.33 V ($7.6 \text{ kcal}\cdot\text{mol}^{-1}$) with respect to DMF + 0.1 M TBABF₄ in carbon electrode and silver electrode (Table 2, entries 1-4 and Table 2, entries 5-8), respectively. This can be explained because the concentration of the counter-cation is considerably lower in DMF than in IL solutions. Moreover, a slightly electrocatalytic effect, 0.07 V ($4.8 \text{ kcal}\cdot\text{mol}^{-1}$), can also be observed when silver is used a cathode (Figure S2b). This effect has been previously described for electrochemical cleavage of carbon-halide reactions (Arnaboldi et al., 2014; Durante et al., 2013, 2009; Gennaro et al., 2004; Isse et al., 2009, 2008, 2006b, 2006a; Isse and Gennaro, 2002; Lugaresi et al., 2013; Mena et al., 2019a; Niu et al., 2009).



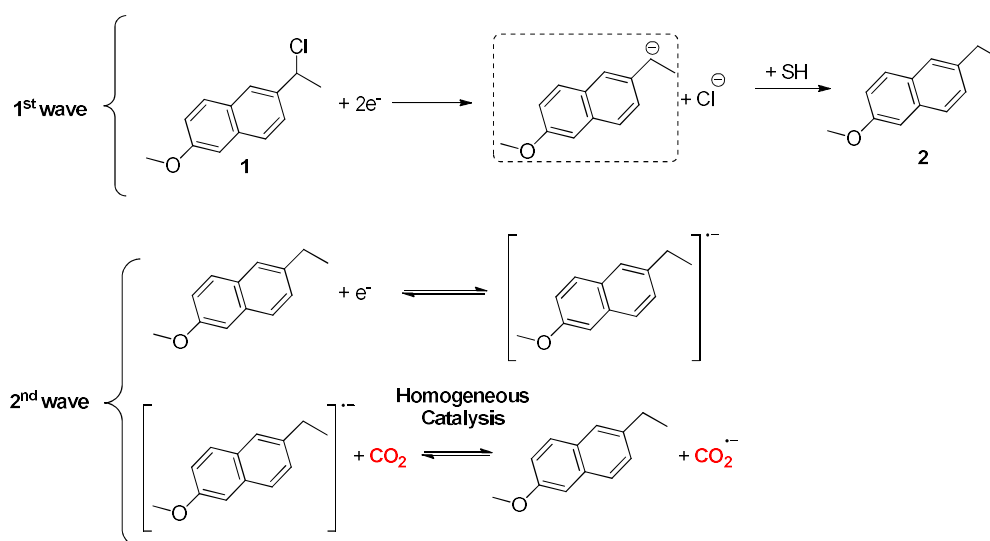
Scheme 6. Electrochemical reduction mechanism of **1**.

3.2. Electrochemical reduction of 2-(1-chloroethyl)-6-methoxynaphthalene (**1**) in CO₂ atmosphere

3.2.1. Carbon vitreous working electrode

The voltammetric response of **1** in CO₂ was the same for all the electrolytes tested (Figure S4). Hence, in the initial cathodic scan a two-electron reduction wave was detected c.a. -2.0 V vs. SCE. The oxidation of chloride ion is detected in the ensuing anodic scan, since an oxidation peak at c.a. 1.1 V vs. SCE is observed (Figure S5a).

Note that the second reduction wave at -2.60 V vs. SCE becomes irreversible and increases its intensity in CO₂ atmosphere. This behaviour typically describes a catalytic process, where product **2** would act as a catalyst to reduce CO₂ through a homogeneous catalytic process (Gennaro et al., 1996a), producing CO₂⁻ (Scheme 7).



Scheme 7. Electrochemical reduction mechanism that describes cyclic voltammogram in CO₂ atmosphere

At this point several electrocarboxylation processes were attempted under CO₂ atmosphere, after pre-saturated with CO₂ the selected electrolyte. Controlled-potential electrolysis of **1**, after its first reduction wave, was performed in DMF and ILs using a carbon graphite bar as a cathode. Cyclic voltammograms were recorded after the passage of different charge amounts in order to monitor the process (Figure S5b). In all cases,

naproxen was obtained in reasonable yields (Table 2), the behaviour and results being the same for classic organic aprotic solvents and ionic liquids. A closer look reveals that the best yields were obtained for imidazolium ionic liquids, since the conductivity and the viscosity of the solution is higher and lower, respectively (Table 1 and Table 3, entries 4 and 5). Only when using BMPyr TFSI is the yield as well as the conversion rate of naproxen reduced probably due to its high viscosity (Table 1 and Table 3, entry 3).

Table 3. Results of Exhaustive Electrolysis of **1** under CO₂ atmosphere to obtain Naproxen (**3**)

Entry	Solvent	E _{applied} (V)	R-COOH (Naproxen isolated, 3)	Reactant (1) (%)	R-H (2) (%)
			Yield (% conversion rate)		
1	DMF + EF ^[a]	-2.25	29 (36%)	20	51
2	N ₁₁₁₄ TFSI	-2.1	26 (31%)	15	59
3	BMPyr TFSI	-2.1	13 (14%)	6	81
4	BMIM TFSI	-2.1	32 (34%)	6	62
5	BMIM BF ₄	-2.1	40 (42%)	5	55

[a] DMF + 0.1 M of TBABF₄

3.2.2. Silver working electrode

Considering the enhanced results obtained with a silver electrode in comparison to a carbon working electrode, thanks to the electrocatalytic effect of the silver electrode in carbon-halogen cleavage reactions, we expected the moderate yields obtained in electrocarboxylation reactions with a carbon cathode to improve with the use of the silver electrode.

Figure 2 shows the CV of **1** in the different solvents in CO₂ atmosphere with a silver electrode. A reduction peak of between c.a. -1.8 or -2.40 V vs. SCE is detected, when ILs or DMF is used as an electrolyte. This reduction peak is assigned to the reduction of **1**

and CO₂ at the same time. It has already been reported by some of us that the electrochemical reduction potential of CO₂ reduction with a silver electrode surface is lower in ILs than in the case of organic aprotic solvents (Reche et al., 2015, 2014a). Hence, the cyclic voltammogram (Figure 2) shows a reduction, which not only involves the electrochemical reduction peak of **1** but also the direct reduction of CO₂ at silver surface.

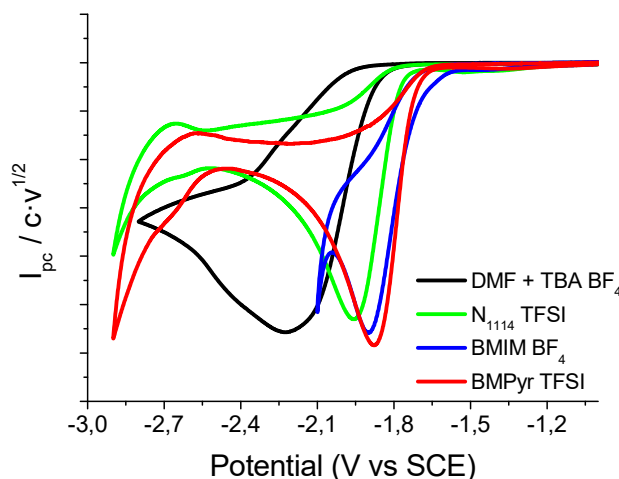
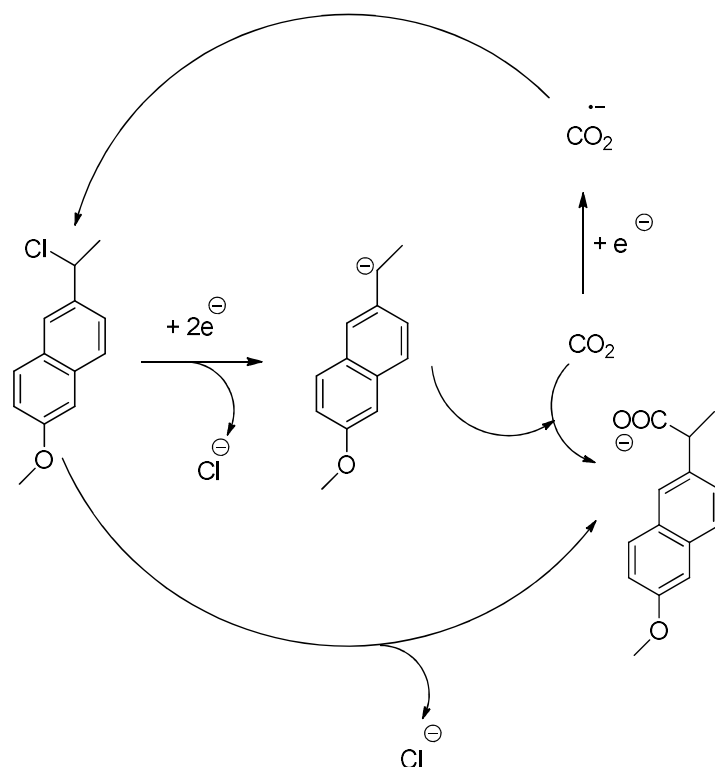


Figure 2. Cyclic voltammograms (scan rate $0.5 \text{ V}\cdot\text{s}^{-1}$) at 25°C on Ag electrode of 5 mM of **1** and 40 mM of CO₂ in the different electrolytes.

Controlled-potential electrolysis of **1** was performed using a silver sheet cathode under CO₂ atmosphere in DMF and ILs applying a potential 0.1 V after the first electron transfer, which was obtained in an inert atmosphere. The electrochemical processes were easily monitored by means of cyclic voltammetry using glassy carbon as a working electrode instead of silver because, CO₂ reduction does not occur with carbon. The behaviour and results being the same for classic organic aprotic solvents and ionic liquids. However, there was an improvement in Naproxen yields from moderate to good compared when silver was used instead of carbon as a working electrode (Table 3). Note that the same general trends in terms of yields and conversion rates of Naproxen were seen for both cathodes. The use of ILs with high conductivity and low viscosity enhances the yields and the conversion rates, allowing to reach values close to the 90 % when BMIM BF₄ and silver are used as electrolyte and cathode, respectively. (Table 3, entry 4). In all cases, naproxen was obtained as the main product with conversion rates higher than 50%.

Table 3. Results of Exhaustive Electrolysis of 1 under CO ₂ atmosphere to obtain Naproxen (3)					
Entry	Solvent	E _{applied} (V)	R-COOH (Naproxen isolated, 3)	Reactant (1) (%)	R-H (2) (%)
			Yield (% conversion rate)		
1	DMF + EF ^[a]	-2.15	55 (58.5%)	6	39
2	N ₁₁₁₄ TFSI	-2.0	65 (66%)	2	33
3	BMPyr TFSI	-2.0	52 (55%)	6	42
4	BMIM BF ₄	-1.8	88.5 (90%)	1.5	10
5	BMIM TFSI	-2.0	70 (63%)	5	35
[a] The DMF + 0.1 M of TBABF ₄					

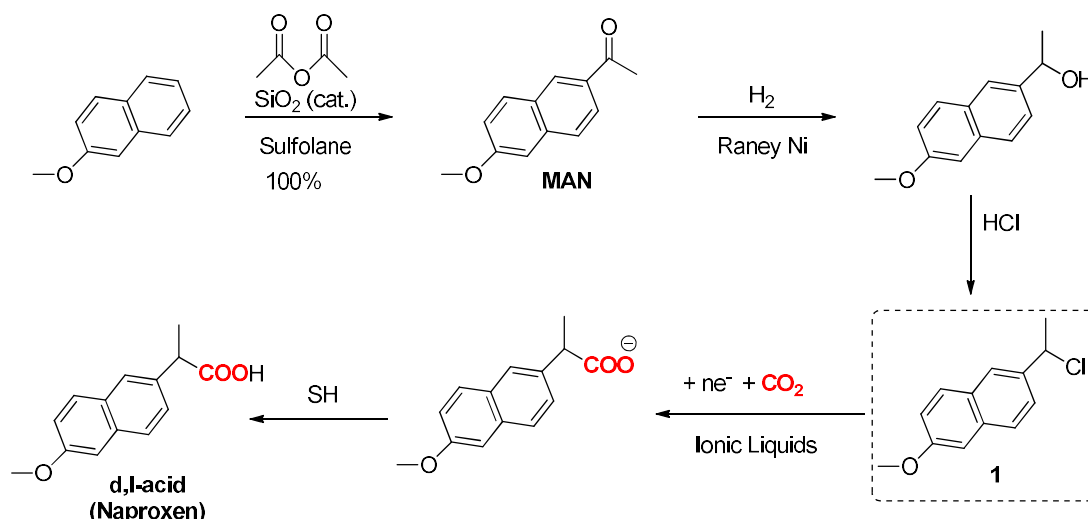
Focusing on our electrochemical procedure, two kinds of mechanism operate concurrently in this reaction depending on the working electrode, and which are summarized in Scheme 8. On the one hand, with the use of the glassy carbon working electrode the mechanism goes through **1**⁻ anion, which improves its nucleophilic behaviour and attaches CO₂, which acts as an electrophile, to its structure (Table 3, entries 1-5). In turn, there is a radical mechanism with the use of a silver electrode, where CO₂ is reduced to obtain CO₂^{-•} on the electrode's surface, and in this case, CO₂ acts as a nucleophile and reacts with **1** (Table 4, entries 1-5). The electrochemically triggered dual reactivity enhances the yield of Naproxen through a carboxylation process.



Scheme 8. Nucleophilic substitution mechanism operates concurrently

3.3. Sustainability of “our” Electrocarboxylation approach.

Our proposed synthesis of Naproxen (Scheme 8) presents an alternative to the other two strategies described in the introduction. In our case, two first steps were obtained as in the case of the Shaw/Schlitzer synthesis. However, we propose to replace the OH substituent of the starting material for a chloride group, since it is a better leaving group (Ayers et al., 2005). Then, with the use of an electrochemical carboxylation process, CO₂ is incorporated into the reactant. In the atom economy analysis (Table 4) of our proposal, we obtain **36%** (**65%** considering recoverability of the resolving agent). These results are very similar to those achieved by Shaw and Schlitzer. Moreover, in our case, despite the use of halogens, one of the catalysts we used were electrons, which are heterogeneous and much cheaper and more widely available than the others, and the use of CO₂ instead of CO enhances the process.



Scheme 9. Naproxen proposed synthesis

Table 4. Atom economy analysis –Our proposed synthesis					
Reagent		Used in Naproxen		Unused in Naproxen	
Formula	MW	Formula	MW	Formula	MW
C ₁₀ H ₇ OCH ₃	158.3	C ₁₀ H ₆ OCH ₃	157.3	H	1.0
C ₄ H ₆ O ₃	102.1	C ₂ H ₃	27.0	C ₂ H ₃ O ₃	75.1
H ₂	2.0	H	1.0	H	1.0
HCl	36.5	-	-	HCl	36.5
e ⁻	-	e ⁻	-	-	-
CO ₂	44.0	CO ₂	44.0	-	-
H	1.0	H	1.0	-	-
C ₁₄ H ₃₁ NO ₅	293.4	-	-	C ₁₄ H ₃₁ NO ₅	293.4
Total		Naproxen		Waste	
C ₄₃ H ₆₃ NO ₁₁ Cl ₂	637.3	C ₁₄ H ₁₄ O ₃	230.3	C ₁₆ H ₃₆ NO ₅ Cl ₂	407

Note that a similar approach was used in the past for the electrochemical synthesis of Naproxen (Fauvarque et al., 1988a), as it has been previously pointed in the introduction section. In this previous work, tetramethylurea (TMU) was identified as the most suitable solvent for performing the electrochemical synthesis in terms of toxicity, high reaction yields and conversion rates. However, the use of TMU as a solvent for electrochemistry involves large quantities of supporting electrolyte (usually tetralkylammonium salts) as well as large-energy-consuming processes for solvent recovery. In this sense, our

electrocarboxylation approach, based on the recyclability of green electrolytes (ILs), would allow to overcome those environmental limitations.

Cost-effectiveness analysis to determine whether an electrocarboxylation approach is a low-cost alternative would strongly depend on the electricity prices and the energy conversion efficiencies. It is reported that for electrosynthesis to become economical viable with traditional fossil fuel-derived processes the electricity generation should come from renewable sources, being the electrochemical conversion efficiencies at least 60% and the electricity price below 4 cents per kWh (De Luna et al., 2019). In 2019, non-household electricity prices in the European Union are between 0.17 and 0.07 cents per kWh depending on the country and 0.13 cents per kWh in United States. Hence, apart from the technical challenges of using electrochemistry for manufacturing marketable products; the main challenge would be to reduce the electricity price at least 4 times. Focussing on electrochemical approach for synthesizing Naproxen, note that when silver is used as cathode not only the conversion efficiencies are close to a 100 % but also ca. 75 % the electrolyte can be recycled and reused at the end of the process.

Conclusions

A description of a sustainable and highly efficient chemical route for synthesizing useful compounds using CO₂ as a C1 syptom through electrocarboxylation reactions is presented. This strategy deals with the used of electrochemical techniques and ILs, which allow introduce some of the Green Chemistry principles for the synthesis of NSAIDs. Controlled potential electrolysis 2-(1-chloroethyl)-6-methoxynaphthalene in CO₂ atmosphere obtains Naproxen in good yields and excellent atom economy compared with the initial ones. This methodology offers a “green” way for the synthesis of different carboxylic acids that could potentially displace the petrochemical process in a future.

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References

- Adelman J.U, Alexander W.J, Barrett P.S, Brandes J.L, Kudrow D, Lener S.E. , O'Carroll C.P., O'Donnell F.J, Spruill S.E, S.S., 2007. Sumatriptan-Naproxen for Acute Treatment of Migraine. *Jama* 297, 1443–1454.
- Alvarez-Guerra, M., Albo, J., Alvarez-Guerra, E., Irabien, A., 2015. Ionic liquids in the electrochemical valorisation of CO₂. *Energy Environ. Sci.* 8, 2574–2599. <https://doi.org/10.1039/C5EE01486G>
- Amatore, C., Savéant, J.M., 1981. Mechanism and Kinetic Characteristics of the Electrochemical Reduction of Carbon Dioxide in Media of Low Proton Availability. *J. Am. Chem. Soc.* 103, 5021–5023. <https://doi.org/10.1021/ja00407a008>
- Arnaboldi, S., Bonetti, A., Giussani, E., Mussini, P.R., Benincori, T., Rizzo, S., Isse, A.A., Gennaro, A., 2014. Electrocatalytic reduction of bromothiophenes on gold and silver electrodes: An example of synergy in electrocatalysis. *Electrochem. commun.* 38, 100–103. <https://doi.org/10.1016/j.elecom.2013.10.025>
- Ayers, P.W., Anderson, J.S.M., Rodriguez, J.I., Jawed, Z., 2005. Indices for predicting the quality of leaving groups. *Phys. Chem. Chem. Phys.* 7, 1918–1925. <https://doi.org/10.1039/b500996k>
- Chen, L., Guo, S.-X., Li, F., Bentley, C., Horne, M., Bond, A.M., Zhang, J., 2016. Electrochemical Reduction of CO₂ at Metal Electrodes in a Distillable Ionic Liquid. *ChemSusChem* 9, 1271–1278. <https://doi.org/10.1002/cssc.201600359>
- Costentin, C., Robert, M., Savéant, J.M., 2013. Catalysis of the electrochemical reduction of carbon dioxide. *Chem. Soc. Rev.* 42, 2423–2436. <https://doi.org/10.1039/c2cs35360a>
- Cruz, H., Gallardo, I., Guirado, G., 2011. Electrochemically promoted nucleophilic aromatic substitution in room temperature ionic liquids - An environmentally benign way to functionalize nitroaromatic compounds. *Green Chem.* 13, 2531–2542. <https://doi.org/10.1039/c1gc15303j>
- Cruz, H., Gallardo, I., Guirado, G., 2008. Understanding specific effects on the standard potential shifts of electrogenerated species in 1-butyl-3-methylimidazolium ionic liquids. *Electrochim. Acta* 53, 5968–5976.

<https://doi.org/10.1016/j.electacta.2008.03.062>

- Damodar, J., Krishna Mohan, S.R., Jayarama Reddy, S.R., 2001. Synthesis of 2-arypropionic acids by electrocarboxylation of benzylchlorides catalysed by PdCl₂(PPh₃)₂. *Electrochem. commun.* 3, 762–766. [https://doi.org/10.1016/S1388-2481\(01\)00263-6](https://doi.org/10.1016/S1388-2481(01)00263-6)
- De Luna, P., Hahn, C., Higgins, D., Jaffer, S.A., Jaramillo, T.F., Sargent, E.H., 2019. What would it take for renewably powered electrosynthesis to displace petrochemical processes? *Science* (80-.). 364. <https://doi.org/10.1126/science.aav3506>
- Durante, C., Isse, A.A., Sandonà, G., Gennaro, A., 2009. Electrochemical hydrodehalogenation of polychloromethanes at silver and carbon electrodes. *Appl. Catal. B Environ.* 88, 479–489. <https://doi.org/10.1016/j.apcatb.2008.10.010>
- Durante, C., Isse, A.A., Todesco, F., Gennaro, A., 2013. Electrocatalytic Activation of Aromatic Carbon-Bromine Bonds toward Carboxylation at Silver and Copper Cathodes. *J. Electrochem. Soc.* 160, G3073–G3079. <https://doi.org/10.1149/2.008307jes>
- Fauvarque, J.F., Jutand, A., Francois, M., 1988a. Nickel catalysed electrosynthesis of anti-inflammatory agents. Part I - Synthesis of aryl-2 propionic acids, under galvanostatic conditions. *J. Appl. Electrochem.* 18, 109–115. <https://doi.org/10.1007/BF01016213>
- Fauvarque, J.F., Jutand, A., Francois, M., Petit, M.A., 1988b. Nickel catalysed electrosynthesis of anti-inflammatory agents. Part II - Monitoring of the electrolyses by HPLC analysis. Role of the catalyst. *J. Appl. Electrochem.* 18, 116–119. <https://doi.org/10.1007/BF01016214>
- Frontana-Urbe, B.A., Little, R.D., Ibanez, J.G., Palma, A., Vasquez-Medrano, R., 2010. Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chem.* 12, 2099. <https://doi.org/10.1039/c0gc00382d>
- Gallardo, I., Soler, S., 2017. Electrochemically promoted arylation of iodoaromatics. *J. Electroanal. Chem.* 799, 9–16. <https://doi.org/10.1016/j.jelechem.2017.05.034>
- Gennaro, A., Isse, A.A., Savéant, J.M., Severin, M.G., Vianello, E., 1996a. Homogeneous electron transfer catalysis of the electrochemical reduction of

- carbon dioxide. Do aromatic anion radicals react in an outer-sphere manner? *J. Am. Chem. Soc.* 118, 7190–7196. <https://doi.org/10.1021/ja960605o>
- Gennaro, A., Isse, A.A., Severin, M.-G., Vianello, E., Bhugun, I., Savéant, J.-M., 1996b. Mechanism of the electrochemical reduction of carbon dioxide at inert electrodes in media of low proton availability. *J. Chem. Soc., Faraday Trans.* 92, 3963–3968. <https://doi.org/10.1039/FT9969203963>
- Gennaro, A., Sánchez-Sánchez, C.M., Isse, A.A., Montiel, V., 2004. Electrocatalytic synthesis of 6-aminonicotinic acid at silver cathodes under mild conditions. *Electrochem. commun.* 6, 627–631. <https://doi.org/10.1016/j.elecom.2004.04.019>
- H.J., J., M., J., E.H., van de L., P.L., van R., C., van W., 2008. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 371, 1854–1860.
- Harrington, P.J., Lodewijk, E., 1997. Twenty years of naproxen technology. *Org. Process Res. Dev.* 1, 72–76. <https://doi.org/10.1021/op960009e>
- Harrison, I.T., Lewis, B., Nelson, P., Rooks, W., Roszkowski, A., Tomolonis, A., Fried, J.H., 1970. Nonsteroidal antiinflammatory agents. I. 6-Substituted 2-naphthylacetic acids. *J. Med. Chem.* 13, 203–205. <https://doi.org/10.1021/jm00296a008>
- Isse, A.A., Berzi, G., Falciola, L., Rossi, M., Mussini, P.R., Gennaro, A., 2009. Electrocatalysis and electron transfer mechanisms in the reduction of organic halides at Ag. *J. Appl. Electrochem.* 39, 2217–2225. <https://doi.org/10.1007/s10800-008-9768-z>
- Isse, A.A., De Giusti, A., Gennaro, A., Falciola, L., Mussini, P.R., 2006a. Electrochemical reduction of benzyl halides at a silver electrode. *Electrochim. Acta* 51, 4956–4964. <https://doi.org/10.1016/j.electacta.2006.01.039>
- Isse, A.A., Falciola, L., Mussini, P.R., Gennaro, A., 2006b. Relevance of electron transfer mechanism in electrocatalysis: the reduction of organic halides at silver electrodes. *Chem. Commun.* 1, 344–346. <https://doi.org/10.1039/B513801A>
- Isse, A.A., Ferlin, M.G., Gennaro, A., 2005. Electrocatalytic reduction of arylethyl chlorides at silver cathodes in the presence of carbon dioxide: Synthesis of 2-arylpropanoic acids. *J. Electroanal. Chem.* 581, 38–45. <https://doi.org/10.1016/j.jelechem.2005.04.007>

- Isse, A.A., Gennaro, A., 2002. Electrocatalytic carboxylation of benzyl chlorides at silver cathodes in acetonitrile the reductive carboxylation of benzyl chlorides (RCl): in trials that are about 0 . 6 V more positive than those of the acids in good to excellent yields . Chem. Commun. 2798–2799.
- Isse, A.A., Gottardello, S., Durante, C., Gennaro, A., 2008. Dissociative electron transfer to organic chlorides: Electrocatalysis at metal cathodes. Phys. Chem. Chem. Phys. 10, 2409–2416. <https://doi.org/10.1039/b719936h>
- Lim, H.K., Kim, H., 2017. The mechanism of room-Temperature ionic-liquid-based electrochemical CO₂ reduction: A Review. Molecules 22. <https://doi.org/10.3390/molecules22040536>
- Liu, Q., Wu, L., Jackstell, R., Beller, M., 2015. Using carbon dioxide as a building block in organic synthesis. Nat. Commun. 6, 1–15. <https://doi.org/10.1038/ncomms6933>
- Lugaresi, O., Minguzzi, A., Locatelli, C., Vertova, A., Rondinini, S., Amatore, C., 2013. Benzyl Chloride Electroreduction on Ag Cathodes in CH₃CN in the Presence of Small Amounts of Water: Evidences of Quantitative Effects on Reaction Rates and Mechanism. Electrocatalysis 4, 353–357. <https://doi.org/10.1007/s12678-013-0161-2>
- Marrucho, I.M., Branco, L.C., Rebelo, L.P.N., 2014. Ionic Liquids in Pharmaceutical Applications. Annu. Rev. Chem. Biomol. Eng. 5, 527–546. <https://doi.org/10.1146/annurev-chembioeng-060713-040024>
- Matthessen, R., Fransaer, J., Binnemans, K., De Vos, D.E., 2014. Electrocarboxylation: Towards sustainable and efficient synthesis of valuable carboxylic acids. Beilstein J. Org. Chem. 10, 2484–2500. <https://doi.org/10.3762/bjoc.10.260>
- Mena, S., Gallardo, I., Guirado, G., 2019a. Electrocatalytic Processes for the Valorization of CO₂ : Synthesis of Cyanobenzoic Acid Using Eco-Friendly Strategies. Catalysts 9, 413. <https://doi.org/https://doi.org/10.3390/catal9050413>
- Mena, S., Mirats, A., Caballero, A.B., Guirado, G., Barrios, L.A., Teat, S.J., Rodriguez-Santiago, L., Sodupe, M., Gamez, P., 2018. Drastic Effect of the Peptide Sequence on the Copper-Binding Properties of Tripeptides and the Electrochemical Behaviour of Their Copper(II) Complexes. Chem. - A Eur. J. 24, 5153–5162. <https://doi.org/10.1002/chem.201704623>

- Mena, S., Sanchez, J., Guirado, G., 2019b. Electrocarboxylation of 1-chloro-(4-isobutylphenyl)ethane with a silver cathode in ionic liquids : an environmentally benign and efficient way to synthesize Ibuprofen. *RSC Adv.* 9, 15115–15123. <https://doi.org/10.1039/C9RA01781J>
- Niu, D., Zhang, J., Zhang, K., Xue, T., Lu, J., 2009. Electrocatalytic carboxylation of benzyl chloride at silver cathode in ionic liquid BMIMBF₄. *Chinese J. Chem.* 27, 1041–1044. <https://doi.org/10.1002/cjoc.200990174>
- Pappenfus, T.M., Lee, K., Thoma, L.M., Dukart, C.R., 2009. Wind to Ammonia: Electrochemical Processes in Room Temperature Ionic Liquids. *ECS Trans.* 16, 89–93. <https://doi.org/10.1149/1.3159311>
- Reche, I., Gallardo, I., Guirado, G., 2015. Cyclic voltammetry using silver as cathode material: A simple method for determining electro and chemical features and solubility values of CO₂ in ionic liquids. *Phys. Chem. Chem. Phys.* 17, 2339–2343. <https://doi.org/10.1039/c4cp05409a>
- Reche, I., Gallardo, I., Guirado, G., 2014a. Electrochemical studies of CO₂ in imidazolium ionic liquids using silver as a working electrode: A suitable approach for determining diffusion coefficients, solubility values, and electrocatalytic effects. *RSC Adv.* 4, 65176–65183. <https://doi.org/10.1039/c4ra11297k>
- Reche, I., Gallardo, I., Guirado, G., 2014b. The role of cations in the reduction of 9-fluorenone in bis(trifluoromethylsulfonyl)imide room temperature ionic liquids. *New J. Chem.* 38, 5030–5036. <https://doi.org/10.1039/c4nj01200c>
- Ruelius, W., Johns, C., Mouelhi, M.E.L., Fenselau, H., Dulik, M.M., 1987. SPECIES-DEPENDENT ENANTIOSELECTIVE GLUCURONIDATION OF THREE 2-ARYLPROPIONIC ACIDS: Naproxen, Ibuprofen, and Benoxaprofen. *Drug Metab. Dispos.* 15, 767–772.
- Senboku, H., Katayama, A., 2017. Electrochemical carboxylation with carbon dioxide. *Curr. Opin. Green Sustain. Chem.* 3, 50–54. <https://doi.org/10.1016/j.cogsc.2016.10.003>
- Shaw, N., Schlitzer, S., 2015. Green Synthesis: Naproxen [WWW Document]. URL <https://es.slideshare.net/NathanShaw3/green-chemistry-synthesis-of-naproxen-54358185>

- Sun, L., Ramesha, G.K., Kamat, P. V., Brennecke, J.F., 2014. Switching the reaction course of electrochemical CO₂ reduction with ionic liquids. *Langmuir* 30, 6302–6308. <https://doi.org/10.1021/la5009076>
- Tateno, H., Nakabayashi, K., Kashiwagi, T., Senboku, H., Atobe, M., 2015. Electrochemical fixation of CO₂ to organohalides in room-temperature ionic liquids under supercritical CO₂. *Electrochim. Acta* 161, 212–218. <https://doi.org/10.1016/j.electacta.2015.01.072>
- Tokuda, M., 2006. Efficient Fixation of Carbon Dioxide by Electrolysis - Facile Synthesis of Useful Carboxylic Acids -. *J. Nat. Gas Chem.* 15, 275–281. [https://doi.org/10.1016/S1003-9953\(07\)60006-1](https://doi.org/10.1016/S1003-9953(07)60006-1)
- Uziel, Y., Hashkes, P.J., Kassem, E., Padeh, S., Goldman, R., Vollach, B., 2000. The use of naproxen in the treatment of children with rheumatic fever. *J. Pediatr.* 137, 269–271. <https://doi.org/10.1067/mpd.2000.107158>
- Williams, D.B.G., Lawton, M., 2010. Drying of organic solvents: Quantitative evaluation of the efficiency of several desiccants. *J. Org. Chem.* 75, 8351–8354. <https://doi.org/10.1021/jo101589h>
- Yamauchi, Y., Fukuhara, T., Hara, S., Senboku, H., 2008. Electrochemical carboxylation of α,α -difluorotoluene derivatives and its application to the synthesis of α -fluorinated nonsteroidal anti-inflammatory drugs. *Synlett* 428–442. <https://doi.org/10.1055/s-2008-1032069>
- Yamauchi, Y., Hara, S., Senboku, H., 2010. Synthesis of 2-aryl-3,3,3-trifluoropropanoic acids using electrochemical carboxylation of (1-bromo-2,2,2-trifluoroethyl)arenes and its application to the synthesis of β,β,β -trifluorinated non-steroidal anti-inflammatory drugs. *Tetrahedron* 66, 473–479. <https://doi.org/10.1016/j.tet.2009.11.053>
- Yoo, W.J., Kondo, J., Rodríguez-Santamaría, J.A., Nguyen, T.V.Q., Kobayashi, S., 2019. Efficient Synthesis of α -Trifluoromethyl Carboxylic Acids and Esters through Fluorocarboxylation of gem-Difluoroalkenes. *Angew. Chemie - Int. Ed.* 58, 6772–6775. <https://doi.org/10.1002/anie.201902779>
- Zhou, F., Liu, S., Yang, B., Wang, P., Alshammari, A.S., Deng, Y., 2015. *Electrochemistry Communications* Highly selective and stable electro-catalytic system with ionic liquids for the reduction of carbon dioxide to carbon monoxide.

Electrochem. commun. 55, 43–46.