Electrosynthesis of Benzolactones by Nickel-Catalyzed Carboxylation of Epoxide-Functionalized Aromatic Halides

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Abstract: The electrochemical, nickel-catalyzed carbon dioxide incorporation into 2-haloaryl epoxides led chemoselectively to different carboxylated products according to the nature of the substrate and to the catalytic system. Whereas terminal epoxide derivatives led to cyclic carbonates in good yields, disubstituted epoxides reacted through a first carbon-halogen bond carboxylation followed by epoxide ring opening. Five-membered ring benzolactones were selectively formed with cyclam as the ligand, whereas 6-membered ring isocoumarine derivatives were obtained using 2,2'-bipyridine.

Key words: electrochemical, benzolactone, nickel, carbon dioxide, epoxide

The synthesis of benzolactone structures such as coumarines or isocoumarines has attracted much attention due to their use as antitumoral, antifungal and antibacterial agents.[1]

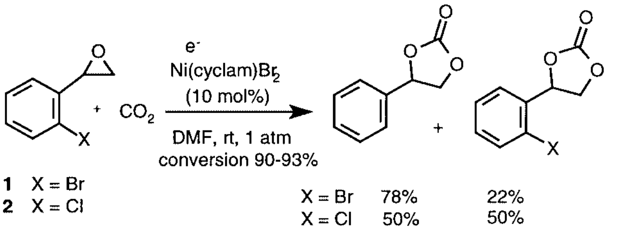
We describe here a new method of synthesis of isocoumarine and other benzolactone derivatives, based on the use of an electrochemical carboxylation of epoxide-containing aromatic halides. The synthesis of isocoumarine structures generally involves the cyclization of functionalyzed benzoic acid derivatives.[2,3] Oxidation reactions of indanones have also been described.[4,5]

The electrochemical reactivity of terminal epoxides with carbon dioxide for the synthesis of cyclic carbonates has been examined.[6] The reaction was catalyzed by Ni(cyclam)Br_2 (cyclam = 1,4,8,11-tetraazacyclotetradecane), but could also be effected in good yields with $Ni(bipy)_3^{2+}$, $2BF_4^-$ as the catalyst (bipy = 2,2'-bipyridine).[7]

We now describe that different chemoselectivities could be observed in the related electrochemical carboxylation of difunctional aromatic compounds **1-4**, bearing epoxide and halogen as the functional groups.[8]

The electrocarboxylation of substrates **1** and **2** in DMF catalyzed by Ni(cyclam)Br_2 in a single-compartment cell led to the selective incorporation of CO_2 into the oxirane ring to form the corresponding cyclic carbonates in quantitative yields [9] (Scheme 1). The best conditions for this reaction were found to be the use of a magnesium anode, with CO_2 bubbling into the solution at atmospheric pressure and KBr as the supporting electrolyte.

The reaction proceeds through the Mg^{2+} and Br^- induced oxirane ring opening and the parallel CO_2 activation by coordination to electrogenerated Ni^I(cyclam)Br complex. The process is followed by the addition of activated CO_2 to the bromoalcoholate and ring closure to the cyclic carbonate with bromide elimination[7].

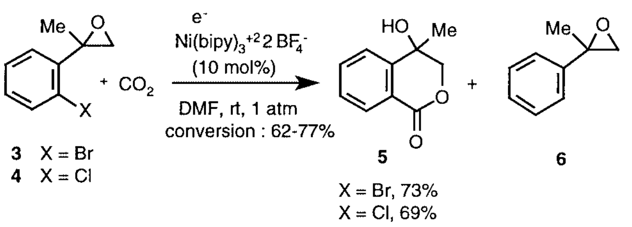


Scheme 1

Two products were isolated; the 2-bromo (or 2-chloro)phenyl carbonate and the corresponding dehalogenated styrene carbonate. The dehalogenation was more important with X = Br. The carboxylation of **1** and **2** catalyzed by $Ni(bipy)_3^{2+}2BF_4^-$ led to very similar results. The presence of KBr as supporting electrolyte (as compared to the use of $Bu_4N^+BF_4^-$), was an important factor to obtain good conversions and yields of cyclic carbonate both with Ni-cyclam and Ni-bipy catalytic systems. Thus, yields of cyclic carbonate went from 80 to 7% by changing from KBr to $Bu_4N^+BF_4^-$ in the $Ni(bipy)_3^{2+}2BF_4^-$-catalyzed electrocarboxylation of styrene oxide.

Interestingly, CO_2 was chemoselectively incorporated into the oxirane ring and no carboxylation of the Ar-X bond was observed, although the efficient electrocarboxylation of aromatic halides has been reported in the presence of Ni-phosphine complexes[10,11] as well as in the presence of consumable anodes.[12,13]

In contrast with the results of the carboxylation of substrates **1** and **2**, when disubstituted epoxide derivatives **3** or **4** were electrolyzed with CO_2 under the same electrochemical conditions, no cyclic carbonate was formed. The reaction involved the activation and the carboxylation of the Ar-X bond, and different reaction products were formed depending on the nature of the catalytic system. Thus, the electrocarboxylation of **3** in the presence of $Ni(bipy)_3^{2+}$ $2BF_4^-$ led to the formation of the isocoumarine derivative, **5**, in 73% selectivity, together with dehalogenated compound **6** (27%), with an epoxide conversion of 77% (Scheme 2).



Scheme 2

The formation of **5** proceeded through the carboxylation of the Ar-Br bond, followed by epoxide ring opening by the carboxylate intermediate. The carboxylic acid-epoxide derivative could be isolated when aliquots were directly hydrolyzed during electrolysis. By-product **6** was formed by reductive cleavage and protonation by the electrolytic medium[14] of the aryl-halogen bond of **3**.

Several experimental conditions were examined for this novel tandem electrochemical carboxylation-cyclization process with substrate **3** as the model compound, as shown in the Table.

The best yields of **5** were obtained with the use of an Al/stainless steel or with Al/C couple of electrodes and with $Bu_4N^+BF_4^-$ as the supporting electrolyte (entries 3, 4). With a Mg anode (entries 1, 2) the isocoumarine **5** was also formed but the reaction favored the formation of **6**. Very low conversions were attained when KBr was used as supporting electrolyte instead of $Bu_4N^+BF_4^-$ (entries 5, 6), in sharp contrast with the results obtained with the carboxylations of substrates **1** and **2**. The use of $Ni(bipy)Br_2$ as the catalyst (entry 7) replacing $Ni(bipy)_3^{2+}2BF_4^-$ afforded low substrate conversion and high selectivity towards dehalogenated **6**.

Table Electrocarboxylation reactions of substrate **3**[a].

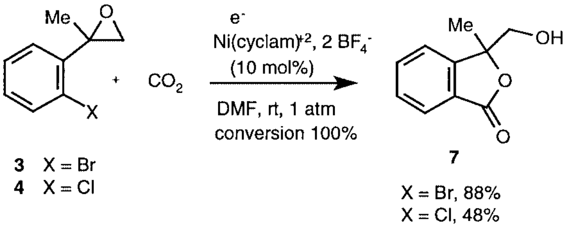
Entry	Catalyst	Supporting electrolyte	Anode / Cathode	Conversion	Selectivity 5	Selectivity 6	Selectivity 7
1	**A**	$Bu_4N^+BF_4^-$	Mg / C	57%	39%	61%	-
2	**A**	$Bu_4N^+BF_4^-$	Mg/stainless steel	80%	32%	62%	-
3	**A**	$Bu_4N^+BF_4^-$	Al / C	65%	77%	23%	-
4	**A**	$Bu_4N^+BF_4^-$	Al/stainless steel	77%	73%	27%	-
5	**A**	KBr	Mg/stainless steel	13%	23%	38%	-
6	**A**	KBr	Al/stainless steel	12%	36%	27%	-
7	**B**	$Bu_4N^+BF_4^-$	"	14%	7%	50%	-
8	**C**	$Bu_4N^+BF_4^-$	"	100%	-	12%	88%
9	**D**	$Bu_4N^+BF_4^-$	"	100%	11%	14%	75%

[a] For general elecrocarboxylation procedure, see ref. 9. Catalyst **A**: $Ni(bipy)_3^{2+}2BF_4^-$; catalyst **B**: $Ni(bipy)Br_2$; catalyst **C**: $Ni(cyclam)^{2+}2BF_4^-$; catalyst **D**: $Ni(cyclam)Br_2$.

The chloroderivative **4** presented the same behaviour and afforded the hydroxybenzolactone **5** in 69% selectivity under the conditions of entry 4 (conversion of 62%, Scheme 2).

When substrate **3** was carboxylated in the presence of $Ni(cyclam)^{2+}2BF_4^-$ as the catalyst, a different 5-membered ring lactone, **7**, was obtained in 88% yield (Scheme 3 and Table, entry 8). The alternative use of $Ni(cyclam)Br_2$ as the catalyst led also to **7** with a selectivity of 75% (entry 9).

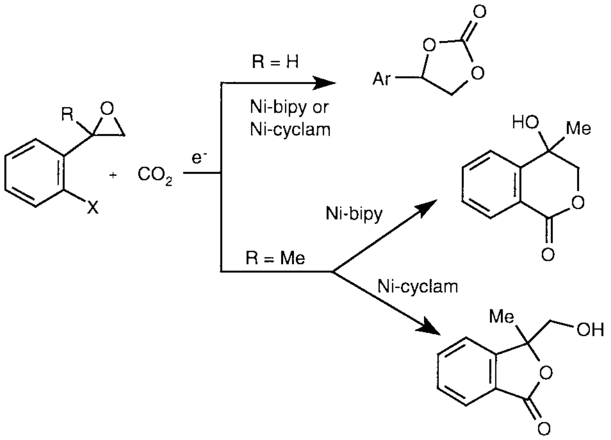
The $Ni(cyclam)^{2+}2BF_4^-$-catalyzed electrocarboxylation of chloro epoxide derivative **4** also afforded lactone **7** in 48% yield (Scheme 3).



Scheme 3

Our results indicate that the electrocarboxylation of difunctional compounds **1-4** can be directed towards different reaction products, depending on the nature of the epoxide and of the catalytic system. Monosubstituted epoxides **1** and **2** led selectively to the formation of cyclic carbonates with partial dehalogenation. In contrast, disubstituted epoxides **3** and **4** reacted exclusively at the aryl-halogen bond with carboxylate formation and further intramolecular cyclization. The nature of the ligand associated to the nickel complex plays a determinant role in the control of the reaction selectivity. Whereas the Ni-cyclam system favors lactone **7** with epoxide ring opening on the most substituted position, the Ni-bipy system directs the reaction towards benzolactone **5**, with carboxylate ring opening on the less substituted epoxide position (Scheme 4).

In conclusion, this reaction presents a high substrate chemoselectivity (cyclic carbonate or lactone according to R = H or R = Me, respectively), as well as an interesting regioselectivity, depending upon the ligands on the nickel catalyst. The important role of the ligand determining the reaction selectivity has already been observed in



Scheme 4

other electrochemical Ni-catalyzed reactions involving allyl aryl ethers.[15] Work is in progress to determine the mechanism and the particular role of the ligands in these electrochemical carboxylation reactions.

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(9) **General electrochemical procedure**: the electrocarboxylations of **1-4** (3 mmol) were run in DMF (30-40 mL), containing the supporting electrolyte (KBr or Bu_4NBF_4, 0.03M) and the corresponding Ni(II) complex (10 mol%) in a single-compartment cell fitted with a Mg or Al/stainless steel couple of electrodes, at room temperature and at atmospheric CO_2 pressure. Electrolyses were conducted at constant current (60 mA) for 7 h, and then the solutions were heated at 50 °C overnight, extracted with diethyl ether and aqueous HCl (0.01M), washed with water, dried over $MgSO_4$ and evaporated. The crude products were purified by column chromatography on silica-gel, with pentane-diethyl ether mixtures as eluents. Products were analyzed by GC, ^1H and ^{13}C NMR and mass spectrometry, and the spectra compared with those of authentic samples for the known compounds.

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