

Kolbe Anodic Decarboxylation as a Green Way To Access 2-Pyrrolidinones

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N ootropic compounds are a group of pharmacologically $active pure elisten = \frac{1}{2}$ active pyrrolidones.¹ These molecules, which enhance cognition properties and possess a large prescription field, are particularly interesting synthetic targets for the pharmaceutical industry.² Synthetic organic electrochemistry takes its roots from the classic works of Faraday³ and Kolbe⁴ on the electrolysis of aliphatic carboxylic acids. Although numerous transformations have been developed since then, 5-9 and many of them were successfully used in several industrial processes,^{10,11} the potential of preparative organic electrochemistry remains underestimated, even though electrosynthesis represents one of the safest and greenest method to perform organic redox reactions. Hopefully, the new commercially available Electrasyn 2.0 electrolysis setup will facilitate the use of electrosynthesis in organic synthetic laboratories.¹² The Kolbe anodic decarboxylation is among the oldest and probably the most famous oxidative electro-organic reactions.⁴ This approach enables the environmentally friendly synthesis of long-chain alkanes from short-chain carboxylic acids, in three steps.^{13,14}

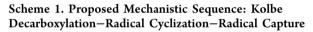
radical cyclization and a radical-radical cross-coupling.

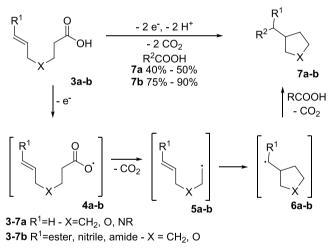
methodology includes a Kolbe decarboxylation, followed by an intramolecular

Schäfer *et al.* have previously shown that the electrogenerated radical **5a** can undergo radical cyclization and that the final cyclic radical **6a** could be trapped by radicals generated by the anodic decarboxylation of a coacid present in excess. An excess of the coacid is used in order to prevent the homocoupling of substrate **6a**. Unfortunately, the yields in cyclic compounds **7a** remains modest (see Scheme 1).¹⁵

Our group has showed formerly that the presence of an electron-withdrawing substituent on the C–C double bound dramatically increases the yield of the desired cyclic compounds 7**b** since the electrodeficient double bond is a better coupling partner for the nucleophilic electrogenerated radical (see Scheme 1).¹⁶ It also stabilizes the cyclic radical.

In this Article, we will describe a new, original, and environmentally friendly electrosynthesis of pyrrolidinones of pharmaceutical interest (see Scheme 2). This process expands





the scope of the synthetic applications of the Kolbe electrocyclization reaction.

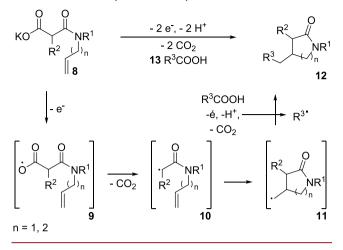
At the outset of this investigation, compounds 8a-8d were synthesized in a straightforward manner, according to the sequence outlined in the Supporting Information. Potassium salts (8a-8d) were used as the substrates of the electrocyclization, because of the instability of the corresponding carboxylic acids.¹⁷ The amide group was functionalized with various groups, such as allyl, benzyl, isopropyl, or neopentyl, to avoid the amide function oxidation under the electrolytic conditions.¹⁸ For instance, the allyl and benzyl protecting

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Scheme 2. Electrosynthesis of Pyrrolidones



groups could easily be deprotected or further functionalized after the oxidative reaction, opening the way to more chemical diversity, which is especially important for drug design.^{19,20}

With the desired precursors in hand, the electrolysis parameters were optimized (see Table 1). Bulk electrolysis that has been performed using previously reported conditions led to the formation of the desired pyrrolidones in very modest yields.³ In order to avoid homocoupling of the radical **11**, the substrate should be highly diluted in methanol (66 mM in methanol), and the current density, which is a key parameter, should be kept between 25 mA/cm² and 37.5 mA/cm². In addition, a temperature between 10 °C and 20 °C, the use of smooth platinum electrodes, and an excess of coacid (5 equiv) provided the optimum results. Finally, the use of 5 equiv of supporting electrolyte (KOH) avoided the decarboxylation of the substrate by maintaining basic conditions.

With the optimized conditions ready, the scope and limitation of the methodology were investigated (see Table 2). The variation of the coacid nature allowed the synthesis of several pyrrolidinones substituted in position 4. The

Table 1. Optimization of the Electrocyclization Reaction

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substitution of that position has been reported to have a major effect on the biological activity of this class of compounds.² In the presence of acetic acid and propionic acid, the electrocyclization proceeded smoothly and afforded aliphatic pyrrolidinones 12a, 12b, 12h, and 12j in good yields (60%-71%). Furthermore, the use of monomethyl hydrogen succinate (13f), ethyl potassium malonate (13e), and 4acetylbutyric acid (13g) as coacids also enables the formation of pyrrolidinones 12e, 12f, 12g, and 12i in good yields. 3,3,3-Trifluoropropionic acid (13d) and fluoropropionic acid (13c) allowed the formation of fluorinated pyrrolidinones 12c and 12d but lower yields are obtained with the latest. This result is due to the higher acidity of the fluoroacetic acid. Besides, comparable yields are obtained in the presence of the four protecting groups, which enables one to produce several Nsubstituted pyrrolidones (12a-12n). In the presence of a benzyl protecting group, there is the formation of the side product 14a, which is generated by the cross-coupling of the radical 10 and the radical which comes from the oxidative decarboxylation of the coacid 13b. This phenomenon might be due to the steric hindrance of substrate 8d, which limits the amide C-N bond rotation or absorption phenomenon of the benzyl-substituted radicals on the electyrode surface. Finally, in order to expand the scope of this electrocyclization reaction, we applied the optimized conditions to substrate 8e bearing a homoallyl function. The reaction of substrate 8e also proceeded smoothly and provided the corresponding 6membered ring product 12l. However, as the 6-exo cyclization is known to proceed at a lower speed, compared to 5-exo cyclization, the primary radical 10 can then dimerize and we observed the formation of the side-product dimer 14c, along with the desired piperidinone.

To broaden the scope of the functionalized pyrrolidinones cyclization, we synthesized the allylic and propargylic substrates 8f and 8g in a straightforward manner, according to the sequence outlined in the Supporting Information. The electrocyclization of those substrates allowed the formation of

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		KONN	<u>- 2 e , - 2 H</u> - 2 CO ₂ CH ₃ CH ₂ COOH	→			
		8a		/	12a		
entry	C (mol/L)	current density (mA/cm ²)	temperature, T (°C)	electrodes	solvent	[KOH] (equiv)	yield (%)
1	0.033	25	10	platinum	MeOH	5	68
2	0.066	25	10	platinum	MeOH	5	71
3	0.132	25	10	platinum	MeOH	5	26
4	0.066	12,5	10	platinum	MeOH	5	56
5	0.066	25	10	platinum	MeOH	5	71
6	0.066	50	10	platinum	MeOH	5	64
7	0.066	25	0	platinum	MeOH	5	29
8	0.066	25	10	platinum	MeOH	5	71
9	0.066	25	40	platinum	MeOH	5	37
10	0.066	25	10	platinum	MeOH	5	71
11	0.066	25	10	platinum	EtOH	5	49
12	0.066	25	10	platinum	CH ₃ CN	5	70
13	0.066	25	10	platinum	MeOH	5	71
14	0.066	25	10	platinum	MeOH	0.05	54
15	0.066	25	10	platinum	MeOH	0.33	66
16	0.066	25	10	platinum	MeOH	5	71

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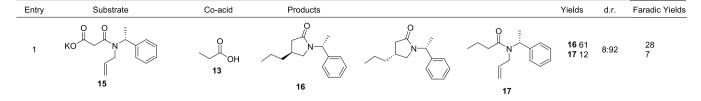
Table 2. Scope and Limitations of Substrates

Entry	Substrate	Co-acid	Products	Yields	Faradic Yields
1	КОССТАНИИ	0 ————————————————————————————————————		61	27
2	8a	о ОН 13b	0 N 12b	71	30
3		о FH ₂ С ОН 13с	FH ₂ C, N- 12c	34	17
4		F₃C ↓ OH 13d	F ₃ C 12d	68	29
5		о 0 13е ОК		70	30
6		O O I 3f		65	28
7		о о Н 13g	0 12g	60	27
8	КОСТОРИ	о он 13ь	0 N 12h	64	27
9	KO N N BC	о О 13f		60	27
10	KO KO Bd	о 13b		12k 55 14a 14	9 25 4 7
11		O O I 3f		N 14b 1	26 1 8
12	ко о компания ве	о И 13b		N 12m 7 14c 13	0 30 3 8
13	KO KO Sf	о Чон 13b	0 N 12m	66	28
14	KO Bg	о 13b		64	29

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Table 3. Diastereoselective Pyrrolidinone Electrosynthesis



the position 5-substituted pyrrolidinones **12m** and **12n**, in 66% and 64% yields, respectively.

Because of the importance of being able to control the chirality while developing bioactive molecules, we investigated the possibility to develop a diastereoselective electrocyclization of pyrrolidinones. Our strategy to induce a stereoselectivity during the cyclization was to incorporate a chiral center in the structure of the precursor. With this intention, substrate 15 was synthesized from the (R)-(+)- α -methylbenzylamine. The desired precursor available for use, the electrochemical reaction was performed using the previously optimized conditions. Finally, the product was analyzed by high-performance liquid chromatography-mass spectroscopy (HPLC-MS). Those analyses have showed a good diastereoselective ratio for this electrochemical transformation. As a result, the use of (R)-(+)- α -methylbenzylamine as chiral inductor has led to the formation of the enantio-enriched pyrrolidinones 16 with a diastereoselective ratio of 96:4 (see Table 3). One of the main advantages of using benzylamine derivatives as chiral inductors is that they can easily be removed after the electrochemical process by catalytic hydrogenation,²¹ catalytic transfer hydrogenation,²² and other reactions.²³

In summary, we have developed methodology for the efficient and environmentally friendly electrochemical synthesis of functionalized pyrrolidinones. Our approach includes a Kolbe decarboxylation, followed by a radical cyclization and, finally, a cross-coupling step between the radical formed and a radical engendered by the concomitant decarboxylation of a coacid. This reaction enables the formation of two carboncarbon bonds in one step. The functional group tolerance of this method proved to be quite broad. Indeed, the electrolysis can be successfully accomplished in the presence of ester, olefin, ketone, halogen, amide, and alkyne functions. Finally, the methodology was successfully transposed toward the synthesis of the stereoenriched pyrrolidinone 16 with a diastereoselective ratio of 96:4 by using a chiral inductor group on the precursors. The methodology represents an attractive procedure for the synthesis of diversely functionalized pyrrolidinones.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00056.

General experimental section; details regarding the synthesis of various compounds used/produced in this work; table of details regarding optimization of the electrocyclization reaction; NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest. [§]Deceased (July 31, 2017).

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