

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

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Cite This: *Org. Lett.* 2020, 22, 1771–1775



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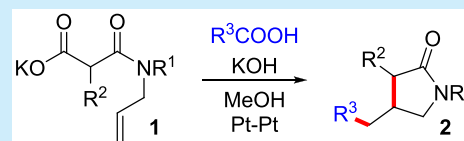


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Supporting Information

ABSTRACT: Nootropic compounds are a group of pharmacologically active pyrrolidones. These molecules, which enhance cognition properties and possess a large prescription field, are particularly interesting synthetic targets for the pharmaceutical industry. In this Article, we disclose an effective and environmentally friendly pyrrolidinone synthesis using electrosynthesis. The newly developed methodology includes a Kolbe decarboxylation, followed by an intramolecular radical cyclization and a radical–radical cross-coupling.



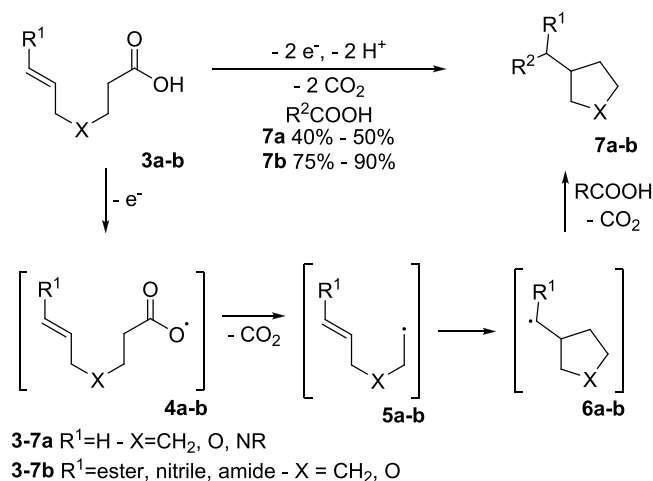
Nootropic compounds are a group of pharmacologically active pyrrolidones.¹ These molecules, which enhance cognition properties and possess a large prescription field, are particularly interesting synthetic targets for the pharmaceutical industry.² Synthetic organic electrochemistry takes its roots from 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}

Schäfer *et al.* have previously shown that the electro-generated 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 bond dramatically increases the yield of the desired cyclic compounds **7b** 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

Scheme 1. Proposed Mechanistic Sequence: Kolbe Decarboxylation–Radical Cyclization–Radical Capture



the scope of the synthetic applications of the Kolbe electrocyclozation 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 electrocyclozation, 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

Received: January 6, 2020

Published: February 18, 2020

Table 2. Scope and Limitations of Substrates

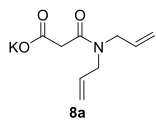

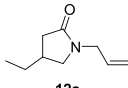

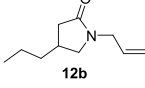

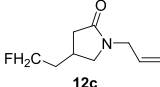

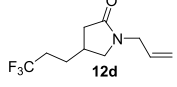
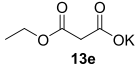
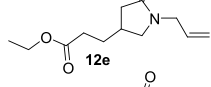
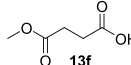
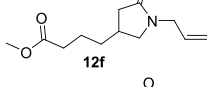
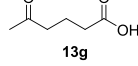
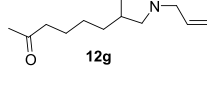
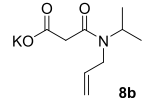

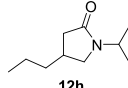
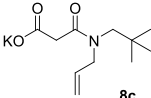
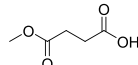
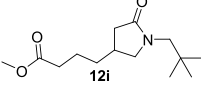
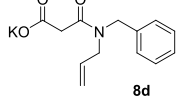

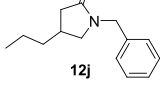
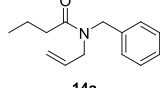
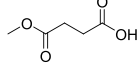
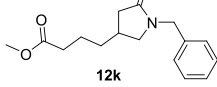
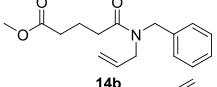
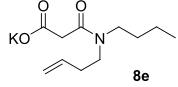

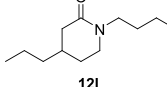
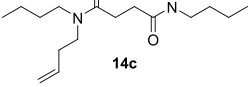
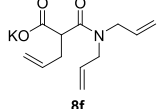

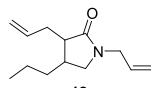
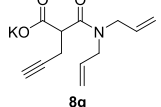

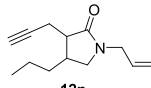
Entry	Substrate	Co-acid	Products	Yields	Faradic Yields	
1				61	27	
2				71	30	
3				34	17	
4				68	29	
5				70	30	
6				65	28	
7				60	27	
8				64	27	
9				60	27	
10					12k 59 14a 14	25 7
11					12l 56 14b 11	26 8
12					12m 70 14c 13	30 8
13				66	28	
14				64	29	

Table 3. Diastereoselective Pyrrolidinone Electrosynthesis

Entry	Substrate	Co-acid	Products	Yields	d.r.	Faradic Yields
1					16 61 17 12	8:92 7

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 carbon–carbon 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

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).

■ ACKNOWLEDGMENTS

Financial support for this research by the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) and the Université Catholique de Louvain are gratefully acknowledged.

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