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Organic electrochemistry applied to the Kolbe anodic cyclisation of functionalised 2-pyrrolidinones

Abstract

Racetams are a class of pharmacologically active 2-pyrrolidones. These molecules, which enhance cognition properties and possess a large prescription field, are exciting synthetic targets for the pharmaceutical industry. In this Article, we disclose an effective, cost-efficient, and environmentally friendly synthesis of 2-pyrrolidinones by the mean of electrosynthesis. The newly developed methodology includes a Kolbe decarboxylation, followed by an intramolecular radical cyclisation, and a final radical-radical cross-coupling.

Keywords

Cyclisation, pyrrolidinone, radical reactions, green chemistry, electron transfer

Scheme 1

1. Introduction

1.1. Racetams

Racetams are a family of molecules that embed a 2-pyrrolidinone core [1]. This group of molecules is well-known for its positive effects on cognitive functions [2]. Indeed, those γ-lactams have a large prescription field and are used for the treatment of central nervous system disorders, cognition and memory problems, Alzheimer disease, epilepsy, seizure, neurodegenerative diseases, stroke, ischaemia, and to deal with stress and anxiety. Due to the strong interest in those compounds and given the increasing demand for environmentally friendly, economic, and versatile methodologies, we decided to design an original cyclisation and functionalisation of 2-pyrrolidinones via organic electrochemistry. Indeed, this technology is currently benefiting from a renewed interest, particularly from the industrial world. Indeed, organic electrochemistry is relatively ecologic, producing a minimum of waste thanks to its capacity to precisely adjust the oxidation potential and to avoid the use of oxidation or reduction reagents. Moreover, this methodology is economic, using the cheapest source of electrons, namely the electricity.

Finally, electrochemical processes are easily scalable.

Organic electrochemistry is a combination of two particular chemistry fields: organic synthesis and electrochemistry. The purpose of this discipline is to study the behaviour of organic molecules under electrolytic conditions. Synthetic organic electrochemistry takes its roots from the classic works of Faraday [3] and Kolbe [4] 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 methods to perform organic redox reactions. Hopefully, the newly commercially available standardised electrolysis setups will facilitate the use of electrosynthesis in synthetic laboratories [12].

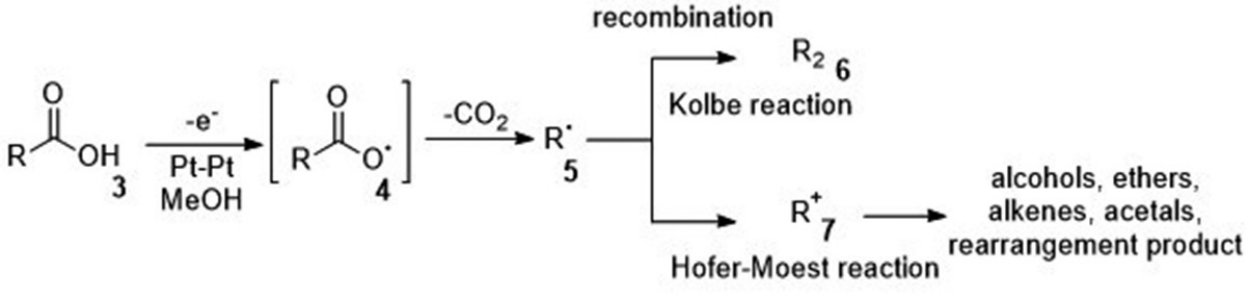
1.2. Kolbe reaction

The Kolbe anodic decarboxylation is among the oldest and probably the most well-known electro-organic reactions [4]. This approach originally enabled the ecological synthesis of long-chain alkanes from short-chain carboxylic acids. The Kolbe reaction involves three elementary steps (see Scheme **2**) [13-14]. Initially, a carboxylic acid **3** loses one electron at the anode to produce the corresponding acyloxy radical **4**. This species is highly unstable and decarboxylates spontaneously to give the corresponding alkyl radical **5**. Finally, due to the high local concentration of radicals at or near the electrode surface, radical recombination occurs, leading to the Kolbe dimer **6**.

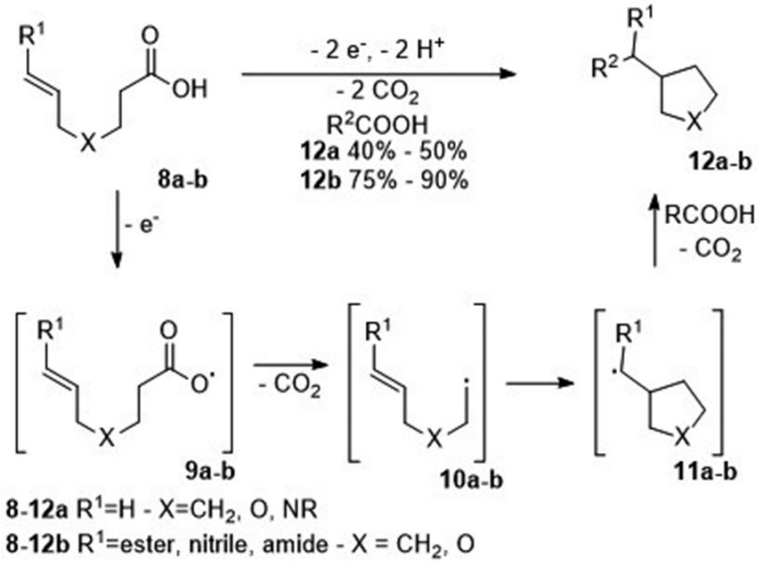
In some cases, the radical **5** can also be oxidised a second time to give the corresponding carbocation **7**. This pathway, usually called the Hofer-Moëst reaction, can lead to various products, such as ethers, acetals, alkenes, and so on. Both processes have their own synthetic interest, and parameters enabling the selective application of either a cationic or a radical pathway have been broadly studied. One of the most significant parameters is the nature of the substrates. Indeed, a primary radical or a radical flanked by an electron-withdrawing group are unlikely to get overoxidised and will mostly undergo radical transformations. In contrast, a radical tertiary species or a radical intermediate substituted by an electron-donating group can easily be oxidised, leading to the corresponding carbocation, which can then undergo classic ionic transformations.

1.3. Kolbe electrocyclisation

In 1993, Schäfer *et al.* have shown that the electrogenerated radical **10a** can undergo radical cyclisation and that the corresponding cyclic radical **11a** could be trapped by a radical generated by the anodic decarboxylation of a co-acid present in excess (see Scheme **3**). An excess of a co-acid has to be used to prevent the homo-coupling of the substrate **11a**. Unfortunately, the yields in cyclic compounds remain modest **12a** [15]. Our group has shown previously that the



Scheme 2



Scheme 3

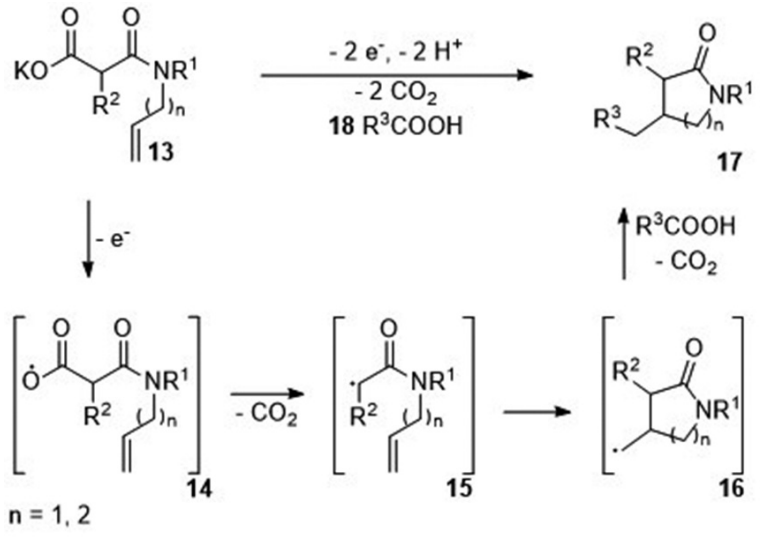
presence of an electron-withdrawing substituent on the C−C double bond dramatically increases the yield of the desired cyclic compounds **12b** since the electrodeficient double bond is a better coupling partner for the nucleophilic electrogenerated radical [16].

2. Results

In this publication, we will describe a new, original, and ecological electrosynthesis of 2-pyrrolidinones of pharmaceutical interest (see Scheme **4**). This process expands the scope of the synthetic applications of the Kolbe electrocyclisation reaction. Furthermore, this newly developed methodology is an elegant way to cyclize and functionalize racetams, in only one process, two C-C bonds are formed.

2.1. Electrocyclisation substrates

At the outset of this investigation, substrates **13a−13d** were readily synthesised using standard



Scheme 4

procedures. Potassium salts (**13a−13d**) were used as the precursors in the electrocyclisation, due to the intrinsic instability of the corresponding carboxylic acids [17]. The amide function was substituted with various groups, such as allyl, benzyl, isopropyl, or neopentyl, to avoid the amide group oxidation under the electrolytic conditions [18]. For instance, the allyl and benzyl protecting substituents could easily be removed or further functionalised post electrolysis, opening the way to more structural diversity, which is especially relevant for drug design [19-20].

2.2. Optimisation of the electrocyclisation of 2-pyrrolidinones

With the desired substrates ready, the electrolysis parameters were optimised (see Table 1). Bulk electrolysis that has been performed using previously reported conditions led to the formation of the desired 2-pyrrolidones in very modest yields. With the aim of avoiding homo-coupling of the radical intermediate **16**, the precursor **13** 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. Additionally, a temperature between 10 °C and 20 °C, the use of smooth platinum electrodes, and an excess of co-acid (5 equiv) provided the optimum yields. Finally, the use of 5 equiv of supporting electrolyte (KOH) prevented the decarboxylation of the reagent **13** by maintaining basic conditions.

2.3. Exemplification of the electrocyclisation of 2-pyrrolidinones

With the optimised conditions in hands, the scope and limitation of our new methodology were investigated (see Table 2). Variation in the co-acid nature enabled the synthesis of various 2-pyrrolidinones substituted in position 4. The functionalisation of that position has been reported to have a significant impact on the biological properties of this class of compounds [2]. In the presence of acetic acid (**18a**) and propionic acid (**18b**), the electrocyclisation proceeded smoothly and afforded the corresponding 2-pyrrolidinones **17a**, **17b**, **17h**, and **17j** in good yields (60%−71%). Moreover, the use of monomethyl hydrogen succinate (**18f**), ethyl potassium malonate (**18e**), and 4- acetylbutyric acid (**18g**) as co-acids led to the generation of

Entry	C (mol/l)	Current density (mA/cm²)	T (°C)	Electrodes	Solvent	KOH equiv.	Yields (%)
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	CH3CN	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

Table 1

2-pyrrolidinones **17e**, **17f**, **17g**, and **17i** in good yields. 3,3,3- trifluoropropionic acid (**18d**) and fluoroacetic acid (**18c**) formed the fluorinated 2-pyrrolidinones **17c** and **17d** with lower yields. This could be explained by the higher acidity of the fluoroacetic acid, which leads to its preferential oxidation over the malonamide. Furthermore, the methodology is mild and tolerates the presence of several types of protecting groups, such as: allyl, benzyl, isopropyl, and neopentyl, which allows synthesising the N-substituted 2-pyrrolidones (**17a−17n**). Nevertheless, the presence of a benzyl protecting group, led to the formation of the side product **19a**, which is generated by the cross-coupling of the radical **15** and the radical generated by the oxidative decarboxylation of the co-acid **18b**. This could be due to an adsorption phenomenon of the benzyl-substituted radicals on the electrode surface or to the steric hindrance of the substrate **13d**, which limits the amide C−N bond rotation. Finally, to further broaden the scope of this transformation, we applied the optimal conditions to substrate **13e** bearing a homoallyl function. The electrolysis of reagent **13e** proceeded smoothly and provided the corresponding 6- membered ring **17l**. However,

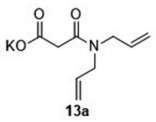
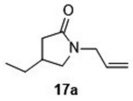
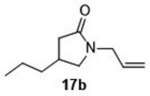
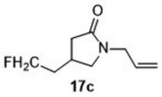
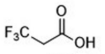
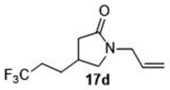
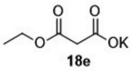
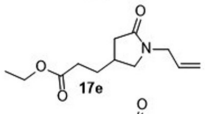
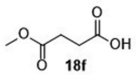
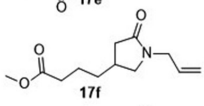
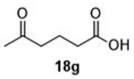
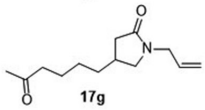
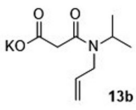
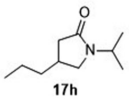
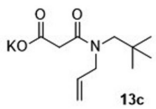
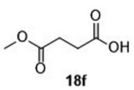
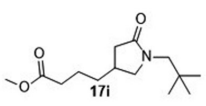
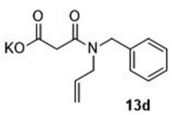
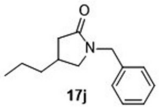
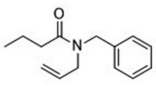
Entry	Substrate	Co-acid	Products	Yields	Faradic Yields
1	 **13a**	 **18a**	 **17a**	61	27
2		 **18b**	 **17b**	71	30
3		 **18c**	 **17c**	34	17
4		 **18d**	 **17d**	68	29
5		 **18e**	 **17e**	70	30
6		 **18f**	 **17f**	65	28
7		 **18g**	 **17g**	60	27
8	 **13b**	 **18b**	 **17h**	64	27
9	 **13c**	 **18f**	 **17i**	60	27
10	 **13d**	 **18b**	 **17j**  **19a**	**17j** 59 **19a** 14	25 7

Table 2

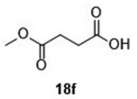
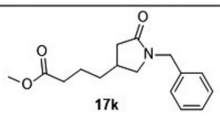
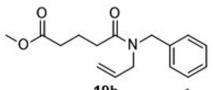
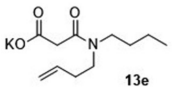
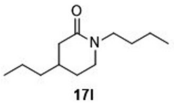
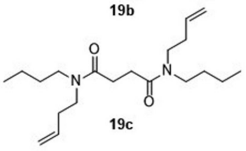
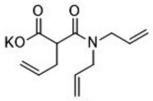
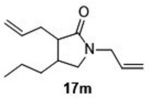
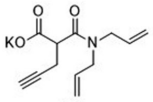
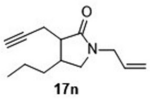
Entry	Substrate	Co-acid	Products		Yields	Faradic Yields
11		 18f	 17k	 19b	**17k** 56 **19b** 11	26 8
12	 13e	 18b	 17l	 19c	**17l** 70 **19c** 13	30 8
13	 13f	 18b	 17m		66	28
14	 13g	 18b	 17n		64	29

Table 2b

as the 6-exo-cyclisation is known to occur at a lower rate, compared to 5-exo-cyclisation, the primary radical **15** can then also dimerise. Indeed, we observed the formation of the dimer **19c**, along with the desired piperidinone **17l**. We also prepared the allylic and propargylic substrates **13f** and **13g**. The electrolysis of those substrates allowed the formation of the 5-substituted pyrrolidinones **17m** and **17n**, in 66% and 64% yields, respectively.

2.4. Diastereoselective electrocyclization

The control of the chirality is a crucial aspect while developing new bioactive molecules. Therefore, we investigated the option of developing a diastereoselective version of our electrocyclisation of 2-pyrrolidinones. Our strategy for inducing a stereoselectivity during the cyclisation step is to incorporate a chiral center in the structure of the substrate. Precursor **20** was synthesised from the (R)-(+)-α-methylbenzylamine and its electrolysis led to the desired cyclic product which was analysed using chiral HPLC-MS. The use of (R)- (+)-α-methylbenzylamine as chiral inductor has led to the generation of the enantio-enriched 2-pyrrolidinones **21** with a good 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 electrolysis by catalytic hydrogenation [21-22] or other means. [23]

3. Conclusion

In summary, we have developed a new methodology for the efficient and ecological electrochemical synthesis of functionalised 2-pyrrolidinones. Our approach includes a Kolbe decarboxylation, followed by a radical

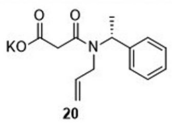
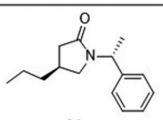
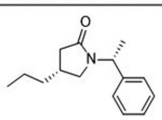
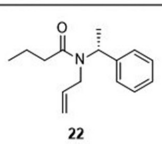
Entry	Substrate	Co-acid	Products			Yields	d.r.	Faradic Yields
1	 20	 18	 21		 22	**21** 61 **22** 12	4:96	28 7

Table 3

cyclisation and, finally, a cross-coupling between the radical formed and a radical generated by the concomitant decarboxylation of a co-acid. This reaction enables the formation of two carbon-carbon bonds in only one step. The functional group tolerance of this method proved to be quite broad. Indeed, the electrolysis can be performed in the presence of alkynes, amides, esters, halides, ketones, and olefins. Finally, the methodology was successfully transposed toward the synthesis of the stereoenriched 2-pyrrolidinone **21** with a diastereoselective ratio of 96:4 by using a chiral inductor group on the precursor **20**. The methodology represents an attractive procedure for the synthesis of diversely functionalised 2-pyrrolidinones.

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