Continuous Flow Electrocyclization and Successive Functionalization of 2-Pyrrolidinones

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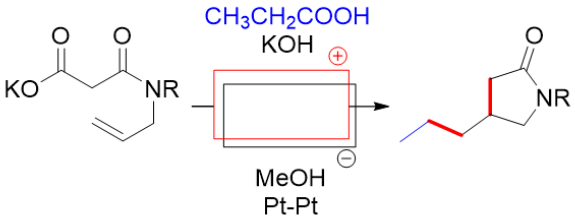
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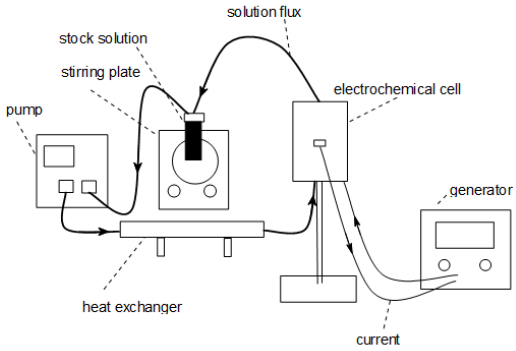
solution flux
stock solution
stirring plate
electrochemical cell
pump
generator
heat exchanger
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2-pyrrolidinones are important scaffolds found in numerous pharmacologically active compounds, such as Brivaracetam and Levetiracetam (antiepileptic drugs) or Piracetam and Pramiracetam (age-related memory impairment drugs). Among the numerous targets, nootropic agents represent an attractive class of compounds since they selectively improve cognitive functions. In this study, we would like to report the successful translation of an electrochemical batch oxidative cyclization/functionalization of 2-pyrrolidinones, using Kolbe reaction, from a batch type cell to a continuous flow electrochemical reactor. Combining organic electrosynthesis with continuous flow chemistry offers numerous advantages over batch electrolysis such as a faster reaction time, and better mixing of the heterogeneous reaction. Moreover, thanks to the use of continuous flow electrochemical cells, which have a precise geometry, a small inter-electrodes gap, and large electrodes surface area to reactor volume ratio, the productivity of organic electrosynthesis can be easily improved. Additionally, the translation of a batch electrochemical transformation to a continuous flow reactor is a critical step in the development of an electrochemical process given that flow chemistry is the most straightforward approach for the scale-up of this type of reactions. In this study, the application of continuous flow electrochemistry in our process allowed for an excellent productivity of 0.40 $g.h^{-1}.ml^{-1}$ and to reach up to 81 % yield of 2-pyrrolidinone within a loop-reactor setup (equipped with a 5 ml container).

Organic electrochemistry, continuous flow chemistry, cyclization, pyrrolidinones, green chemistry, radical reactions, Kolbe electrolysis.

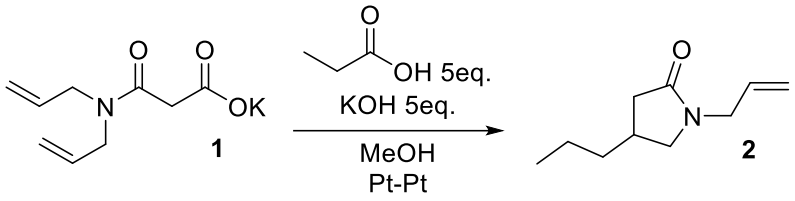
Introduction

Racetam molecules represent a family of pharmacologically active 2-pyrrolidinones[1-4]. These compounds, enhancing cognition properties and possessing a large prescription field, are particularly attractive synthetic targets for the pharmaceutical industry.[5]

Organic electrochemistry has a lot to offer to synthetic chemists given the large array of transformations accessible via electrolysis.[6] This technology is currently benefiting from a renewed interest, particularly from the industrial world.[7] In fact, organic electrosynthesis is not only a greener alternative to classical synthesis,[8] producing a minimum of waste, but it also achieves highly selective transformations under mild conditions due to its capacity to precisely tune the electrodes' potential. Moreover, this methodology is economically-relevant since it uses the cheapest source of electrons, namely electricity. Nevertheless, classical electrolysis in batch reactors still suffer from significant drawbacks that have severely impeded their scale-up. Fortunately, the use of continuous flow electro-reactors circumvents these issues. Indeed, over the last years, the development of continuous flow electrochemical cells has enabled the combination of organic electrosynthesis with continuous flow chemistry.[9] This union leads to the development of more efficient and sustainable processes. It rapidly achieves highly selective transformations in high yields due to the electrodes' larger surface areas and smaller volume reactors used in continuous flow compared to batch reactors. Such a large surface area also offers better temperature control.[10] Flow electrosynthesis improves reproducibility thanks to the precise geometry of the reactors used. During the electrolysis, a high degree of conversion can be achieved via a single pass through the cell. They also benefit from having a small inter-electrodes gap that decreases the system's impedance and avoids using a wasteful supporting electrolyte. Therefore,

unsurprisingly, the application of continuous flow electrolysis has shown to be the major route for scaling-up an organic electrochemical transformations.[11]

We have previously described a new, original, and environmentally respectful electrosynthesis of 2-pyrrolidinones of pharmaceutical interest under batch electrochemical conditions (see Scheme 1).[12] In the present article, we will disclose the transposition of our previous batch methodology to a continuous flow electrochemical reactor in order to demonstrate the industrial potential of this process. Indeed, an electrochemical transformation has only a real ecological interest if the reaction could be performed at an industrial scale and the scale-up of an electrochemical reaction is preferentially performed via continuous flow chemistry. Therefore, the transposition of an electrochemical process to a continuous flow reactor is a crucial step in the development of an electrochemical reaction. We decided to optimize the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one **2** using a continuous flow electrochemical reactor (Scheme 1), and we decided to study the electrocyclization of this substrate because this molecule gave the best results in our previous batch process.[12]



Scheme 1 electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 2

Results

To transpose the electrosynthesis of functionalized 2-pyrrolidinones, an IKA ElectraSyn Flow setup[13] was used (see Figures 1 and 2). This reactor is a modular parallel plate electrochemical cell (see Figure 3). The flow consists of two half cells (13 cm/4.6 cm/4 cm), held together with two

stainless steel plates using eight screws (see Figure 4). The two Teflon half-cells are equipped with platinum plated electrodes (12 cm^2 = 2 cm/6 cm), and are connected to an E36100 series DC power supply. A spacer with a thickness of 0.5 mm is located between the two electrodes, which creates a cell volume of 0.6 ml. The spacer slightly overlaps the electrodes in order to ensure a tight seal between the Teflon and the electrodes. The electrolytic solution is pumped through the system using a two-piston pump Knauer with a flow rate ranging from 1 ml/min to 10 ml/min.

Additionally, a heat exchanger was assembled and added to the set-up to cool the solution before it entered into the electrochemical cell since our previous studies have shown that the control of the temperature was crucial to avoid the formation of side products. In the continuous flow electrolysis, the stock solution is first pumped through the heat-exchanger, and then through the electrochemical cell, where the anodic oxidation occurs. The solution containing the desired pyrrolidinone leaves the cell, along with any unreacted substrate, and flows back to the stock container. The cycle is repeated until the complete consumption of the starting material. It is noteworthy that, at the cathode surface, the methanol solvent is reduced which leads to the formation of hydrogen. Fortunately, this transformation has no major impact on the course of the process.

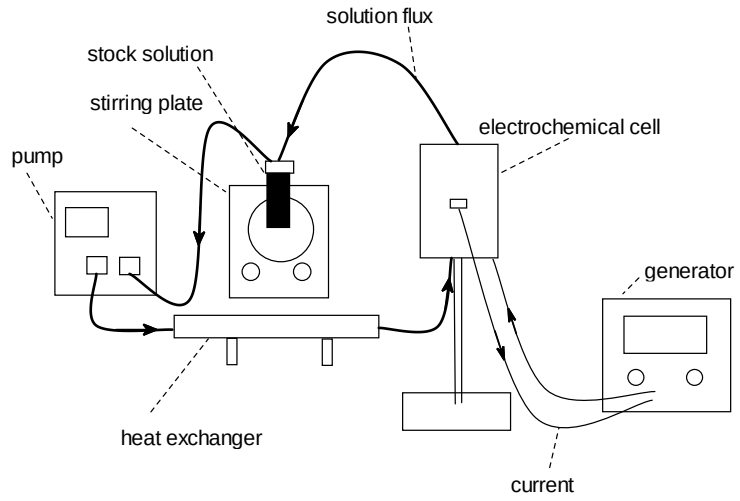


Figure 1 ElectraSyn Flow set-up

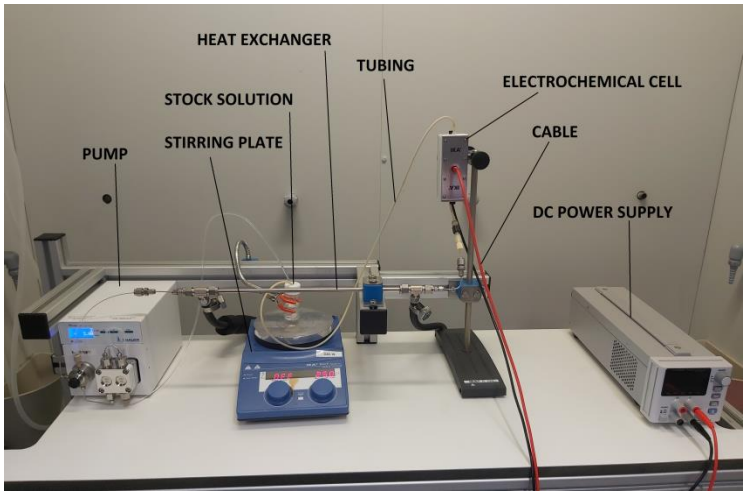


Figure 2 ElectraSyn Flow set-up

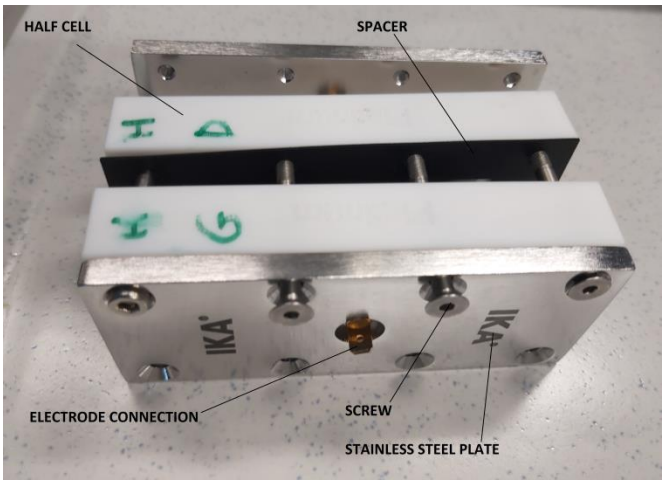


Figure 3 electrochemical cell

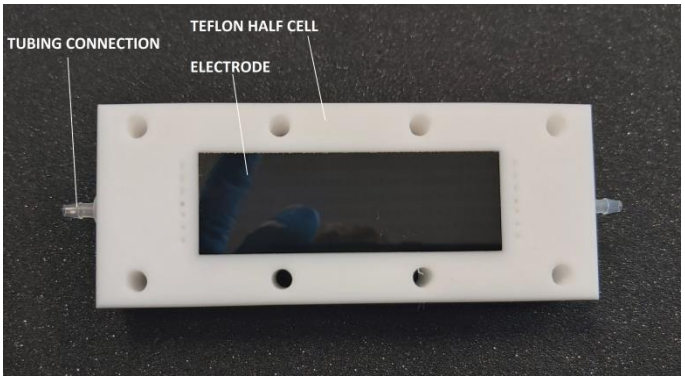


Figure 4 half cell

The conditions for the anodic electrocyclization and subsequent functionalization of 2-pyrrolidinones were previously established. As mentioned before, since in the case of Kolbe cyclization and cross-coupling reactions,[14] the control of the temperature in the electrochemical cell is of the utmost importance, a preliminary study was carried out to determine the optimum temperature of the heat exchanger, and study its impact on the yields, conversions, and productivities. For this purpose, three electrolyses were run, for 30 minutes, at a constant current density of 41.66 mA/cm², with a flow rate of 4 ml/min, and a concentration in substrate of 33 mmol/l. During these three runs, the heat exchanger's temperature was set at 0, 5, and 20°C. The striking effect of the cooling system was immediately apparent via UPLC-MS analysis of the crude reaction mixtures. Optimal results were observed when the heat exchanger was set at 5°C (Table 1, Entry 2) while lower or higher temperatures led to a dramatic drop in yield (Table 1, Entries 1 and 3). In our previous study[12], the temperature chosen to control our process in a double jacketed batch cell was 10°C. In this case, we decided to work with a heat exchanger temperature of 5°C given that, in this study, the solution is cooled before its entrance in the flow cell and therefore the control of the temperature inside the cell is less optimal than in a jacketed cell.

Table 1 Heat exchanger temperature study (T = heat exchanger temperature, Conv. = conversion, Prod. = productivity)

Entry	T (°C)	Conv. (%)	Yield (%)	Prod. ($g.h^{-1}.ml^{-1}$)
1	0	99	48	0.088
2	**5**	**96**	**73**	**0.135**
3	20	76	35	0.065

Subsequently, a design of the experiment was conducted to optimize the remaining variables of the Kolbe electrocyclization and functionalization of 1-allyl-4-propylpyrrolidin-2-one **2** in the continuous flow set-up (see Table 2). For reasons of simplicity and efficiency, a manual design of experiment with three factors; each factor had three values, was chosen. These three factors were: the substrate concentration (33, 66, 99 mmol/l), the current density (41.66, 62.50, and 83.33mA/cm²), and the flow rate (2, 3, and 4 ml/min). This experimental plan allowed us to study the effect of these three independent variables on the yields, conversions, and productivities of this transformation. The different electrolyses were carried out for 30 minutes, with a heat exchanger temperature of 5°C, and platinum electrodes, and the crude reaction mixtures were analyzed using UPLC-MS (Table 2). The yields and conversions were calculated via a calibration curve. Between each run, the flow set-up was washed with water, acetone, and methanol; and the electrodes were additionally washed with an aqueous solution of HCl 37 %, when impurities were still noticeable on the electrodes.

Table 2 Design of experiment with three factors (J = current density, C = substrate concentration, F = solution flow rate, Conv. Conversion, Prod. = productivity)

Entry	J (mA/cm²)	C (mmol/l)	F (ml/min)	Conv. (%)	Yield (%)	Prod. ($g.h^{-1}.ml^{-1.}$)
1	41.66	99	2	11	1	0.005
2	83.33	33	2	36	4	0.007
3	62.50	33	2	15	10	0.030
4	83.33	33	4	99	16	0.030
5	62.50	66	3	76	34	0.125
6	83.33	66	3	60	34	0.125
7	41.66	33	2	82	36	0.067
8	62.50	33	4	95	38	0.070
9	83.33	99	2	56	44	0.243
10	41.66	99	4	61	55	0.303
11	62.50	66	3	65	64	0.235
12	**83.33**	**99**	**4**	**74**	**72**	**0.397**
13	**41.66**	**33**	**4**	**96**	**73**	**0.135**

An analysis of the effect of the flow rate of the solution on conversions, yields, and productivities of the electrocyclization process has shown that, under comparable reaction conditions (constant current density and constant substrate concentration), a faster flow rate leads to better yields and higher conversions and productivities (see Table 2, Entries 12 and 13). Two hypotheses could account for this observation. On the one hand, a fast flow rate lessens the residence time in the cell, which allows the product to leave the cell quickly after it has been formed, thus avoiding possible over oxidations. On the other hand, given that the solution is cooled upstream from the electrochemical cell, a faster flow rate allows for better control of the cell's temperature, limiting the formation of undesirable side products. The impact of the current density on the reaction shown that a higher current density globally leads to higher conversions (see Table 2, Entries 4 and 12). Indeed, a higher current density means that more electrons are transferred per surface unit, which leads to a higher substrate consumption. Unfortunately, this could also favor a possible overoxidation of the products. Therefore, a compromise had to be found, with a substrate concentration of 33 mmol/l, a lower current density leads to better yields since higher current

densities increase the number of side-reactions. The productivity has shown to increase with the substrate concentration (see Table 2, Entries 9, 10, and 12). Finally, the best conditions found were to use a cell current density of 41.66 mA/cm², a flow rate of 4 ml/min, and a substrate concentration of 33 mmol/l. Using these conditions, we could form the desired product with an excellent yield of 73 % and a productivity of 0.13 $g.h^{-1}.ml^{-1}$. Interestingly, we could reach an excellent productivity of 0.40 $g.h^{-1}.ml^{-1}$ for a reactor volume of 0.6 cm^3 and an excellent yield of 72 % by using a cell current density of 83.33 mA/cm², a substrate concentration of 99 mmol/l, and a flow rate of 4 ml/min. Therefore, the optimization of an electrochemical transformation is of upmost importance to minimize the formation of side-products.

With the preliminary optimal conditions in hand, we further optimized the reaction. These electrolysis were performed using a substrate concentration of 33 mmol/l and a constant current density of 41.66 mA/cm². Flow rates of 6 ml/min (see Figure 5) and 10 ml/min (see Figure 6) were used since we have established that fast flow rates positively impacted the yield. Samples were taken every 5 minutes inside the stock solution and analyzed via UPLC-MS during the electrolysis. The graphs of the yield and conversion as a time function are depicted below.

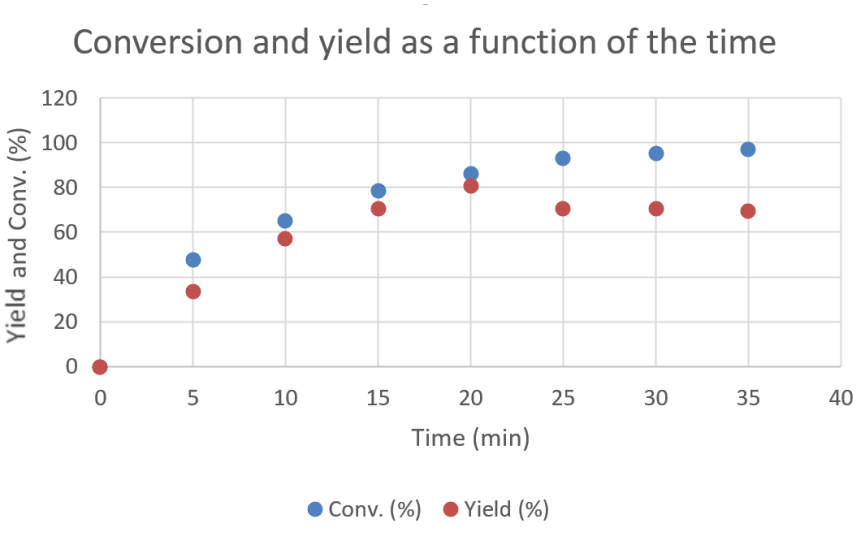


Figure 5 kinetic study of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 2 using a flow rate of 6 ml/min

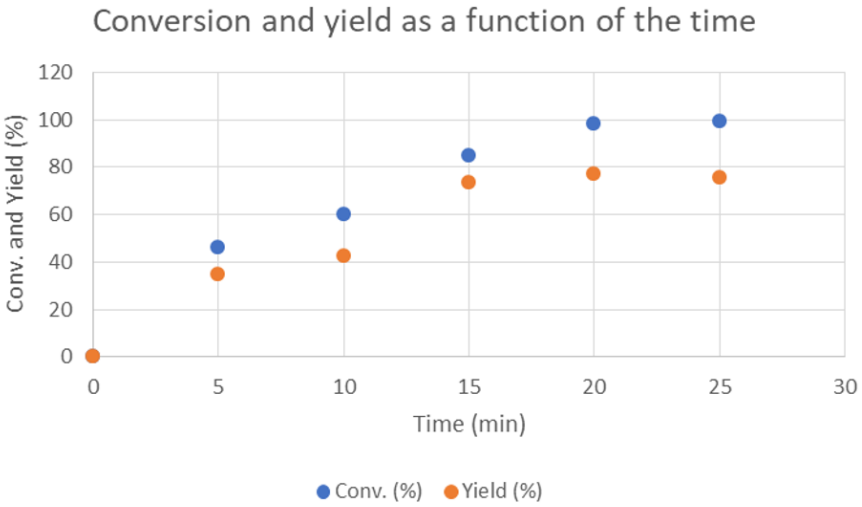
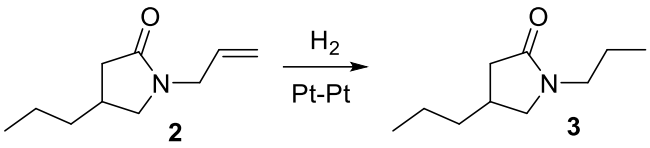


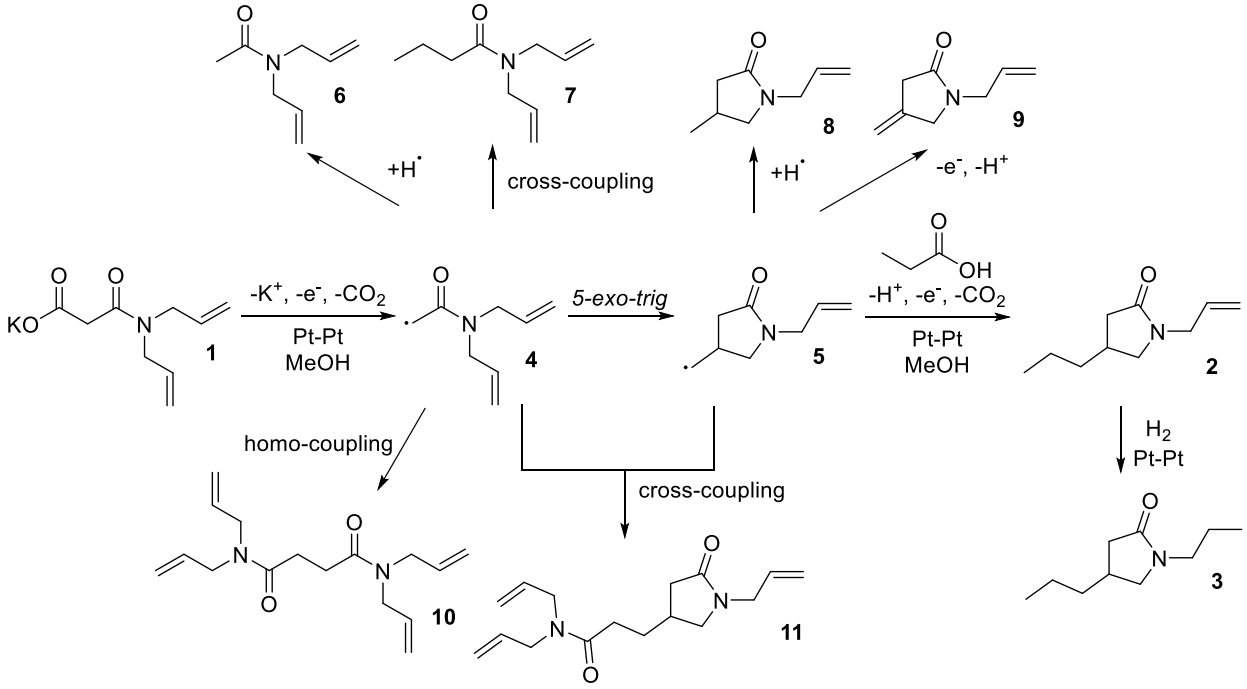
Figure 6 kinetic study of the electrocyclization of 1-allyl-4-propylpyrrolidin-2-one 2 using a flow rate of 10 ml/min

Figures 5 and 6 show that using a flow rate of 6 ml/min or 10 ml/min enables to get the best yield in only 20 minutes. This rapid kinetic study allowed us to shorten the reaction time to 20 minutes, which led to an increased yield of 81 %. Interestingly, after 20 minutes of electrolysis, product **2** has shown to start to degrade. Indeed, after 20 minutes, UPLC-MS analyzes showed the presence of an impurity **3** with a m/z of 170 deduced to be an impurity of 169 g/mol which could be the product **3** where the olefin has been reduced. It is plausible that a small amount of **2** could be reduced into the corresponding 1-propyl-pyrrolidin-2-one **3** (see Scheme **2**). The hypothesis is that the presence of platinum and hydrogen formed at the cathode could enable this reduction process. Finally, if this hypothesis is correct, the use of a divided cell should prevent the formation of this impurity, as the product **2** is formed at the anode surface and the impurity **3** should be formed at the cathode.



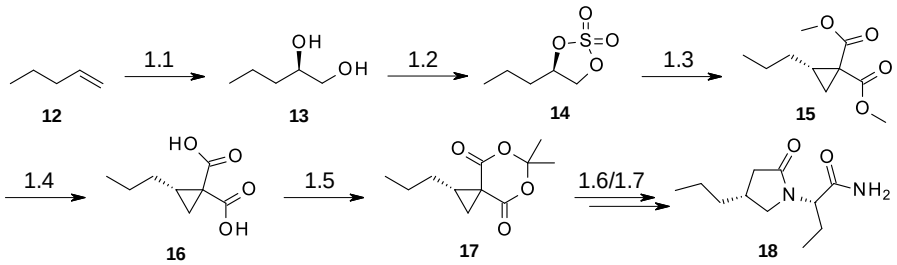
Scheme 2 reduction of the 1-allyl-4-propylpyrrolidin-2-one 2 into the corresponding 1-propyl-pyrrolidion-2-one 3

The UPLC-MS analyzes showed that a variety of side-products are formed during electrolyzes (see Scheme **3**). For instance, impurity **10** is formed via the homo-coupling of radical **4**. Moreover, impurity **11** comes from the cross-coupling of radical **4** and radical **5** and impurity **7** derives from the direct cross-coupling between radical **4** and the ethyl radical formed by the oxidative decarboxylation of propionic acid. Furthermore, side-product **3** is most probably formed by reducing the final product **2. 9** derives from the over-oxidation and successive elimination of **5**. Finally, impurities **6** and **8** are respectively derived from radical **4** and radical **5**. Therefore, the optimization of this process's reaction conditions is crucial to limit the formation of these impurities.



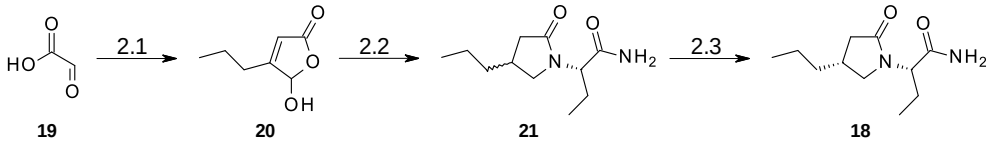
Scheme 3 electrocyclization process impurities

As the transposition of an electrochemical reaction to a flow-cell allows the perspective of its scaling-up, our methodology for the electrochemical functionalization of 2-pyrrolidinones was thus envisaged for synthesis of a compound of interest which is already industrially produced. The selected compound is the antiepileptic drug brivaracetam, (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide.[1] Over the last two decades, a large variety of synthetic strategies were devised to achieve the production of brivaracetam. Ates *et al.*[15] reported in 2007 a synthetic process, using an asymmetric dihydroxylation for chiral induction and the preparation of a cyclopropane-1,1-dicarboxylic acid intermediate **16** for the construction of a N-substituted 4-propylpyrrolidinone (Scheme **4**).



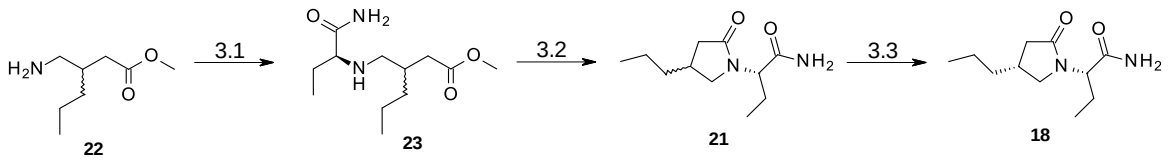
Scheme 4 Synthesis of brivaracetam (Ates *et al.*, 2007)

In 2009, Surtees *et al.*[16] proposed a much straightforward synthesis, using hydrogenation and chiral separation of diastereoisomers by chromatography with chiral stationary phase (Scheme **5**).



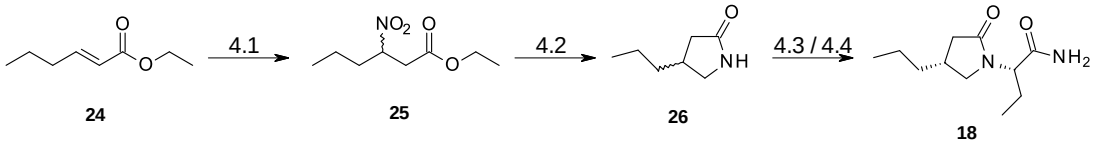
Scheme 5 Synthesis of brivaracetam (Surtees *et al.*, 2009)

Another route, also developed by Surtees *et al.*[17] in 2012, is based on a rather complex starting material which is converted in the desired N-substituted 4-propylpyrrolidinone, after chiral separation of diastereoisomers by chromatography with chiral stationary phase (Scheme **6**).



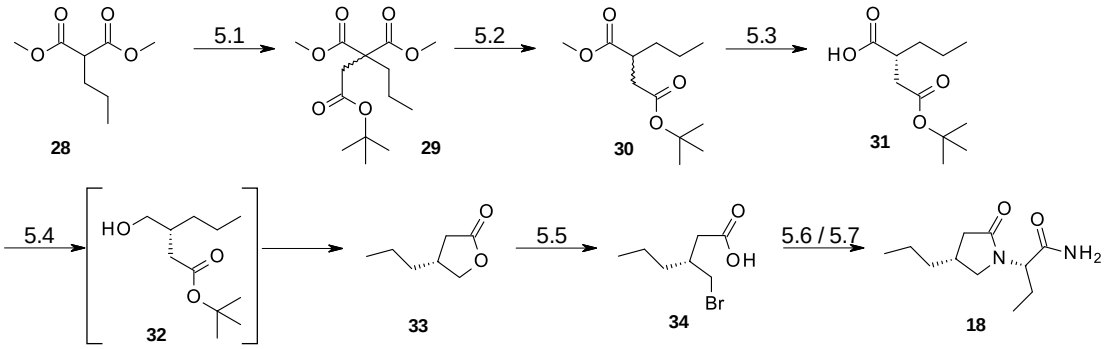
Scheme 6 Synthesis of brivaracetam (Surtees *et al.*, 2012)

Ates *et al.*[18]developed in 2015 a different strategy, based on a Michael addition of nitromethane on α,β-unsaturated ester **24**, followed by the reduction of the nitro group with Raney nickel, the cyclization of pyrrolidinone, and finally the chiral separation of enantiomers by chromatography with chiral stationary phase (Scheme **7**).



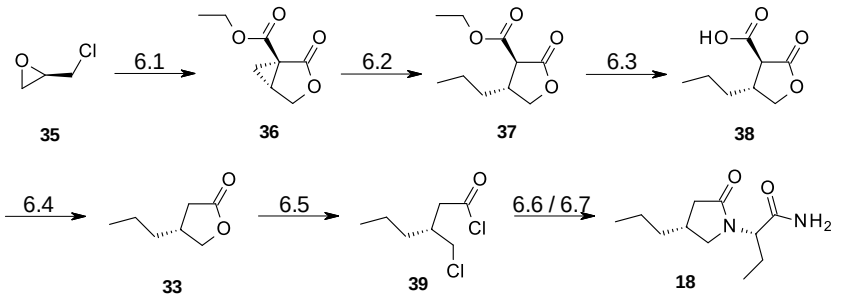
Scheme 7 Synthesis of brivaracetam (Ates *et al.*, 2015)

In 2016, Schülé *et al.*[19] proposed a biocatalytic route towards N-substituted 4-propylpyrrolidinone, allowing the resolution of the diester intermediate **30** in the process (Scheme **8**).



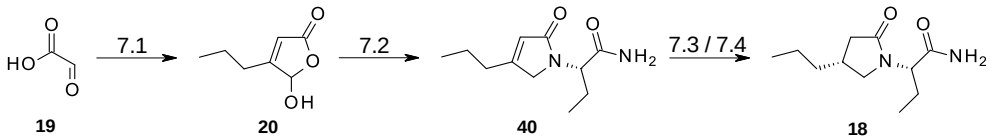
Scheme 8 Synthesis of brivaracetam (Schülé *et al.*, 2016)

The same year, Wang *et al.*[20] published an alternative synthetic route (selected process n°6), using ethyl 2-oxo-3-oxabicyclo[3.1.0]hexane-1-carboxylate **36** as the key intermediate in the process (Scheme **9**).



Scheme 9 Synthesis of brivaracetam (Wang *et al.*, 2016)

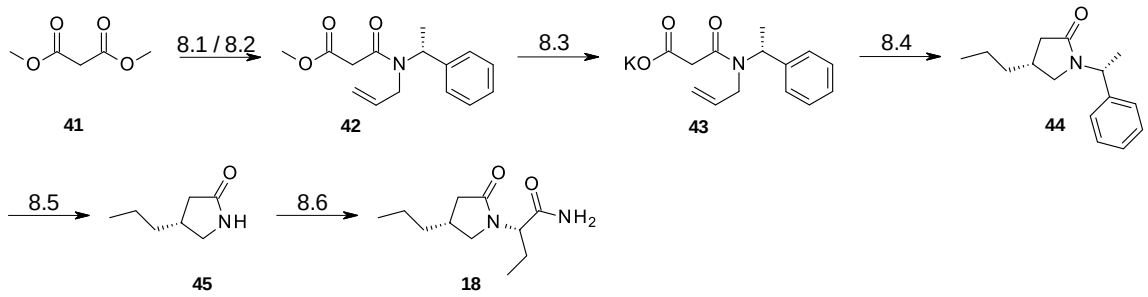
The synthetic route, published by Defrance *et al.*[21] in 2019, is an improved version of the strategy proposed by Surtess *et al.* in 2009 (Scheme **10**).



Scheme 10 Synthesis of brivaracetam (Defrance *et al.*, 2019)

Most of these synthetic strategies rely on chiral chromatography to achieve a satisfactory chiral purity of the pyrrolidone carbon bearing the propyl group.

As previously reported,[12] our methodology of electrochemical functionalization of 2-pyrrolidinones allows the control of chirality during the cyclization thanks to an existing chiral centre in the structure of the precursor. Based on this strategy, a proposal for an alternative synthesis of brivaracetam was envisaged, yet to be tested (Scheme **11**).



Scheme 11 Proposal for synthesis of brivaracetam based on electrocyclization

(R)-(+)-α-methylbenzylamine used as chiral inductor,[12] and incorporated in the electrocyclization precursor **43** allows the formation of the pyrrolidone **44** with diastereoselective ratio of 96:4. However, in this proposal of synthesis of brivaracetam, the removal of the chiral inductor and the final coupling with the butyramide moiety were not yet tested. Therefore, the molar yields of these steps 8.5 and 8.6 were hypothesised from published examples,[22,18] with the respective values of 90% and 60%. A first comparison of these previously presented processes and our electrochemical approach was performed based on the performances of these processes (Table **3**).

Table 3 Comparative study of performances of selected processes for the synthesis of brivaracetam

Entry	Process	Yield (%)	# Steps	# Solvents	Metals	Haz. Reagents	Chiral control
1	Ates *et al.* **2007** WO2007065634	**7.6**	**7**	**9**	Ru	NaH, NaIO4, SOCl2	Induction (AD-mix β)
2	Surtees *et al.* **2009** US7629474	**30.0**	**3**	**5**	Pd/C	H2	Chiral chromatography
3	Surtees *et al.* **2012** US8338621	**32.0**	**3**	**4**	-	-	Chiral chromatography
4	Ates *et al.* **2015** US8957226	**33.6**	**3**	**7**	Ni Raney	-	Chiral chromatography
5	Schülé *et al.* **2016** OPRD, 2016, 1566-1575	**9.1**	**7**	**7**	-	TFA, NaBH4, HBr	Biocatalytic resolution
6	Wang *et al.* **2016** WO2016191435	**31.0**	**7**	**8**	Cu(I), Mg, Zn (II)	EtMgBr, SOCl2	Chiral building-block
7	Defrance *et al.* **2019** US10421717	**58.6**	**4**	**6**	Pt/C	NaBH4, H2	Chiral chromatography
8	*Our proposal (Scheme 11)*	**23,1**	**6**	**3**	(Pt), Pd/C	DCC, H2	Induction (N-substituent) Diastereoisomers crystallization Racemization

Despite a relatively low expected yield (23,1%), our electrochemical approach (Table **3**, entry 8) even with a relatively modest development work, revealed to be quite a promising candidate for industrial application, in comparison to other existing alternatives. Indeed, our electrochemical approach would not rely on chiral chromatography as the chirality of the 4-position of the pyrrolidinone is induced instead by a chiral substituent on the N position.

In summary, we have successfully achieved the transposition of the electrocyclization and subsequent functionalization of 2-pyrrolidinones from a batch electrochemical cell to a continuous flow reactor. This study has shown that a good control of the electrolysis variables and the presence

of a cooling system are the keys to limit the formation of side products and to improve the yield and productivity of the process. Moreover, the use of a continuous flow electrochemical cell leads to an excellent productivity of 0.40 $g.h^{-1}.ml^{-1}$ for a reactor volume of 0.6 cm^3 using a cell current density of 83.33 mA/cm^2, a substrate concentration of 99 mmol/l, and a flow rate of 4 ml/min. Additionally, a good chemical yield of 81 % and faradic yield of 31 % were obtained in only 20 minutes using a flow rate of 6 ml/min, a current density of 41.66 mA/cm^2, and a substrate concentration of 33 mmol/l. In comparison with the results obtained using a batch electrochemical cell (yield = 71 %, faradic yield = 19 %, and productivity = 0.0032 $g.h^{-1}.ml^{-1}$), the electrochemical flow process offers a better productivity, a 10% increase in chemical yield and a 12% increase of the faradic yield. Finally, if the electrocyclization is proved to be successfully optimized and scaled-up with a flow-cell equipped with larger area electrodes in parallel to operate in a single pass, then our electrochemical approach for the functionalization of 2-pyrrolidinones may be envisaged for the production at large scale of compounds of interest, such as brivaracetam.

Experimental Section

In general, conversions and yields were determined by UPLC-MS of the effluent. A solution containing KOH (0.0925 g, 1.65 mmol, 5 eq.) and propionic acid (0.125 ml, 1.65 mmol, 5 eq.) in 5 ml of MeOH was sonicated before the electrolysis to ensure complete dissolution. The stock container was then filled with this solution and a solution containing (0.0730 g, 0.33 mmol, 1 eq.) of substrate **1** in 5 ml of MeOH. Subsequently, the cell was filled with MeOH at a flow rate of 6 ml/min, the heat-exchanger was set to a temperature of 5°C, and the power supply was set to a constant current of 500 mA. After 5 minutes, the cell was switched to the reactant solution. The

reaction was continued for 20 minutes. After each electrolyzes, the flow cell set-up was washed with water, acetone, and methanol; and the electrodes were washed with an aqueous solution of HCl 37 %, if impurities remain at the electrode surface.

ASSOCIATED CONTENT

Supporting Information.

General experimental section, procedures, NMR spectrum, and data tables for PMI-LCA comparative study.

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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. ‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

CCR2, CC chemokine receptor 2; CCL2, CC chemokine ligand 2; CCR5, CC chemokine receptor 5; TLC, thin layer chromatography.

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