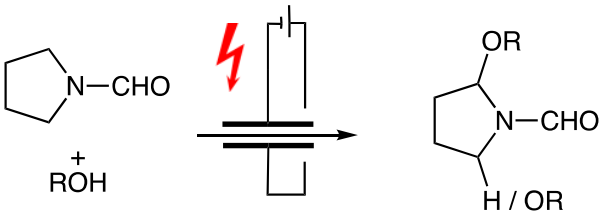
Efficient Flow Electrochemical Alkoxylation of *N*-Formylpyrrolidine

Nasser Amri,[a] Ryan A. Skilton,[b] Duncan Guthrie,[b]
Thomas Wirth[a,*]

[a] School of Chemistry, Cardiff University, Park Place, Cardiff, CF10 3AT, UK

[b] Vapourtec Ltd, 21 Park Farm Business Centre, Bury St Edmunds, IP28 6TS, UK

wirth@cf.ac.uk



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Abstract: We report on the optimization of the alkoxylation of *N*-formylpyrrolidine using a new electrochemical microreactor. Precise control of reaction conditions allow the synthesis of either mono- or dialkoxylated reaction products in high yields.

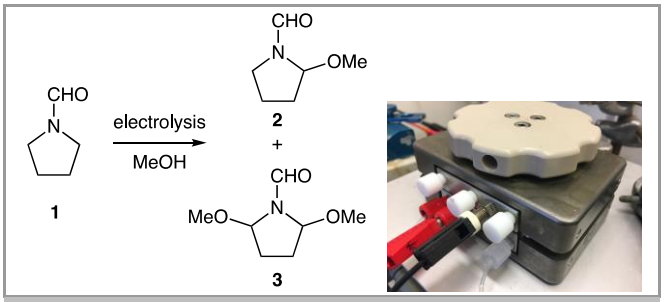
Key words C-H activation, electrochemistry, flow chemistry, heterocycles, methoxylation

Electrochemical organic synthesis currently receives renewed interest from synthetic chemists as a powerful activation mode to enable versatile chemical transformations. The application of electrons as traceless reagents can avoid the use of hazardous or toxic oxidizing or reducing agents and mild conditions can be employed for sustainable processes in chemistry.[1] Electrochemical transformations can be powerful methods used for making C–C, C–X or even X–X bonds, which is paramount in the synthesis of new organic compounds and modification of existing ones. Their advantages do not stop at the use of electrons as reagents over toxic or hazardous reagents, it also requires only small amounts of reacting species, and highly specific reactions avoid the formation of side products. In most cases, the electrolysis via anionic and cationic radical species formed from the neutral organic molecule is carried at room temperature and atmospheric pressure, so the reaction conditions are considered to be mild.[2]

As with many organic methods, organic electrochemistry has its own shortcomings and limitations especially in the batch process as many organic solvents used for chemical reactions have low conductivity. This necessitate the addition of supporting electrolytes and their removal at the end of the reaction while the relatively large distance between the electrodes in batch processes leads to high current gradients. Some of these limitations in batch electrochemistry can be addressed using the continuous flow reactors designed with small distances between electrodes to avoid large current gradients and minimize or eliminate the use of supporting electrolytes.[3] In addition, modifications to the electrode surface can show an effect on the overall reaction rate.[4]

Development and use of microreactors in continuous flow electrosynthesis have been reported by number of organic chemists.[5] Also our group has contributed to the development of electrochemical flow microreactors[6] while further developments by Vapourtec Ltd. have now provided commercial equipment.[7]

Herein, we report the methoxylation of *N*-formylpyrrolidine **1** which was used as a reaction to assess the efficiency of the much improved electrochemical microreactor.[7] Different factors and parameters were assessed in this study to determine their effects in the reaction which will further control the efficiency of the improved reactor by comparing the results from literature[8] for that particular methoxylation reaction (Scheme 1).

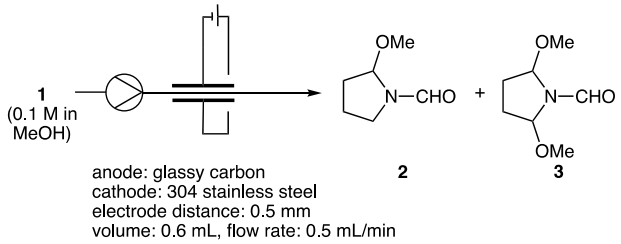


Scheme 1 Methoxylation of *N*-formylpyrrolidine **1** with the Ion electrochemical microreactor (right).

The Ion electrochemical reactor[7] has demonstrated high efficiency in the selectivity of this reaction. Many factors were varied in order to achieve the highest conversion and optimal selectivity. For the initial optimization of the electrochemical oxidation of *N*-formylpyrrolidine **1** to 2-methoxy-*N*-formylpyrrolidine **2** glassy carbon (GC) was used as anode and 304 stainless steel[9] as cathode. The distance between the electrodes is defined through a Teflon spacer (0.5 mm) containing the channel with a total volume of 0.6 mL resulting in an exposed electrode area of 2 x 12 cm^2. A 0.1 M solution of **1** in methanol was pumped at a flow rate of 0.5 ml/min with 0.05 M tetraethylammonium tetrafluoroborate (Et_4NBF_4) as supporting electrolyte. A current of 100 mA (1.25 F) with a residence time of 1.2 minutes at room temperature formed only

75% of the desired product (Table 1, entry 1). A current increase from 100 mA to 140 mA (Table 1, entries 2-4) led to approximately 90% of the product **2** with formation of a side product **3**, which is methoxylated at positions 2 and 5 in about 2% as determined by GC. When the current was increased further, the amount of the product **2** was reduced and the dimethoxylated product **3** increased (Table 1, entries 6 and 9), although the amount of electricity passed through the reactor was identical due to the higher flow rate of the substrate. The same course of reaction was observed when the concentration of the substrate was increased to 1 M. The reaction was not complete and side product **3** was formed (Table 1, entry 10). In this reaction, temperature did not have any impact as the results are identical whether the reaction is performed at room temperature, 30 ºC or at 60 ºC (Table 1, entries 7, 11, 12). It was also found that the use of graphite electrode did suppress the formation of the dimethoxylated product **3** (Table 1, entry 7). Conducting a paired electrolysis is possible using the same equipment[7] by separating the cathodic and the anodic reaction by a Nafion membrane. The cathodic hydrogen generation is now observed by using a methanolic solution of 0.05 M tetraethylammonium tetrafluoroborate while the reaction products **2** and **3** are formed in the anodic half reaction (Table 1, entry 8). Unfortunately, better selectivity could not be obtained in the paired electrolysis.

Table 1 Optimization of the electrochemical methoxylation of **1**.



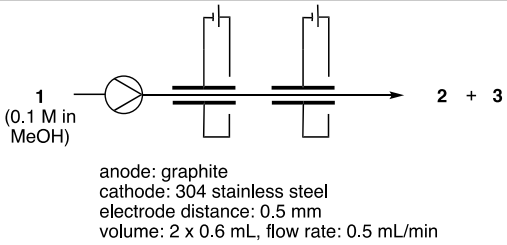
Entry	Conditions	Conversion **2** [%][a]	Conversion **3** [%][a]
1	100 mA (1.25 F)	75	0
2	120 mA (1.5 F)	84	0
3	130 mA (1.6 F)	86	0
4	140 mA (1.75 F)	91	2
5	150 mA (1.88 F)	89	3
6	160 mA (2 F)	90	3
7	160 mA (2 F) [b]	85	0
8	160 mA (2 F) [b,c]	80	6
9	320 mA (2 F) [d]	76	12
10	1250 mA (2 F) [e]	94 (87[i])	3
11	1600 mA (2 F) [b,f]	73	18
12	160 mA (2 F) [b,g]	88	0
13	160 mA (2 F) [b,h]	86	0
14	640 mA (8 F)	8 [i]	83 [i]

[a] Determined by GC analysis of the crude product solution. [b] Graphite anode. [c] divided cell. [d] flow rate: 1.0 mL/min. [e] flow rate: 2 mL/min, cooling applied. [f] Concentration of **1**: 1 M in MeOH. [g] 30 °C. [h] 60 °C. [i] Isolated yield.

All results shown in the Table 1 did not give the product with full conversion and without formation of product **3**. However, a further increase of the current to 640 mA (8 F) resulted in a conversion of 83% to the dimethoxylated product **3**, where now only 8% monomethoxylation product **2** remained in the reaction mixture (Table 1, entry 14). Using higher flow rate and higher current leads to the generation of heat. By applying cooling to the reactor, the temperature could be maintained at 25 ºC and 94% conversion (87% isolated yield) with a production rate of 1.35g / h was achieved (Table 1, entry 10).

The selective but uncomplete reaction to product **2** (Table 1, entry 7) was further optimized by the attachment of a sequential second electrochemical microreactor with identical specifications. Only a very few reactions have been carried out with two electrochemical microreactors in line.[10] Other approaches for optimization in electrochemical reactors have been reported through recirculating the reaction mixture in the electrochemical reactor until complete conversions were achieved,[11] or stacking of electrochemical reactors in one device.[12]

Table 2 Reaction of **1** in two sequential electrochemical reactors.



Entry	Conditions	Conversion after first reactor **2** + **3** [%][a]	Conversion after second reactor **2** + **3** [%][a]
1	100 mA (2.5 F)	66 + 0	90 + 0
2	130 mA (3.2 F)	77 + 0	94 + 0
3	150 mA (3.76 F)	80 + 0	95 + 2
4	160 mA (4 F)	84 + 0	95 + 5
5	120 mA (3 F) [b]	83 + 0	53 + 47

[a] Determined by GC analysis of the crude product solution. [b] Glassy carbon anode.

Four different current values were investigated in the sequential arrangement of two electrochemical microreactors. With a flow rate of 0.5 mL/min, the reaction is not complete after the first reactor. After optimization, almost full conversion after the second reactor can be achieved by using 150 mA (Table 2, entry 3). If the current is increased to 160 mA (4 F), small amounts of the dimethoxylated product **3** can be detected (Table 2, entry 4). Full conversion, however, is essential as it seems almost impossible to chromatographically separate the starting material **1** from **2**. If only one reactor is used for these experiments, half the flow rate (0.25 mL/min) will provide the same amount of electricity to the substrate during the reaction (residence) time. With 2 F (80 mA) only 80% conversion is achieved while with 4 F (160 mA) starting material remains and **2** and **3** are formed with 78% and 16% conversion, respectively.

The optimized conditions were then applied also to the reaction of *N*-formylpyrrolidine **1** with other alcohols on a larger scale (5.5 mmol). Compounds **2**, **4**, **6**, **8** and **10** (Figure 1) have been obtained in good yields by reactions with different alcohols. While the residence time in the reactors is only 2.4 minutes, the reaction time for processing 5.5 mmol starting material is just under two hours. The observed results relate to current efficiencies between 21 and 45%. The monoalkoxylated formylpyrrolidines have been as mixtures of two atropisomers in an approx. 9:1 ratio as determined by NMR due to the restricted rotation around the amide bond.[13] Also *N*-formylmorpholine reacts under the optimized reaction conditions

forming **12** in 67% yield. The observed atropisomers of **12** have already been characterized.[13a]

If the same electrode materials of 304 stainless steel and graphite (1 cm^2) are used in a batch reaction, only 60% conversion to **2** was observed after 160 min reaction time (10 mA, 2F).

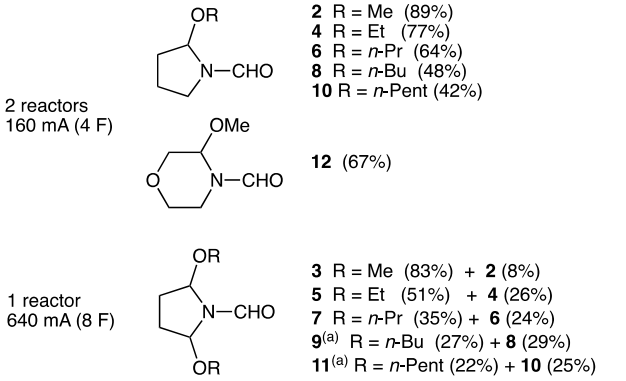


Figure 1 Alkoxylation of *N*-formylpyrrolidine and *N*-formylmorpholine. (a) two reactors, 320 mA.

Applying reaction conditions for one electrochemical reactor as shown in Table 1, entry 12, double alkoxylations are possible and have been carried out also on a 5.5 mmol scale leading to reaction products **3**, **5** and **7** as shown in Figure 1. While compound **3** is obtained as an approx. 1:2 ratio of the *cis* and *trans*-stereoisomer,[14] only one stereoisomer (not assigned) of compounds **5**, **7**, **9** and **11** was generated as judged by ^{1}H NMR spectroscopy. The reason for the observed stereoselectivity in the double alkoxylation is not clear at present. Using *n*-butanol and *n*-pentanol as solvents, the conductivity was very low. The voltage had to be reduced to 320 mA in two reactors to avoid too high voltages in the formation of **9** and **11**.

In conclusion, we have demonstrated the efficient use of a new electrochemical reactor for the selective mono- or dialkoxylation of *N*-formylpyrrolidine as an exemplar substrate.

Acknowledgment

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Supporting Information

Yes.

Primary Data

No.

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