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Efficient Flow Electrochemical Alkoxylation of Pyrrolidine-1carbaldehyde

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^{≤ 94%} conversion to monoalkoxy product ≤ 83% conversion to dialkoxy product

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Abstract We report on the optimization of the alkoxylation of pyrrolidine-1-carbaldehyde by using a new electrochemical microreactor. Precise control of the reaction conditions permits the synthesis of either mono- or dialkoxylated reaction products in high yields.

Key words C–H activation, electrochemistry, flow chemistry, heterocycles, alkoxylation, pyrrolidinecarbaldehyde

Electrochemical organic synthesis is currently receiving renewed interest from synthetic chemists as a powerful activation mode that permits 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 transformation can be powerful method for making C-C, C-X, or even X-X bonds, which is paramount in the synthesis of new organic compounds and in modification of existing ones. The advantages of electrochemical transformations do not stop at the use of electrons as superior reagents to toxic or hazardous chemicals, as these transformations also require only small amounts of reacting species and can provide highly specific reactions that avoid the formation of byproducts. In most cases, 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 batch processes, as many organic solvents used for chemical reactions have low conductivities. This necessitate the addition of supporting electrolytes and their subsequent 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 by the use of continuous-flow reactors designed with small distances between electrodes to avoid large current gradients and to minimize or eliminate the need for supporting electrolytes.³ In addition, modifications to the electrode surface can affect the overall reaction rate.⁴ The development and use of microreactors in continuous-flow electrosyntheses have been reported by a number of organic chemists.⁵ Also, our group has contributed to the development of electrochemical flow microreactors,⁶ while further developments by Vapourtec Ltd. permit the provision of commercial equipment.⁷

Here, we report the methoxylation of pyrrolidine-1-carbaldehyde (1) in a reaction that is used to assess the efficiency of the much-improved electrochemical microreactor.⁷ Various factors and parameters were assessed in this study to determine their effects on the reaction, which, through comparison with results from the literature for this particular methoxylation reaction,⁸ should permit better control of the efficiency of the improved reactor (Scheme 1).



Scheme 1 Methoxylation of pyrrolidine-1-carbaldehyde (1) with the lon electrochemical microreactor (right).

The Ion electrochemical reactor⁷ demonstrated high efficiency in performing this reaction regioselectively. Many factors were varied to achieve the highest conversion and

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optimal selectivity. For the initial optimization of the electrochemical oxidation of pyrrolidine-1-carbaldehyde (1) to 2-methoxypyrrolidine-1-carbaldehyde (2), glassy carbon (GC) was used as the anode and 304 stainless steel⁹ as the cathode. The distance between the electrodes is defined by means of a Teflon spacer (0.5 mm) containing a channel with a total volume of 0.6 mL, resulting in an exposed electrode area of 2×12 cm². A 0.1 M solution of aldehyde **1** in methanol was pumped at a flow rate of 0.5 mL/min with 0.05 M tetraethylammonium tetrafluoroborate (Et₄NBF₄) as a supporting electrolyte. A current of 100 mA (1.25 F) with a residence time of 1.2 minutes at room temperature gave the desired product in only 75% yield (Table 1, entry 1). An increase in the current from 100 mA to 140 mA (entries 2-4) led to approximately 90% of product 2 together with the 2,5-dimethoxylated byproduct 3 in about 2% yield, as determined by GC. When the current was increased further, the amount of product 2 was reduced and that of the dimethoxylated product **3** increased (entries 6 and 9), although the amount of electricity that passed through the reactor was identical due to the higher flow rate of the substrate. A similar course of reaction was observed when the concentration of the substrate was increased to 1 M: the reaction was incomplete, and byproduct **3** was formed (entry 10). In this reaction, temperature did not have any impact, as the results were identical whether the reaction was performed at room temperature, 30 °C or at 60 °C (entries 7, 11, and 12). It was also found that the use of a graphite electrode suppressed the formation of the dimethoxylated product 3 (entry 7). Conducting a paired electrolysis was possible in the same equipment⁷ by separating the cathodic and anodic reactions with a Nafion membrane. Cathodic hydrogen generation was then observed with a methanolic solution of 0.05 M tetraethylammonium tetrafluoroborate, while reaction products 2 and 3 were formed in the anodic half reaction (entry 8). Unfortunately, better selectivity could not be obtained in the paired electrolysis.

In none of the cases shown in the Table 1 was the product obtained with full conversion without formation of byproduct **3**. However, a further increase of the current to 640 mA (8 F) resulted in an 83% conversion to the dimethoxylated product **3**, with only 8% of the monomethoxylated product **2** remaining in the reaction mixture (Table 1, entry 14). The use of a higher flow rate and a higher current led to the generation of heat. By applying cooling to the reactor, the temperature could be maintained at 25 °C, resulting in a 94% conversion to product **3** (87% isolated yield) at a production rate of 1.35 g/h (Table 1, entry 10).
 Table 1
 Optimization of the Electrochemical Methoxylation of Pyrrolidine-1-carbaldehyde (1)



Entry	Conditions	Conversion ^a to 2 (%)	Conversion ^a to 3 (%)
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) ^ь	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) ^f	3
11	1600 mA (2 F) ^{b,g}	73	18
12	160 mA (2 F) ^{b,h}	88	0
13	160 mA (2 F) ^{b,i}	86	0
14	640 mA (8 F)	8 ^f	83 ⁱ

^a Determined by GC analysis of the crude product solution.

^b Graphite anode.

^c Divided cell (Nafion membrane). ^d Flow rate: 1.0 mL/min.

^e Flow rate: 2 mL/min; cooling applied.

f Isolated yield.

^g Concentration of 1: 1 M in MeOH.

^h At 30 °C.

i At 60 °C.

The selective but incomplete reaction to give product **2** (Table 1, entry 7) was further optimized by the attachment of a sequential second electrochemical microreactor with identical specifications. Only a few reactions have previously 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 by stacking of electrochemical reactors in one device.¹²

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Table 2 Reaction of Pyrrolidine-1-carbaldehyde (1) in Two Sequential

 Electrochemical Reactors



Entry	Conditions	Conversion after first reactor ^a 2 + 3 (%)	Conversion after second reactor ^a 2 + 3 (%)
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 ^b	120 mA (3 F)	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 was incomplete after the first reactor. After optimization, almost full conversion after the second reactor could be achieved by using a current of 150 mA (Table 2, entry 3). When the current was increased to 160 mA (4 F), small amounts of the dimethoxylated product **3** were detected (entry 4). Full conversion, however, is essential as it appears to be almost impossible to separate the starting material 1 from product 2 chromatographically. 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 an 80% conversion was achieved, whereas with 4 F (160 mA), starting material remained and 2 and 3 were formed with 78% and 16% conversion, respectively.

The optimized conditions were then applied to the reactions of pyrrolidine-1-carbaldehyde (1) with other alcohols on a larger scale (5.5 mmol). Compounds **2**, **4**, **6**, **8**, and **10** (Figure 1) were obtained in good yields by reactions with various alcohols. Whereas the residence time in the reactors was only 2.4 minutes, the reaction time for processing 5.5 mmol of starting material was just under two hours. The observed results relate to current efficiencies of between 21 and 45%. The monoalkoxylated formylpyrrolidines were obtained as mixtures of two atropisomers in an approximately 9:1 ratio, as determined by NMR spectroscopy; this atropisomerism is due to restricted rotation around the amide bond.¹³ Furthermore, morpholine-4-carbaldehyde reacted under the optimized conditions to give the monomethoxylated product **12** in 67% yield. The observed atropisomers of **12** have already been characterized.^{13a}



Figure 1 Alkoxylations of pyrrolidine-1-carbaldehyde and morpholine-4-carbaldehyde ^a Two reactors, 320 mA.

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

By applying the reaction conditions for one electrochemical reactor shown in Table 1, entry 12, double alkoxylations were possible; these were carried out on a 5.5 mmol scale to give reaction products **3**, **5**, and **7**, as shown in Figure 1. Whereas compound **3** was obtained as an approximately 1:2 ratio of the *cis*- and *trans*-stereoisomers,¹⁴ only one stereoisomer (not assigned) of compounds **5**, **7**, **9**, and **11** was generated, as judged by ¹H NMR spectroscopy. The reason for the observed stereoselectivity in the double alkoxylation is not clear at present. With butan-1-ol or pentan-1-ol as the solvent, the conductivity was very low. In the formation of **9** and **11**, the current had to be reduced to 320 mA in the two reactors to avoid voltages that were too high.

In conclusion, we have demonstrated the efficient use of a new electrochemical reactor for the selective mono- or dialkoxylation of pyrrolidine-1-carbaldehyde as an exemplar substrate.¹⁵

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611774.

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References and Notes

- (1) (a) Little, R. D.; Moeller, K. D. Chem. Rev. 2018, 118, 4483.
 (b) Francke, R.; Schille, B.; Roemelt, M. Chem. Rev. 2018, 118, 4631. (c) Yoshida, J. I.; Shimizu, A.; Hayashi, R. Chem. Rev. 2018, 118, 4702. (d) Moeller, K. D. Chem. Rev. 2018, 118, 4817.
 (e) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Chem. Rev. 2018, 118, 4834.
- (2) (a) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. *Green Chem.* **2010**, *12*, 2099. (b) Organic Electrochemistry, 5th ed.; Hammerich, O.; Speiser, B., Ed.; CRC Press: Boca Raton, **2015**. (c) Horn, E. J.; Rosen, B. R.; Baran, P. S. ACS Cent. Sci. **2016**, *2*, 302.
- (3) (a) Yoshida, J. Electrochem. Soc. Interface 2009, (Summer) 40.
 (b) Folgueiras-Amador, A. A.; Wirth, T. J. Flow Chem. 2017, 7, 94.
 (c) Atobe, M.; Tateno, H.; Matsumura, Y. Chem. Rev. 2018, 118, 4541.
 (d) Pletcher, D.; Green, R. A.; Brown, R. C. D. Chem. Rev. 2018, 118, 4573.
 (e) Folgueiras-Amador, A. A.; Wirth, T. In Flow Chemistry in Organic Synthesis; Jamison, T. F.; Koch, G., Ed.; Thieme: Stuttgart, 2018, Chap. 5, 147.
- (4) Yoo, S. J.; Li, L.-J.; Zeng, C.-C.; Little, R. D. Angew. Chem. Int. Ed. 2015, 54, 3744.
- (5) (a) Horii, D.; Atobe, M.; Fuchigami, T.; Marken, F. Electrochem. Commun. 2005, 7, 35. (b) Horcajada, R.; Okajima, M.; Suga, S.; Yoshida, J.-i. Chem. Commun. 2005, 1303. (c) He, P.; Watts, P.; Marken, F.; Haswell, S. J. Angew. Chem. Int. Ed. 2006, 45, 4146. (d) Kuleshova, J.; Hill-Cousins, J. T.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Underwood, T. J. Electrochim. Acta 2011, 56, 4322. (e) Attour, A.; Dirrenberger, P.; Rode, S.; Ziogas, A.; Matlosz, M.; Lapicque, F. Chem. Eng. Sci. 2011, 66, 480. (f) Kashiwagi, T.; Elsler, B.; Waldvogel, S. R.; Fuchigami, T.; Atobe, M. J. Electrochem. Soc. 2013, 160, G3058.
- (6) (a) Watts, K.; Gattrell, W.; Wirth, T. Beilstein J. Org. Chem. 2011, 7, 1108. (b) Arai, K.; Watts, K.; Wirth, T. ChemistryOpen 2014, 3, 23. (c) Arai, K.; Wirth, T. Org. Process Res. Dev. 2014, 18, 1377. (d) Folgueiras-Amador, A. A.; Philipps, K.; Guilbaud, S.; Poelakker, J.; Wirth, T. Angew. Chem. Int. Ed. 2017, 56, 15446. (e) Folgueiras-Amador, A. A.; Qian, X.-Y.; Xu, H.-C.; Wirth, T. Chem. Eur. J. 2018, 24, 487. (f) Gao, W.-C.; Xiong, Z.-Y.; Pirhaghani, S.; Wirth, T. Synthesis 2019, 51, 276. (g) Islam, M.; Kariuki, B. M.; Shafiq, Z.; Wirth, T.; Ahmed, N. Eur. J. Org. Chem. 2019, 1371.
- (7) For details of the Ion electrochemical reactor, see: https://www.vapourtec.com/products/flow-reactors/ion-electrochemical-reactor-features/ (accessed Mar 15, 2019).

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- (8) (a) Kuleshova, J.; Hill-Cousins, J. T.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Underwood, T. J. *Electrochim. Acta* **2012**, 69, 197.
 (b) Green, R. A.; Brown, R. C. D.; Pletcher, D.; Harji, B. *Org. Process Res. Dev.* **2015**, *19*, 1424. (c) Green, R. A.; Brown, R. C. D.; Pletcher, D.; Harji, B. *Electrochem. Commun.* **2016**, 73, 63.
 (d) Folgueiras-Amador, A. A.; Jolley, K. E.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Pickering, S.; Sharabi, M.; de Frutos, O.; Mateos, C.; Rincón, J. A. *Electrochem. Commun.* **2019**, *100*, 6.
- (9) 18% Cr, 8% Ni.
- (10) Amemiya, F.; Kashiwagi, T.; Fuchigami, T.; Atobe, M. *Chem. Lett.* **2011**, *40*, 606.
- (11) Cedheim, L.; Eberson, L.; Helgee, B.; Nyberg, K.; Servin, R.; Sternerup, H. Acta Chem. Scand., Ser. B **1975**, 29, 617.
- (12) Chapman, M. R.; Shafi, Y. M.; Kapur, N.; Nguyen, B. N.; Willans, C. E. Chem. Commun. **2015**, *51*, 1282.
- (13) (a) Liebner, R.; Schmid, P.; Adelwöhrer, C.; Rosenau, T. *Tetrahedron* 2007, 63, 11817. (b) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* 1970, 70, 517.
- (14) Mitzlaff, M.; Warning, K.; Jensen, H. *Liebigs Ann. Chem.* **1978**, 1713.
- (15) 2-Methoxypyrrolidine-1-carbaldehyde (2); Typical Procedure

A 0.1 M solution of aldehyde 1 in MeOH (60 mL) containing $Et_{4}NBF_{4}$ (0.05 M) was sonicated to ensure complete dissolution of the reactant, then pumped through one microreactor at 0.5 mL/min by using a syringe pump or the Vapourtec E series, while a constant current of 640 mA was applied. The first 5 mL were discarded, and the remaining reaction mixture was collected for 110 min (55 mL). MeOH was removed under reduced pressure, and the crude product was washed with H₂O (50 mL), to remove the supporting electrolyte, then extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried (MgSO₄), filtered, evaporated, and dried under high vacuum. The residue was purified by chromatography [silica gel, hexane-EtOAc (1:1)] to give a colorless oil; yield: 629 mg (89%). The NMR spectra showed the presence of a ~5:1 mixture of rotamers.¹H NMR (400 MHz, CDCl₃): δ (major) = 8.40 (s, 1 H), 4.92 (d, I = 4.8 Hz, 1 H), 3.58–3.40 (m, 2 H), 3.26 (s, 3 H), $2.13-1.79 (m, 4 H); \delta (minor) = 8.29 (s, 1 H), 5.37 (d, J = 4.8 Hz, 1$ H), 3.58-3.40 (m, 2 H), 3.38 (s, 3 H), 2.13-1.79 (m, 4 H). ¹³C NMR $(101 \text{ MHz}, \text{CDCl}_3)$: δ (major) = 161.4, 89.7, 54.4, 42.7, 31.8, 21.4; δ (minor) = 162.6, 85.5, 56.6, 45.2, 31.9, 22.1.