

Supporting Electrolyte-Free Electrochemical Methoxymethylation of Alcohols Using a 3D Printed Electrosynthesis Continuous Flow Cell System

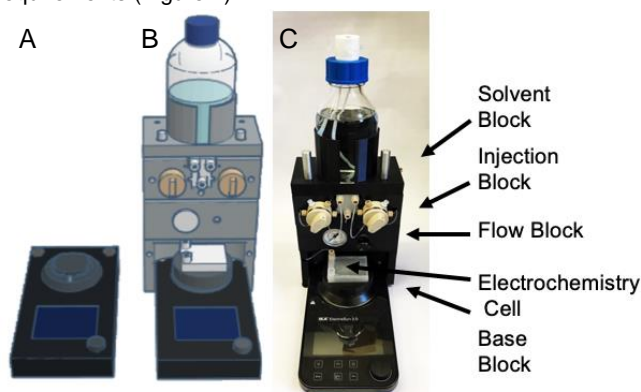
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Dedication ((optional))

Abstract: In this present study, we describe the development of a novel low-cost small footprint 3D printed electrosynthesis continuous flow cell system that was designed and adapted to fit a commercially available Electrasyn 2.0. The utility and effectiveness of the combined flow/electrochemistry system over the batch process was demonstrated in the development of an improved and supporting electrolyte-free version of our anodic methoxymethylation of alcohols.

The protection of functional groups constitutes an integral part of organic synthesis. Among the numerous protecting groups available to protect hydroxyl groups, methoxymethyl (MOM) ethers are a popular choice due to their broad compatibility with a wide range of reaction conditions.^[1–4] In addition to being protecting groups, methoxymethyl ethers are also oxonium ion precursors that may be used to promote further transformations. Methoxymethyl ethers are traditionally prepared by using chloromethyl methyl ether (MOMCl).^[5–7] The severe carcinogenicity of MOMCl has prompted us and others to develop alternative electrochemical methoxymethylations that avoid the use of highly toxic reagents.^[8–10] Although these anodic oxidations are easily run using a classical electrochemical setup, using galvanostatic conditions, they suffer from a few drawbacks such as a low current efficiency, a possible over-oxidation of the MOM ether over time or the need for a high concentration of salts to reach the desired current. These drawbacks could readily be overcome by using a flow electrolysis cell instead of a batch cell. However, typical continuous flow setups remain expensive costing in excess of \$20,000 and are typically space consuming in a laboratory. Following the growing impetus to develop affordable electrochemical flow systems with a small size footprint,^[11,12] we would like to disclose the optimisation of our previously developed anodic methoxymethylation methodology using a readily available and low-cost 3D printed electrosynthesis

continuous flow cell that relies only on the use of compressed gas and any that can be used with any simple DC power source. Although the proposed system could be readily adapted to fit any bespoke electrosynthesis systems by the mean of electrode connectors (see Figure 3B and Supporting Information), we were intrigued by the possibility of developing it around the recently released Electrasyn 2.0 platform which was designed to carry out electrochemistry under batch conditions. Our aim was to reach both experts and new-comers in the electrosynthesis field and demonstrate that any batch based system could readily be converted into a continuous flow one.^[13] Following our previous studies on developing a continuous flow system for use with stirrer hotplates using 3D printing,^[14] we first measured the Electrasyn 2.0 using Vernier callipers and then modified our previously designed flow system to take into account the reduction in size of each of the components. In addition, the flow electrode section was also designed to be attachable to any power supply via the electrode connectors (Figure 3B). The aim was that it could be used as intended with the supplied vials or when continuous flow was required, the flow system could simply be attached to the Electrasyn 2.0, and the experiment run in continuous flow mode. Once continuous flow was no longer required, it could be easily removed from the system and stored (Supplementary Information). The system is designed around our previously described flow system and is comprised of five units, covering the dock for the electrochemistry cell (direct electrical connection to the Electrasyn 2.0), base unit (for compressed air control), flow control unit (to set pressure), injection unit (for addition of reagents) and solvent block (to hold and provide solvent for the reaction) (Supplementary Information).^[14] These are analogous to HPLC stacks where units can be varied to match individual requirements (Figure 1).



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Figure 1. A) CAD diagram of Electrasyn 2.0; B) CAD design of proposed Electrasyn 2.0 Continuous Flow system; C) Realised and 3D Printed design.

The continuous flow electrochemistry system was designed to be powered by compressed air and the flow rates mediated by restricted capillary flow as per our previous investigations to reduce the cost of the overall system.^[14,15] Individual components were 3D printed using PLA (for structural components) or polypropylene (PP) for solvent exposed components as required (supplementary information).^[14] The system is comprised of a solvent block, injection block for reagents, flow control and base block for connection as well as a holder for the flow electrochemistry reactor (Figure 1). The flow cell was designed to incorporate carbon electrodes and to be 3D printed from polypropylene (PP) with the electrodes placed in the cell during printing by pausing the print at the requisite layer heights. Each electrode was 3 mm thick by 40 mm x 50 mm. The reactor was designed to have screw thread adaptors for fitting of standard PEEK connectors and electrode connectors. During 3D printing, the process was paused, and electrodes and connectors added once their layer heights were reached. The flow channel was designed to place the electrodes 2.0 mm apart, shrinking to 1.75 mm at the end of each channel and with flow channels 2 mm wide giving an overall volume of 2 mL (Figure 2).

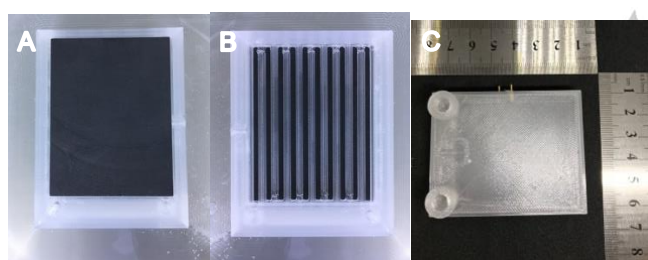


Figure 2. A) Placement of lower electrode in printed flow cell; B) Printed flow channels; C) Final printed flow cell.

In order to attach the cell to the Electrasyn 2.0 base, the electrode connectors were measured using Vernier callipers and a locking unit, analogous to that supplied with the Electrasyn 2.0, was designed using Tinkercad free online software (Autodesk) and printed on an Ultimaker 3 using PLA filament (Figure 3).

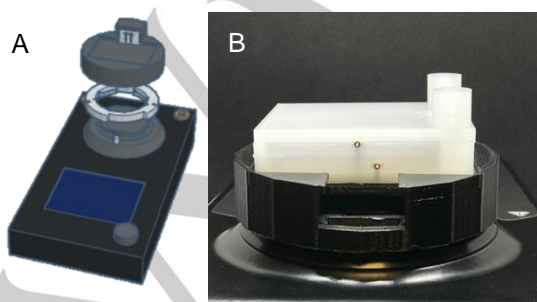


Figure 3. A) CAD diagram of flow cell attachment for Electrasyn 2.0; B) Realised design and locking of flow cell onto the Electrasyn 2.0 base – connection to the

reactor is via the addition attachment to the two electrodes (Supplementary Information).

With the printed continuous flow reactor prepared, we next began our investigations into MOM ether formation and synthesised a series of MOM ether precursors, α -alkoxy carboxylic acids **3**, in good yields using a standard Williamson etherification.

Table 1. Preparation of α -alkoxy carboxylic acids precursors

$\text{R}^1\text{-OH} + \text{Br-CH}_2\text{-COOH} \xrightarrow[0^\circ\text{C - reflux}]{\text{NaH, THF}} \text{R}^1\text{-O-CH}_2\text{-COOH}$			
Entry	Alcohol 1	Acid 3	Yield (%) ^[a]
1			42
2			50
3			62
4			52
5			87
6			80
7			79
8			89
9			66

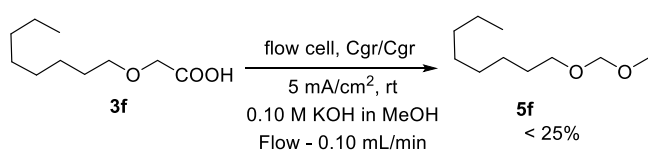
[a] Yields of pure and isolated compounds

To be able to compare the flow reaction results to the ones previously obtained through a batch system, a relatively small reaction scale had to be used. In order to achieve that 0.2 mmol of **3** was dissolved in 2 mL of methanol and the solution was then injected manually through the integrated 2 mL loops on the

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injection unit, after which it was carried by the solvent (pure methanol from the pressurised bottle), prior to reaching the electrochemical flow cell.

First, we tried to directly transpose our previously developed synthetic and workup batch conditions^[8] to the continuous flow setup using a 0.1 M methanolic KOH solution in which the desired acid **3** would be added through the injection loop. The electrolysed solution would then be submitted to a similar basic workup as the one previously used under batch conditions. Unfortunately, these conditions proved to give a low conversion of the starting material, even at the lowest flow rate (see Scheme 1). The passivation of the electrodes was also observed due to the anodic oxidation of methanol into paraformaldehyde.



Scheme 1. Direct conversion from batch to flow conditions.

In order to improve the conversion, to detect the passage of the reagent in the flow cell and limit the passivation of the electrodes, the carboxylic acid **3** was converted into its potassium salt **4**. By employing **4**, the use of a wasteful supporting electrolyte (KOH in methanol) is now superfluous,^[16–19] and the passivation of the electrodes could be completely suppressed by alternating their polarity every 30 seconds. The ionic nature of **4** makes its detection through the cell straightforward: when the Electrasyn 2.0 was used in a galvanostatic mode set to 100 mA, a large voltage (30 V) and a low current (1 to 3 mA) was observed when only pure methanol was flowing through the cell. However when the methanolic solution of **4** entered the flow cell, the current progressively increased to 100 mA and the voltage decreased to about 5 V. The endpoint was easily detected by observing the current/voltage couple returning to their initial values, rendering any other forms of detection superfluous (Figure 4).

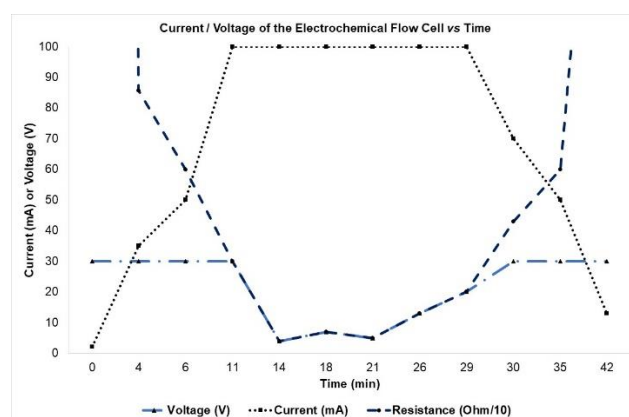


Figure 4. Current (I), voltage (V) and resistance ($R = V/I$) of the flow cell over time before, during and after the passage of 0.164 mmol of **4f** (originally dissolved in 2 ml of MeOH and injected through a 2 mL loop).

The impact of the flow and of **4**'s concentration on the fate of the reaction was then investigated (see Table 2).

Table 2. Flow Optimisation studies

Entry	Flow (mL.min ⁻¹)	Concentration of 4f (mol.L ⁻¹)	Yield (%) ^[a]
1	0.10	0.164	93
2	0.15	0.164	77
3	0.15	0.328	55
4	0.30	0.164	53

[a] Yields of pure and isolated compounds

As reported previously, high yields of MOM ethers could be achieved without the need to use strictly dry or deoxygenated conditions. The flow was shown to mainly impact the residence time (entries 1, 2 and 4). A lower flow rate ensures that the compound spends enough time in the cell to reach complete conversion but also increases the risk to produce overoxidation side products. In the same vein, increasing the concentration (entry 3) leads to a decrease in yield of the MOM ether due to the residence time being too short to convert all the substrate.

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Table 3. Anodic methoxymethylation of alcohols using the 3D printed flow cell.

$\text{R-O-CH}_2\text{-COOK} \xrightarrow[\text{MeOH 5 mA/cm}^2, \text{rt}]{\text{Flow cell, Cgr/Cgr}} \text{R-O-CH}_2\text{-O-CH}_3$ Flow - 0.15 mL/min			
Entry	Potassium carboxylate 4	MOM Ether 5	Yield (%) ^[a]
1			94 ^[d] 0 ^[c]
2			95 ^[b] 84 ^[c]
3			99 ^[b] 88 ^[c] 78 ^[e]
4			95 ^[b]
5			80 ^[b] <5 ^[c]
6			93 ^[b] 90 ^[c]
7			98 ^[b] 0 ^[c]
8			98 ^[b] 91 ^[c]
10			45 ^[f] 83 ^[c]
11			76 ^[b]

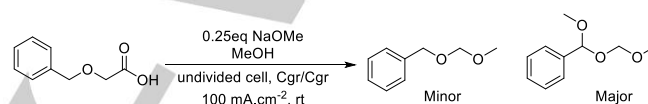
[a] Yields of pure and isolated compounds [b] under flow conditions. [c] under batch electrolysis conditions from ref 8 [d] Using a flow of 0.10 mL/min [e] on 1 g of starting material [f] NMR yield – highly volatile ether

For most compounds, an optimal flow rate of 0.15 mL/min was found to provide the clean MOM ether in good yields without the need for further purification. Lower flow rates tended to lead to slightly higher yields, but also to the formation of side products that would require tedious and time-consuming purifications. Only **4** provided the pure MOM ether using a flow rate of 0.10 mL.min⁻¹.

When the electrolysis of the cyclohexanol derivative (Table 3, entry 3) was conducted on a larger scale (1 g), its potassium salt was directly dissolved in 500 mL of methanol within the pressurised bottle itself rather than injected in the system via a loop. The flow electrolysis was run for 56 hours showing that the system could be run under traditional continuous flow conditions.

When compared to batch experiments (Table 3, yields [c]), flow experiments (Table 3, yields [b]) lead to similar or slightly higher yields. In each case, a complete conversion of the starting material and a high selectivity was observed as it can be seen from the high yields obtained for the isolated MOM ethers.

Remarkably, easily oxidisable compounds, bearing benzylic groups, are now tolerated under flow conditions whilst under batch conditions the benzylic positions are readily oxidised and methoxylated.^[20]

**Scheme 2.** Benzyl oxidation under batch conditions.

Finally, an excellent current efficiency ranging from 75% to 80% was observed when considering a theoretical consumption of 2 F/mol of substrate, a flow of 0.15 mL/min and a pathway of 2 mL within the cell. Such high current efficiency is unusual for Kolbe/Hoefer-Moest reactions and might be explained by the facts that a potassium carboxylate was used and by the very small gap between the two electrodes.^[21,22]

In conclusion, we have developed a practical, compact and cost-effective 3D printed electrochemical flow setup that could easily be used in most synthetic organic laboratories. The flow setup has successfully been applied to improve our previously developed anodic methoxymethylation methodology rendering it supporting electrolyte-free and compatible with easily oxidised substrates such as benzylic compounds.

Experimental Section

Procedure for the Synthesis of α -alkoxy Carboxylic Acids **3**:

All starting materials were purchased from commercial suppliers and used without further purification. A flame dried 250 mL three-necked flask was equipped with a magnetic stir bar and a reflux condenser. Sodium hydride (60% dispersion in mineral oil, 3 eq.) was then suspended in dry THF at 0 °C under argon. Alcohol **1** (1 eq.), dissolved in dry THF, was then added slowly. After 30 min, bromoacetic acid **2** (1 eq.), dissolved in dry THF, was added dropwise. The mixture was heated to reflux, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, as shown by TLC, the mixture was cooled down to room temperature and diluted with water (60 mL). The mixture was

extracted with hexane (2 x 30 mL), the aqueous layer was acidified with HCl until pH < 3 was reached and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel (petroleum ether / ethyl acetate) to give the pure α -alkoxy carboxylic acids **3**.

General Electrolysis Procedure:

A flow system was assembled using a 3D printed undivided electrochemical flow cell (total volume of 2 mL) equipped with two rectangular shaped graphite electrodes (5 cm x 4 cm) connected to an Electrasyn 2.0. 3D printing files for the continuous flow carbon electrode reactor and connector for the Electrasyn 2.0 are available from the authors account on Thingiverse.²⁴

The α -alkoxy carboxylic acid **3** (0.164 mmol) was dissolved in 2 mL of MeOH and neutralized with KOH (0.164 mmol). The solution was then sonicated for 10 minutes to ensure its homogeneity. Pure methanol was then allowed to flow (0.15 mL/min by applying a pressure of 6 PSI using argon in the system) through the system, and the Electrasyn 2.0 was set up in a galvanostatic mode with an alternating (every 30 s) current of 100 mA. The solution of potassium carboxylate was then injected using 2 mL solvent loops attached to the injection valves (Supplementary information) in the system and the reaction was monitored by following the resistance as described in the text. Once the reaction had finished, an additional 2 mL of MeOH was collected. The methanolic solution was then washed with a 1 M KOH in water (50 mL) and extracted with DCM (3 x 50 mL). The organic layers were combined, washed with a saturated solution of sodium carbonate (50 mL), dried over Na₂SO₄, and carefully concentrated under reduced pressure to yield the clean MOM ether without the need for any further purification (MOM ethers are volatiles). In between experiments, the flow cell was cleaned by circulating the following solvents: methanol, acetone, 0.1 M sulphuric acid in water and again methanol for 2 minutes each, with an overall pressure of 3 to 5 PSI.

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