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An extended channel length microflow electrolysis cell for convenient laboratory synthesis

Robert A. Green^{a,*}, Richard C.D. Brown^{a,*}, Derek Pletcher^a, Bashir Harji^b^a Department of Chemistry, University of Southampton, Southampton SO17 1 BJ, UK^b Cambridge Reactor Design Ltd, Unit D2, Brookfield Business Centre, Cottenham, Cambridgeshire CB24 8PS, UK

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ABSTRACT

A spiral, extended channel length microflow cell designed for routine and convenient application in an organic synthesis laboratory is described. The performance of the cell is demonstrated using two syntheses and it is shown that high selectivities and high conversions in a single pass can be achieved as well as the formation of products at a rate of up to 25 mmol/h (~3 g/h). The cell is also well suited to carrying out the optimisation of reaction conditions with electrolyses completed on a timescale of minutes.

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1. Introduction

Despite a history going back >150 years and some examples of industrial applications, organic electrosynthesis has never established a position in routine laboratory synthesis. One reason is the reliance on beaker cells and H-cells when slow conversions and poor/ill-defined conditions hamper yields and reproducibility [1]. There is a clear need for cells for convenient and straightforward use by synthetic organic chemists. In designing and operating such cells, the emphasis is on convenience of use, high yield of product and ease of product isolation through a high conversion of reactant to product, the use of no/low electrolyte concentration and clean counter electrode chemistry. On the scale of laboratory synthesis, current efficiency is only important as far as competing electrode reactions can degrade product purity. Energy consumption only becomes important if and when the laboratory synthesis is to be scaled for manufacture.

One approach to meeting this need employs microflow electrolysis cells with an extended channel length [1–5]. They have been demonstrated to make possible

- very high conversions in a single pass
- operation with poorly conducting reaction media
- rapid electrolysis with residence time of reactant in the cell restricted to minutes
- selective chemical change for a number of synthetic reactions

The present paper describes a small cell intended for use in a synthetic organic chemistry laboratory. It is an undivided parallel plate reactor where a spacer is employed to achieve a spiral channel with extended length and narrow interelectrode gap. It is designed for studies relating to optimising reaction conditions and for synthesising product on a scale of 100 mg–10 g and is a smaller version of a cell described previously [5]. A variety of electrosynthetic microflow reactors have been reported in the literature [7–14]. The majority of these cells contain a short path lengths (<10 cm), necessitating low flow rates of electrolyte to achieve high conversion in a single pass, which consequently restricts the rate of product formation. The performance of the cell, reported here, is demonstrated using two reactions: the methoxylation of *N*-formylpyrrolidine (Scheme 1), a reaction used to test performance in earlier microflow cells [2–5]; and the cleavage of the 4-methoxybenzyl protecting group from 3-phenyl-1-propanol (Scheme 2). This reaction will be reported in more detail in a further publication [15]. In both syntheses, the counter electrode reaction is the reduction of methanol to hydrogen and methoxide, the latter minimising the build-up of protons in the electrolyte along the cell channel.

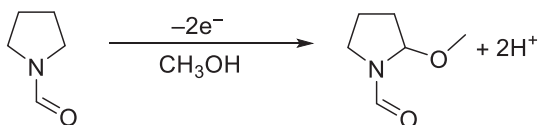
2. Experimental

2.1. Electrolysis cell

The cell was manufactured by Cambridge Reactor Design and is now available for purchase as the Ammonite 8 electrolysis cell [6]. The anode was a disc of carbon-filled polyvinylidene fluoride (C/PVDF), type Sigracet BMA5, supplied by Wilhelm Eisenhuth GmbH, Germany – diameter 85 mm and thickness 5 mm. The cathode was a circular 316 L

* Corresponding authors.

E-mail addresses: rag206@soton.ac.uk (R.A. Green), R.C.Brown@soton.ac.uk (R.C.D. Brown).



Scheme 1. The methoxylation of *N*-formylpyrrolidine.

stainless steel plate (Castle Metals Ltd., UK), diameter 85 mm and thickness 5.0 mm, with a spiral groove, depth 0.5 mm machined into it. The gasket/spacer was cut to fit into the groove and was fabricated from a 1.0 mm thick sheet of KALREZ perfluoroelastomer (James Walker LTD, UK). The C/PDVF composite electrode had a copper disc backing plate to improve the potential distribution along the electrolyte channel. The cell was compressed between an aluminium base plate and a Perspex top via a central bolt and 6 bolts around the perimeter. The cell is rapid to dismantle, clean and reassemble. The solution entered and exited the cell through steel tubing (1/8th inch diameter) to which connection could be made via standard fittings. There were separate reservoirs for reactant and product and solution was pumped with an Ismatec Reglo digital peristaltic pump with flow rates 0.25–3.0 cm³ min⁻¹. Electrolyses were controlled with a Rapid Electronics switching mode power supply (85–1903).

2.2. Chemicals and analysis

Methanol (Fisher Scientific, HPLC grade) and *N*-formylpyrrolidine (Sigma-Aldrich, >98%+) were used without purification. Tetraethylammonium tetrafluoroborate was recrystallized from hot methanol and dried at 363 K in a vacuum oven (~10 mbar) for 48 h. The protected alcohol was prepared by the method of Kern et al. [16].

Conversion and selectivity were determined by gas chromatography using a Shimadzu GC-2014 equipped with an autosampler, FID detector and Agilent Technologies HP5 column. A calibration curve was obtained for starting materials and products of both reactions, by testing a range of solutions of known concentration. Comparison of the unknown reaction solutions to the calibration curve allowed for conversion, yield and selectivity to be calculated for each reaction.

3. Results and discussion

3.1. Cell design

The cell is designed to have (a) an extended length electrolysis channel (1 m) in order to achieve a high conversion of reactant to product in a single pass at flow rates compatible with carrying out reactions at a rate of g/h (b) a narrow interelectrode gap to permit use of poorly conducting media including those with low/no electrolyte (c) a short residence time of reactant/product within the cell to minimise the competition of unwanted homogeneous reactions. It is undivided but the absence of a separator is not necessarily a disadvantage. Indeed, it can be turned to advantage since the counter electrode reaction can be used to maintain a constant reaction environment along the channel, e.g. when carrying out oxidations, the cathode can be used to stop the build up of protons along the channel by generating an equivalent quantity of base. The cell is conveniently controlled with a constant cell current. For full conversion, this cell current is calculated using Faraday's

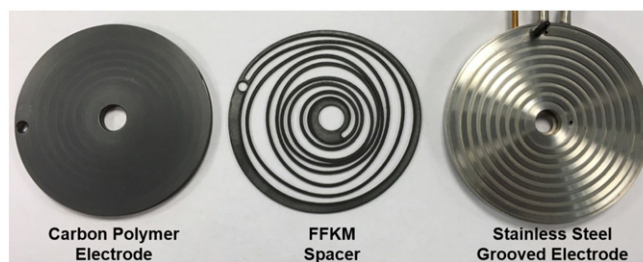


Fig. 1. Components of the extended channel length microflow electrolysis cell.

laws for the concentration of reactant and flow rate of the solution (provided the desired reaction has a high enough rate – preferably mass transfer controlled [1–5]). It should, however, be recognised that the cell current is, in fact, the integral of the local currents along the channel as they drop from a high value at the channel entry towards zero at the exit (as the reactant concentration drops with conversion) [1–5].

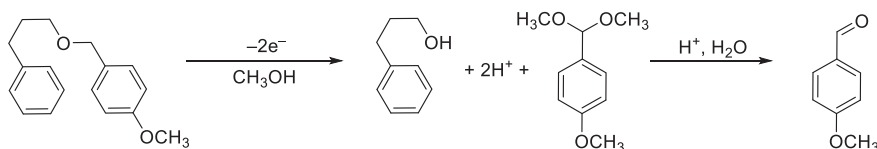
The electrolysis cell is a parallel plate reactor based on two circular plate electrodes, diameter 85 mm, but with a spiral electrolyte channel between them. The spiral electrolyte channel permits an extended channel length within a device with small dimensions and a smooth electrolyte flow regime along the channel. The spiral electrolyte channel is created with a spiral spacer (see Fig. 1) held rigidly in place within a spiral groove machined into one of the electrodes (see Fig. 1). The other electrode is a smooth plate. The interelectrode gap is fixed through the depth of the groove and the thickness of the polymer spacer. In the present cell, the electrodes are 316L stainless steel and C/PDVF composite material and the spacer fabricated from KALREZ perfluoroelastomer; this polymer was selected because of its resistance to oxidation/reduction and its stability in many organic media. The C/PDVF anode has a copper disc backing plate to improve the uniformity of the potential distribution across its surface – ideally the potential should be constant along the cell channel. The machining of the spacer and the groove leads to an electrolyte channel 1000 mm in length and 2 mm in width while the interelectrode gap is 0.5 mm. The volume of the cell is therefore 1.0 cm³ and when assembled (see Fig. 2) has the dimensions 110 mm (diameter) × 60 mm (height). Materials and suppliers as well as other details are given in the [Experimental](#) section.

3.2. Cell performance

The performance of the cell was established using two syntheses, the methoxylation of *N*-formylpyrrolidine, reaction (scheme 1), and the cleavage of the 4-methoxybenzyl protecting group from 3-phenyl-1-propanol, reaction (scheme 2).

Table 1 reports the results from a series of electrolyses with *N*-formylpyrrolidine (Scheme 1). The initial electrolysis were carried out with solutions containing 0.10 M *N*-formylpyrrolidine and 0.05 M tetraethylammonium tetrafluoroborate and using a cell current ~20% above the theoretical optimum value calculated from the equation

$$I_{\text{cell}} = \frac{xnF}{t} \quad (1)$$



Scheme 2. The electrochemical cleavage of 4-methoxybenzyl to give 3-phenyl-1-propanol.

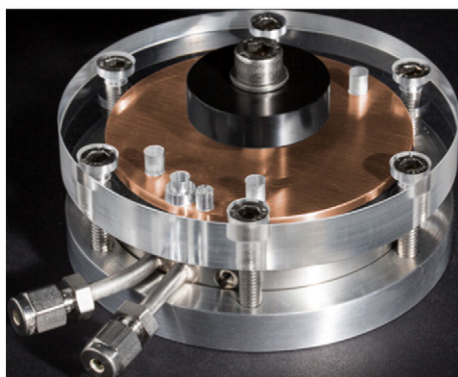


Fig. 2. The complete cell.

where x is the number of moles of reactant, n the number of electrons involved in the conversion of reactant to product, F the Faraday constant and t the time for the reactant solution to pass through the cell (determined by the flow rate of solution through the cell). The excess charge improved the conversion without significant loss in selectivity. This approach leads to current efficiencies of 60–80%, but it should again be stressed that current efficiency and energy consumption are not important for a laboratory electrosynthesis.

It can be seen that, indeed, a high conversion in a single pass with a good selectivity can be achieved over a range of conditions. At the slower flow rates, the methoxylation reaction goes close to completion while there is a small decline as the flow rate is increased. Using a higher cell current again leads to a higher conversion. The fractional reaction selectivity is always well above 0.8 and can reach 0.95. At the slowest flow rate the product formation rate is 0.17 g h^{-1} and this can be increased using a higher flow rate and/or concentration of reactant and several grams per hour is readily achieved. A five-fold increase in reactant concentration necessitates a five-fold increase in cell current but the conversion and selectivity are hardly affected. The increase in reactant concentration allows a large increase in product formation rate. Of course, the amount of product can also be increased using a larger volume of reactant solution and a longer electrolysis time. It should be noted that at the highest flow rate, the residence time of the reactant in the cell is only 20 s. Electrolyses are also possible with lower electrolyte concentration.

Table 2 reports data from experiments where the reaction of interest is the removal of a protecting group from an alcohol [15], a reaction where further oxidation of products could lead to loss of selectivity (Scheme 2). Again, the solution was usually 0.10 M reactant and 0.05 M electrolyte and a cell current above the theoretical optimum value used to enhance the conversion. The fractional conversions and fractional selectivities are always high. With increased flow rates, however, there is a slight decay in fractional selectivity and this probably

Table 1

Performance of the cell for the methoxylation of *N*-formylpyrrolidine (Reaction 1). MeOH/ Et_4NBF_4 (0.05 M). Electrolysis time 20 min using volumes of reactant solution of 5–60 cm^3 . Product analysed by gas chromatography.

Concentration M	Flow rate $\text{cm}^3 \text{ min}^{-1}$	Cell current A	Fractional conversion	Fractional selectivity	Product formation rate g h^{-1}
0.1	0.25	0.1	0.99	0.88	0.17
	0.5	0.2	0.99	0.95	0.37
	1.0	0.4	0.86	0.95	0.64
	2.0	0.8	0.86	0.94	1.26
	3.0	1.5	0.92	0.83	1.18
0.5	0.25	0.5	0.88	0.91	1.86
	0.5	1.0	0.96	0.89	0.82
	1.0	2.0	0.95	0.87	1.60
			0.93	0.88	3.16

Table 2

Performance of the cell for the cleavage of the 4-methoxybenzyl protecting group from 3-phenyl-1-propanol (Reaction 2). MeOH/ Et_4NBF_4 (0.05 M). All reactions were performed on 5 cm^3 samples (electrolysis time 10 or 20 min) except the 1.0 $\text{cm}^3 \text{ min}^{-1}$ experiment when the sample was 10 cm^3 (electrolysis time 10 min). Product analysed by gas chromatography.

Concentration M	Flow rate $\text{cm}^3 \text{ min}^{-1}$	Cell current A	Fractional conversion	Fractional selectivity	Product formation rate g h^{-1}
0.1	0.25	0.13	0.93	0.99	0.19
	0.5	0.27	0.99	0.82	0.33
	1.0	0.54	0.99	0.79	0.64
0.2	0.25	0.27	0.99	0.87	0.35
	0.5	0.67	0.99	0.87	0.88

arises from overoxidation with the higher cell currents needed for full conversion. Hence, this synthesis was generally carried out with a lower flow rate.

Both syntheses remain possible with a low electrolyte concentration with no significant loss in performance. For example, the cleavage of the protecting group was repeated using a flow rate of $0.25 \text{ cm}^3 \text{ min}^{-1}$ and an electrolyte concentration of 5.0 mM; the fractional conversion was 0.99 with a fractional selectivity of 0.83. The drawback is the necessary increase in applied cell voltage, $\sim 5.5 \text{ V}$ with 5 mM electrolyte compared to $\sim 3.5 \text{ V}$ with 50 mM electrolyte. This is not a problem for these syntheses and the conditions used. Potentially, however, higher applied voltages can lead to more rapid Joule heating of the cell, changing the reaction dynamics and possibly a loss in selectivity. If necessary, with the cell described, the temperature can be controlled by contact of the base of the reactor with laboratory cooling/heating/cooling equipment regulated via a temperature probe fitted into the stainless steel electrode. It should also be noted that in both syntheses the tetraethylammonium tetrafluoroborate is easily recovered by precipitation from the crude reaction mixture, and can be reused many times.

4. Conclusions

The cell with an extended channel length achieved using a spiral design is shown to be a convenient laboratory tool for electrosynthesis. It allows very high conversion of reactant to product with good selectivity in a single pass of solution through the cell using flow rates that are compatible with the formation of product at a rate of g/h. With complete electrolyses possible in a few minutes, the cell is ideal for exploring the influence of reaction conditions on selectivity and yield. Indeed, several reaction conditions can be investigated with a single filling of the reactant reservoir.

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References

- [1] R.A. Green, R.C.D. Brown, D. Pletcher, Electrosynthesis in extended channel length microfluidic electrolysis cells, *J. Flow Chem.* 6 (2016) 191–197.
- [2] J. Kuleshova, J.T. Hill-Cousins, P.R. Birkin, R.C.D. Brown, D. Pletcher, T.J. Underwood, A simple and inexpensive microfluidic electrolysis cell, *Electrochim. Acta* 56 (2011) 4322–4326.
- [3] J. Kuleshova, J.T. Hill-Cousins, P.R. Birkin, R.C.D. Brown, D. Pletcher, T.J. Underwood, The methoxylation of *N*-formylpyrrolidine in a microfluidic electrolysis cell for routine synthesis, *Electrochim. Acta* 69 (2012) 197–202.
- [4] R.A. Green, R.C.D. Brown, D. Pletcher, Understanding the performance of a microfluidic electrolysis cell for routine organic electrosynthesis, *J. Flow Chem.* 5 (2015) 31–36.

- [5] R.A. Green, R.C.D. Brown, D. Pletcher, B. Harji, A microflow electrolysis cell for laboratory synthesis on the multigram scale, *Org. Process. Res. Dev.* 19 (2015) 1424–1427.
- [6] <http://www.cambridgereactor.com/ammonite/ammonite.html>. Accessed 23/09/2016.
- [7] S. Suga, M. Okajima, K. Fujiwara, J. Yoshida, "Cation flow" method: a new approach to conventional and combination organic synthesis using electrochemical microflow systems, *J. Am. Chem. Soc.* 123 (2001) 7941–7942.
- [8] D. Horii, T. Fuchigami, M. Atobe, A new approach to anodic substitution reaction using parallel laminar flow in a micro-flow reactor, *J. Am. Chem. Soc.* 129 (2007) 11692–11693.
- [9] K. Bouzek, V. Jiřičný, R. Kodým, J. Křišťál, T. Bystrouň, Microstructured reactor for electroorganic synthesis, *Electrochim. Acta* 55 (2010) 8172–8181.
- [10] A. Ziogas, G. Kolb, M. O'Connell, A. Attour, F. Lapique, M. Matlosz, S. Rode, Electrochemical microstructured reactors: design and application in organic synthesis, *J. Appl. Electrochem.* 39 (2009) 2297–2313.
- [11] A. Attour, P. Dirrenberger, S. Rode, A. Ziogas, M. Matlosz, F. Lapique, A high pressure single-pass high-conversion electrochemical cell for intensification of organic electrosynthesis processes, *Chem. Eng. Sci.* 66 (2011) 480–489.
- [12] K. Watts, W. Gattrell, T. Wirth, A practical microreactor for electrochemistry in flow, *Beilstein J. Org. Chem.* 7 (2011) 1108–1114.
- [13] K. Watts, A. Baker, T. Wirth, Electrochemical synthesis in microreactors, *J. Flow Chem.* 4 (2014) 2–11.
- [14] C. Gütz, M. Bänziger, C. Bucher, T.R. Galvão, S.R. Waldvogel, Development and scale-up of the electrochemical dehalogenation for the synthesis of a key intermediate for NSA inhibitors, *Org. Process. Res. Dev.* 19 (2015) 1428–1433.
- [15] R.A. Green, R.C.D. Brown, A.A.M. Al-Hadedi, K.E. Jolley, D. Pletcher, D.C. Harrowven, D. Klauber, O. De Frutos, C.M. Gutierrez, (in preparation).
- [16] N. Kern, T. Dombay, A. Blanc, J.-M. Weibel, P. Pale, Silver(I)-catalyzed deprotection of p-methoxybenzyl ethers: a mild and chemoselective method, *J. Organomet. Chem.* 77 (2012) 9227–9235.