Microflow electroorganic synthesis without supporting electrolyte†

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Anodic methoxylation of several organic compounds has been successfully achieved in the absence of intentionally added supporting electrolyte using an electrochemical microflow system.

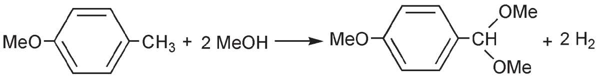
The electrochemical reactions serve as powerful methods for the synthesis of organic compounds because highly reactive species can be easily generated under very mild conditions. The electrochemical reactions have been well-known for many years. However, the use of supporting electrolytes has been a hurdle for synthetic chemists. Although SPE[1] (solid polymer electrolyte) technology has been developed for electrolyte-free electrolysis, an approach based on microchemical systems also seems to be attractive. Herein we report a new method for microflow electroorganic synthesis without adding supporting electrolyte.

Electrochemical microflow reactors[2] have received significant research interest. High electrode surface to reactor volume and short distance between electrodes are advantageous from view points of reaction efficiency and conductivity. Effective temperature control and short residence time are also favourable when highly reactive species generated by the electrochemical processes are involved. Recently, Marken and coworkers reported electrochemical microflow process without adding supporting electrolyte.[3] In their system, two electrodes are placed facing each other in a distance of millimetre order and the substrate solution flows through the chamber between them. Therefore, they design a system where the liquid flow and the current flow are perpendicular.

We have developed a microsystem like the one shown in Fig. 1 to achieve electrolyte-free electrosynthesis. In this system, two carbon fiber electrodes[4] were separated by a spacer in a distance of micrometer order. A substrate solution is fed in the anodic chamber, flows through the spacer and the cathode, and leaves the cell from the cathodic chamber as products. As a spacer, a hydrophobic porous PTFE membrane (ADVANTEC T010A, pore size: 3 μm, thickness: 75 μm) was found to be suitable for the present purpose.

In our system, the electric current flow and the liquid flow are parallel, whereas they are in perpendicular orientation in the Marken system. It is also noteworthy that in our system the whole electrochemical chamber is filled with the carbon felt electrode, in contrast with the Marken reactor that has an empty space between the cathode and anode. Therefore, the electrode surface area is greater in our system. Furthermore, our electrochemical microsystem allows higher flow rate and higher current, which could be an advantage for future scaling up.

First, we focused on the anodic methoxylation of *p*-methoxytoluene [eqn. (1)] because this process is well-known and industrially important.[5,1c]



(1)

1 **2**

A solution of *p*-methoxytoluene (**1**) in methanol (0.05 M, 2 mL h^{-1}) was fed into the electrochemical microflow system. The reaction was carried out under the constant current condition (11 mA at room temperature, 4 F mol^{-1} based on *p*-methoxytoluene, cell voltage: 21–25 V) to obtain the desired product **2** in more than 90% yield based on consumed starting material (*ca.* 30% conversion) as shown in Fig. 2. It was difficult, however, to increase the current. The application of 22 mA of the current gave rise to breaking of the membrane.[6]

Although the conversion of the starting material was low, the success of the present reaction can be interpreted in terms of the following scheme (Fig. 3).

The anodic methoxylation of compound **1** accompanied proton generation. Protons and acetal **2** thus formed were immediately

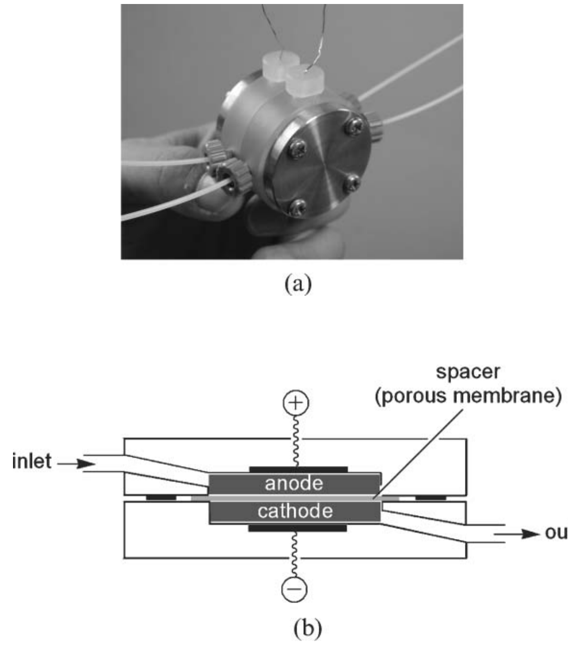


Fig. 1 Electrochemical microflow system: (a) outside, (b) system diagram.

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† Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/cc/b4/b417388k/

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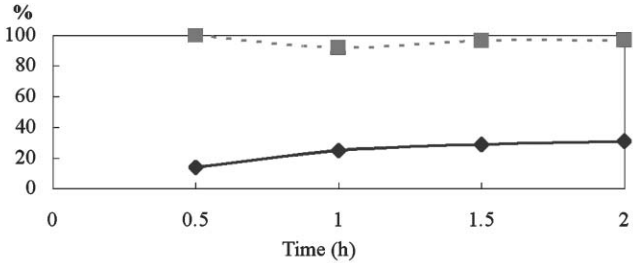


Fig. 2 Progress of the electrochemical reaction of **1** (11 mA). Solid line: conversion. Dotted line: conversion yield. Flow rate 2 mL h^{-1}.

transferred to the cathodic chamber through the porous spacer membrane. At the cathode, protons were reduced to hydrogen. Thus, acetal **2** and hydrogen gas came out at the outlet of the system. We assumed that the flow of protons from the anodic to the cathodic chamber should be responsible for the conductivity in the solution.

As stated above, it is most likely that protons are the carriers of the electricity. However, at the initial stage of the reaction, the concentration of proton in the system should be very low, and this situation is unfavourable for the reaction. As a matter of fact, the conversion was very low at the initial stage (Fig. 2). Therefore, it is reasonable to consider that the addition of protons in the reactor only at the initial stage could be advantageous. In fact, the pre-treatment of the reactor with a solution of TfOH (0.125 M in methanol, 0.5 mL) before electrolysis gave rise to a significant decrease of the cell voltage (6–6.5 V), although no TfOH was added during the course of the electrolysis. The conversion and yield were constant during the course of the reaction. Due to the low value of the cell voltage, it was easy to increase the current up to 22 mA giving rise to a significant improvement in the conversion of the starting material without significant increase of the cell voltage (6–7 V) (Fig. 4).[7]

The flow rate is an important factor that must be controlled. When the methoxylation of **1** was done at 3 mL h^{-1}, the conversion dropped from 73 to 34%. The decrease of the flow rate to 1 mL h^{-1} caused an increase of the voltage. Therefore, the flow rate of 2 mL h^{-1} seems to be the optimum conditions.

The very small distance between the electrodes seemed to be responsible for the success of the current flow. Accordingly, we examined the effect of the thickness of the spacer and observed that the use of two sheets of the porous PTFE membrane (75 μm thickness) as a spacer gave rise to a significant increase of the cell voltage, with eventually breaking of the spacer membrane. The pore size of the membrane was also important. The use of spacer of smaller pore size (0.1 μm) resulted in significant increase of the cell voltage (100–110 V).[8]

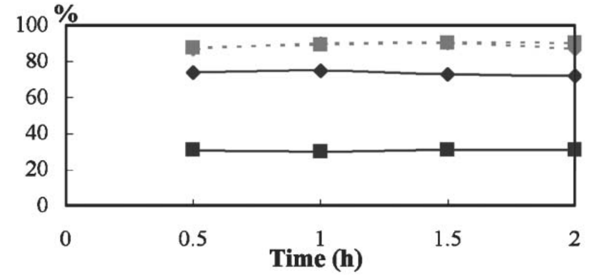


Fig. 4 Progress of the electrochemical reaction of **1** with acid pre-treatment. Flow rate 2 mL h^{-1}. Solid line: conversion. Dotted line: conversion yield. (■) 11 mA. (◆) 22 mA.

The spacer membrane, however, does not seem to change or be modified during the course of the reaction. When a membrane used in the electrolysis with the acid pre-treatment (22 mA) was washed with methanol (5 mL) and reused in an electrolysis without acid pre-treatment (22 mA), we observed an increase of the cell voltage (35–37 V) and decrease in the conversion (25%). Then again, the use of the same spacer membrane in a following electrolysis with acid pre-treatment (22 mA) achieved typical values of cell voltage (7.3–7.9 V) and conversion (69%) for this type of reactions.

With the standard conditions (the use of one sheet of the spacer membrane of 3 μm pore size) under control, we examined other types of electrochemical oxidation using the microflow system like the methoxylation of *N*-methoxycarbonyl pyrrolidine (**3**)[9] and the methoxylation of acenaphthylene (**6**).[10] These results are summarized in Table 1.

In summary, we have demonstrated the "proof-of-principle" of our strategy for electrolysis without adding supporting electrolyte using microflow systems. It is hoped that the present principle will be applied to various reactions that are useful for organic synthesis.

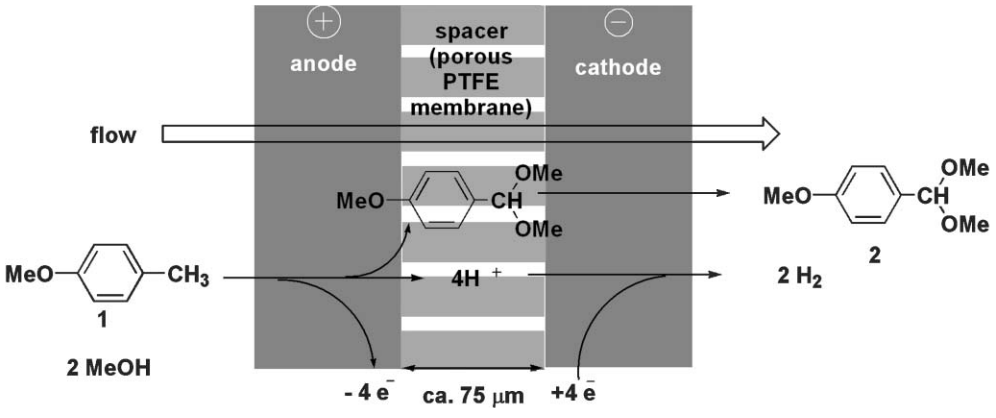
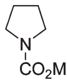


Fig. 3 Schematic diagram of electrochemical oxidation of **1** in methanol using the electrochemical microflow reactor without adding supporting electrolyte.

Table 1 Electrochemical methoxylation of organic compounds without supporting electrolyte[a]

Starting material	Current/ mA	Conversion/ %	Product	Conversion yield/%
3	11	77	**4** and **5**	57 (**4**), 40[b] (**5**)
3	22	86	**4** and **5**	46 (**4**), 47[b] (**5**)
6	11	25	**7**	56[b]
6[c]	11	75	**7**	65[b]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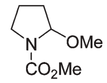
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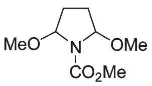
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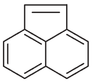
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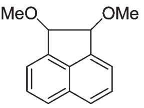
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[a] Flow rate 2 mL h^{-1}. [b] A mixture of *cis* and *trans* isomers. [c] 50 °C.

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Notes and references

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3 C. A. Paddon, G. J. Pritchard, T. Thiemann and F. Marken, *Electrochem. Commun.*, 2002, **4**, 825.

4 A textile carbon felt made from carbon fiber (*ca.* 60 mg, Nippon Carbon JF-20-P7) was used as electrode. This carbon fiber electrode was dried before use by heating at 250 °C for 2 h.

5 BASF Information 15.10.98, company brochure, BASF, Ludwigshafen.

6 The cell voltage and the feature of the reaction strongly depend on the purity of methanol solvent. Throughout this study dried and distilled methanol (water content <70 ppm) was used. The use of methanol containing higher than 300 ppm of water gave rise to much higher cell voltage and lower conversion of the starting material. The use of methanol dried over molecular sieves without distillation resulted in lower cell voltage in the case where thicker spacer was used. Presumably, a small amount of impurities, which dissolved into methanol from molecular sieves are responsible for better conductivity. More data, however, should be accumulated before elucidation of the detailed explanations of these observations.

7 The current efficiency under standard operating conditions was 36%.

8 No appreciable change in the resistance of the flow was observed when two sheets of membrane were used as a spacer.

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