An electrochemical flow cell for the convenient oxidation of Furfuryl alcohols

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Abstract

Effecting oxidation reactions electrochemically dispenses with the need for reactive and potentially toxic reagents but barriers remain towards wide adoption of the technique, in part because of negative prior experiences with batch-mode reactions. Electrochemical flow set-ups fix the electrodes to maintain a uniformly narrow gap, and can operate continuously until a desired quantity of substrate has been processed. We describe the fabrication of an electrochemical flow cell and its application in the transformation of furfuryl alcohols into hydroxypyrones. The cell is simple to operate with inexpensive equipment under a constant current regime, flow rate being controlled by a standard laboratory syringe pump. With the addition of a trace of NaClO₄ as electrolyte to provide a stable current flow, the oxidations proceed routinely with a current efficiency of around 60%.

Keywords Electrochemistry · Anodic oxidation · Furans · Achmatowicz reaction · Hydroxypyrones

Introduction

Oxidative rearrangements of furans are widely employed in the synthesis of natural products [1]. Among these, the Achmatowicz reaction converts furfuryl alcohols into hydroxypyrones en route to cyclic ethers, carbohydrates, and precursors for oxidopyrylium cycloadditions [2]. The overall process comprises the reaction of furfuryl alcohols **1** (Scheme 1) with bromine in methanol (the Clauson-Kaas reaction) [3–5], then acidic hydrolysis of the intermediate 2,5-dimethoxy dihydrofuran derivatives **2** during which the hydroxyl group cyclises onto the distal carbonyl group. Subsequently, other oxidants were reported to effect the overall reaction directly; for example: pyridinium chlorochromate [6], *N*-bromosuccinimide [7], peroxy acids [8], dimethyldioxirane

[9], *t*-butyl hydroperoxide / vanadyl acetylacetonate [10], singlet oxygen followed by hydrolysis [11], and more recently biocatalysts [10–15].

The application of electrochemistry to generate 2,5-dimethoxy dihydrofurfuryl alcohols had been described nearly 20 years before Achmatowicz's report [16–20]. The mechanism proposed [21] for the anodic oxidation of furans (**A**) in methanol depicted in Scheme 2 involves one-electron oxidation of the furan at the anode ($\rightarrow$ **B**), trapping by a molecule of solvent ($\rightarrow$ **C**), then further oxidation ($\rightarrow$ **D**), and capture by a second solvent molecule ($\rightarrow$ **E**); in parallel, reduction at the cathode generates hydrogen gas. Electrochemically-generated 2,5-dimethoxy-dihydrofurfuryl alcohols were later employed in Achmatowicz reactions for the synthesis of maltol and analogues [22–26], a process effected on multi-tonne scale by Otsuka Chemical Company. Applications of this process more widely have not been reported, perhaps a reflection of the relatively low adoption of electrochemical methods within the mainstream synthesis community. This, in turn, may be due to a perceived need for specialised equipment, and lack of familiarity with some of the less tangible experimental parameters that are often crucial to success in synthetic electrochemistry.

Advances in reaction technology have made electrochemical synthetic methodologies more accessible, and recent high-profile reviews will help the approach to gain traction among mainstream synthetic chemists [27–31]. In this context, flow chemistry has emerged as a major enabling technology in

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Scheme 1 Achmatowicz reaction of furfuryl alcohols yielding hydroxypyrones

organic synthesis [32], and the construction of electrochemical flow cells [33–37] allows the reactions to be performed in the absence of an added electrolyte by virtue of the very close proximity of the two electrodes [38–40]. Furthermore, reactions may be performed using simple equipment under a constant current regime, without the need for a considerably more expensive potentiostat. Synthetic electrochemical transformations have been reported in which the power source is a lantern battery [41], a D-cell battery [42], a mobile phone charger [43], or a photovoltaic cell [44, 45], among others.

Our group has worked extensively on oxidative dearomatisation reactions of furan derivatives en route to mostly spirocyclic natural products. Of most relevance is a method based on stepwise electron- and proton-transfer steps mediated by DDQ [46]. The extended alkylidene spiroacetals generated in this reaction were found to be poorly stable in the presence of the oxidant and acceptable results could only be obtained by running the reaction at $-90\text{ }^{\circ}\text{C}$ and keeping the reaction time short; the reactions were then clean but incomplete. An electrochemical flow variant of this process could, in principle, achieve complete oxidation by fine control of the flow rate / residence time. In related work [47], we described the formation of butenolide spiroacetals from 2-(4-hydroxybutyl)furan derivatives either directly, using an excess of MCPBA, or in two steps, using sequential oxidations with MCPBA and PDC, with overall yields of 60–65%. Again, an electrochemical variant of this reaction would remove the need to employ reactive chemical oxidants and then separate the spent reagent from the desired product. This paper describes a preliminary project to fabricate a suitable device, that could be deployed in any organic chemistry laboratory, and illustrate its effectiveness in a transformation of value to synthetic chemists. The aim was to

develop a flow method for the anodic oxidation of furfuryl alcohol derivatives under constant current conditions, employing a commercial power supply, and then determine the synthetic potential of the approach for accessing side-chain functionalised hydroxypyrones derivatives.

Results and discussion

Cell design and construction

The electrochemical cell was designed using Vectorworks 2015 (Nemetschek/Techlimits), and constructed using a Roland MDX-40 desktop milling machine (Roland DG) using VCarvePro 7.5 CAM software (Vectric). The cell, depicted in Fig. 1, consists of two polyether ether ketone (PEEK) mounts. The upper mount (Fig. 1a) supports the carbon anode (Fig. 1b) in a slot akin to the one that hosts the platinum cathode (Fig. 1c) in the lower mount (Fig. 1d) [48]. This slot (Fig. 1e) features a series of grooves to facilitate adhesion of the electrodes to the PEEK using Araldite® epoxy resin glue. Once the electrodes had been fastened into the sockets they were polished flush into the mounts using diamond polishing suspensions down to 50 nm in a metallographic grinder. Both electrodes were polished to a mirror finish.

Electrical connection to the electrodes was achieved using three spring-loaded pins (Preci-dip) with a standard pitch separation of 2.54 mm, and hidden in a straight socket (Fig. 1f) to facilitate the attachment of a cable. The upper mount also includes fluidic threaded ports (Fig. 1g) to match M660 1/16" super flangeless fittings (Upchurch Scientific). Solutions were driven in and out the cell through 1/16" outer diameter PTFE tubing (Cole Parmer). Inside the cell, the inlet and outlet are 1 mm in diameter (Fig. 1h). Suitable gaskets (Fig. 1i) were manufactured in thin sheets (25–100 μm) from a variety of materials – including PEEK, PTFE, FEP, and Kapton – using a Roland GX-24 CAMM cutter plotter (Roland DG). For operation, the cell is held together by ten M3 screws. Detailed 2D and 3D diagrams are available as [Supporting Information](#), and the original Vectorworks file will be provided by the authors upon request.

Cell testing and optimisation

The flow cell was tested by effecting anodic oxidation of a 20 mM solution of furfuryl alcohol **4** in methanol. A Keithley 2200-72-1 programmable power supply was used as the power source, and all runs were performed under constant current conditions. In contrast to Atobe's report [48], initial runs in the absence of supporting electrolyte were plagued by inconsistent results, with

Scheme 2 Anodic oxidation of furans in methanol $\rightarrow$ dimethoxydihydrofurans

Fig. 1 Flow cell schematic. **a**) PEEK mount; **b**) glassy carbon anode; **c**) platinum cathode; **d**) PEEK mount showing a recess for the electrodes; **f**) port for electrical connection; **g**) and **h**) the inlet ports for the reaction solution; **i**) gasket; **j**) the complete assembly

the solution conductivity being too low for useful current densities to be reached. Decreasing the electrode distance from 100 μm to 25 μm via use of a thinner gasket provided no improvement. It was found subsequently that addition of a trace of NaClO_4 to the substrate solution (ca. 0.05 mM, corresponding to 0.25% with respect to the substrate) considerably increased the conductivity and rendered all subsequent runs perfectly reproducible. Table 1 summarises the results of a brief examination of the conversions obtained with varying current densities and flow rates. Increasing the current density up to 5.8 mA cm^{-2} provided an improvement in conversion, while further increases made no difference. A flow rate of $165 \mu\text{L min}^{-1}$ was deemed ideal, balancing substrate throughput and conversion; decreasing the rate to $118 \mu\text{L min}^{-1}$ gave only a marginal increase in conversion.

Table 1 Optimisation of electrolysis parameters (25 μm Kapton gasket)

Entry	Potential /V	Current /mA	Current density /mA cm ⁻²	Flow rate / $\mu\text{L min}^{-1}$	Conversion ^a /%
1	2.6	7.3	2.9	330	22
2	3.4	20.0	8.0	330	65
3	2.7	14.6	5.8	330	46
4	3.3	14.6	5.8	165	78
5	3.9	14.6	5.8	118	80
6	4.1	17.0	6.8	165	79

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

Application to substituted furfuryl alcohols

Table 2 summarises the results of applying these parameters in the electrolysis of representative furfuryl alcohols, with side-chains bearing common simple functionality. Alkanes, alkenes, and alkynes are well tolerated; phenyl rings are compatible with the oxidation but entry 4 reveals a low yield that we attribute to a competing decomposition pathway resulting in the extrusion of benzaldehyde (Scheme 3), evident in the ^1H NMR spectrum of the crude electrolysis mixture. Moving the phenyl substituent to a position where it cannot interfere mechanistically in this way largely obviated this problem (entry 5).

In general, separate oxidations were conducted back-to-back over the course of a day without the need to disassemble the cell and clean the electrodes. To begin,

Table 2 Substrate screening for the flow anodic oxidation of furfuryl alcohols (25 μm Kapton gasket)

Entry	R-	Conversion ^a /%	Isolated yield /%
1	1a,2a Bu-	82	66
2	1b,2b $\text{H}_2\text{C}=\text{CHCH}_2\text{-}$	84	71
3	1c,2c $\text{HC}\equiv\text{CCH}_2\text{-}$	79	54
4	1d,2d Ph-	100	24
5	1e,2e Bn-	100	57

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

Scheme 3 Loss of benzaldehyde during the oxidation of substrate **1d** may occur either immediately following loss of one electron ($Z = \bullet$) or after capture by methanol and loss of a second electron ($Z = \text{OMe}$)

the electrodes were wiped in a figure-of-eight motion with a paper towel, the cell was assembled and the various substrates were oxidised sequentially, typically in two runs of 20 min for each substrate. For cleaning between substrates, methanol was flowed through the cell via syringe. No drop in performance of the cell was noted during these daily runs, which required 2.0–2.5 h in total. At the end of a set of oxidations, the cell was disassembled, the electrodes were wiped over with methanol, and the cell assembled with a blank gasket (no channel) between the electrodes for storage. All the oxidations described in this article were performed without the need to re-polish the electrode surfaces and no passivation was observed by adhering to this regime.

Based on previous studies [47, 49], it was expected that the process could be extended to form spirocycles by siting the alcohol group further from the furan ring, as in compound **6** ($\rightarrow$ **7**, Fig. 2). Formation of the spirocycle **7** was indeed successful and an approximately equimolar mixture with dimethoxylated compound **8** was obtained from the electrolysis reaction; however, as a solution in CDCl_3 (NMR sample), this product mixture converted over 6 days into just the spirocycle **7**.

The current efficiency of the process is calculated to be ~60%, based on substrate conversion measured by GC analysis of the crude product solution. Loss of efficiency may result from methanol oxidation to form formaldehyde and/or formic acid; for comparison, Atobe's flow oxidation method demonstrated an efficiency of <10% due to solvent oxidation [48].

Compounds **2a–e** were converted directly into hydroxypyrones **3a–e** by acidic hydrolysis of the residue obtained from the crude electrolysis mixture following evaporation of the methanol and dissolution in THF (Table 3). In most cases the yield over the two steps paralleled that for the oxidation step. An attempt was made to perform the hydrolysis and rearrangement of **2** $\rightarrow$ **3** in flow mode. When an aqueous methanol solution of the product mixture from the electrolysis of compound **1a** was passed through a short column of Dowex 50 W-X8 or Amberlyst 15, a mixture of unidentified products

Fig. 2 Spirocyclisation substrate (**6**) and products (**7** and **8**)

Table 3 Synthesis of hydroxypyrones (**3**) by anodic oxidation then hydrolysis

Entry	R-	Isolated yield /%	dr ^a
1	1a,3a Bu-	62	70:30
2	1b,3b $\text{H}_2\text{C}=\text{CHCH}_2$ -	69	70:30
3	1c,3c $\text{HC}\equiv\text{CCH}_2$ -	31	70:30
4	1d,3d Ph-	17	75:25
5	1e,3e Bn-	32	65:35

^a Determined by integrating the *CH*R resonance in the ^1H NMR spectrum (values rounded to the nearest 5)

was obtained. These results indicate that strongly acidic sulfonic acid resins may not be ideal for this transformation, and alternatives should be investigated [50].

Conclusions

In conclusion, an electrochemical flow cell has been constructed and its utility demonstrated by the anodic oxidation of furfuryl alcohols **1**, with the resulting compounds affording hydroxypyrones **3** following acidic treatment. This method works well when the substrates lack features that promote fragmentation (cf. Scheme 3). Applications of the cell to oxidations more broadly are being trialled within the group.

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