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Electrochemical oxidation of furans into 2,5-dimethoxy-2,5-dihydrofurans

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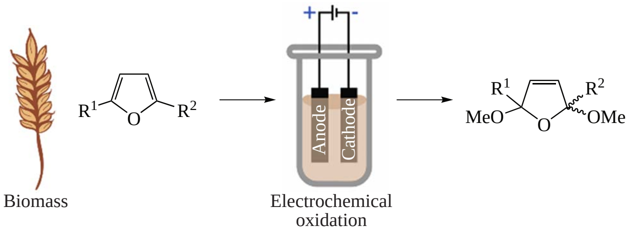
Substituted 2,5-dimethoxy-2,5-dihydrofurans (*cis*/*trans* isomer mixtures) were obtained *via* the electrochemical oxidation of the corresponding furans in an undivided cell in methanol in the presence of bromides as mediators. The method is suitable for furans containing electron-donating groups.



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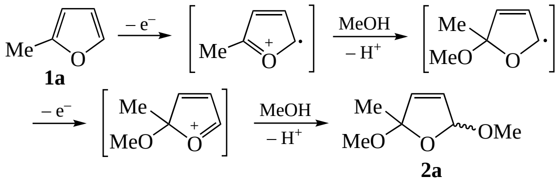
The problem of the rapid consumption of non-renewable fuel resources and the associated environmental pollution is particularly acute nowadays.[1–3] One of the options for its solution, the modern chemical science can provide, is to develop novel approaches to biomass conversion.[4–8] Although until now the main source of large-scale chemical production is plant oil and its products, biomass can also provide various carbohydrates, the conversion of which yields furan derivatives.[9–14] Unfortunately, its practical application in industry is currently limited by low catalytic activity and product selectivity in the processes studied.[15] In this paper, we propose preparation of highly demanded furan derivatives, namely, 2,5-dimethoxy-2,5-dihydrofurans suitable for the Diels–Alder synthesis,[16,17] the preparation of substituted pyridazines and pyrroles,[18–23] which, in turn, are widely used in neurobiology, as well as in the creation of various drugs and herbicides.[24]

2,5-Dihydrofurans (2,5-DHFs) represent a family of organic compounds widely spread in nature as structural units of various biologically active substances.[25–31] Moreover, lately, being the unsaturated compounds, 2,5-DHFs found use as a dienophile in Diels–Alder reaction, while their adducts with common dienes can be used as monomers for production of various polymer materials.[32,33] The common way for the synthesis of 2,5-DHFs is the oxidation of furans with toxic lead(IV) salts.[34] The safer Grubbs metathesis reaction,[35] although giving good yields, is still pretty costly. On the other hand, electrochemical oxidation of furan[36] looks to be a reasonable option. Being one of the cheapest and nature-friendly oxidizers, electric current is ideal for industry.[37] The first examples of electrochemical oxidation of furans to functionalized 2,5-DHFs implied the use of an undivided cell with nickel and carbon electrodes.[38] Methanol was used as a solvent and simultaneous methoxy-group donor, and bromine was used as an auxiliary oxidizer. Such composition of the reaction mixture leads to its significant corrosiveness, limiting its use in industry. Thus, it is clear that more studies should be carried out towards clean, cheap and effective route to 2,5-DHFs.

In this work we aimed to avoid using molecular bromine as well as to improve yields of desired 2,5-DHFs by optimizing the electrolysis conditions, *e.g*., electrode material, current density and the reaction temperature. Initially we reproduced the well-known procedure for 2,5-dimethoxy-substituted 2,5-DHFs.[39] So, 2-methylfuran **1a** was converted into 2,5-dimethoxy-2-methyl-2,5-dihydrofuran **2a** *via* electrochemical oxidation in methanol with the addition of tetrabutylammonium bromide (Bu_4NBr) being both supporting electrolyte and bromine source. The general mechanism of furan oxidation is exemplified in Scheme 1: furan **1a** as an example would be oxidized at the anode to radical cation, then subsequent nucleophilic reactions with methanol or methoxide occur resulting in 2,5-dimethoxy-derivatized 2,5-DHF **2a**.[40] The reaction was conducted in an undivided electrochemical cell at –20 °C with graphite/nickel electrodes and current density of *ca*. 80 mA cm^{-2}. The full conversion of 2-methylfuran **1a** was reached in 1 h upon passing of ~1.86 F mol^{-1} electricity, although the yield of **2a** was less than 10%. Whilst higher current density fastens the oxidation process, it also fastens side reactions. Thus, a compromise between selectivity and speed should be reached. We decreased the current density by half (40 mA cm^{-2}) and were able to isolate product **2a** with the yield of 33%. The further decrease in current density did not result in any improvements.



Scheme 1

Table 1 Optimization of electrooxidation of 2-methylfuran **1a** into product **2a**.[a]

Entry	Cathode	Anode	Electrolyte	GC yield (%)
1	Ni	Pt	Bu_4NBr	27
2	Ni	C (glassy carbon)	Bu_4NBr	2
3	Ni	C (graphite)	Bu_4NBr	33
4	Pt	C (glassy carbon)	Bu_4NBr	90
5	Pt	C (graphite)	Bu_4NBr	38
6	C (glassy carbon)	C (glassy carbon)	Bu_4NBr	20
7	C (glassy carbon)	RVC[b]	Bu_4NBr	21
8	Ni (foam)	Pt	Bu_4NBr	0
9	Steel	C (glassy carbon)	Bu_4NBr	23
10	Pt	Pt	Bu_4NBr	>90 (36,[c] 46[d])
11	Pt	Pt	$MeONa/NH_4Br$	>90 (50[e])

[a] Conditions: undivided cell, **1a** (0.5 M), Bu_4NBr (0.6 M) or $MeONa/NH_4Br$ (95 : 5), MeOH, –20 °C, j = 40 mA cm^{-2}, 1 h ($Q \approx 1.86$ F mol^{-1}). [b] Reticulated vitreous carbon. [c] At –5 °C. [d] At –45 °C. [e] Isolated yield.

The next step of optimization process was the investigation of the dependence of electrode material on the reaction outcome (Table 1). All reactions were held under the same conditions of current density (40 mA cm^{-2}), 2-methylfuran **1a** concentration (0.5 M), Bu_4NBr concentration (0.6 M) and temperature (–20 °C). In fact, material of both anode and cathode did truly influence the yield of **2a**. The best results were achieved by using Pt–Pt or Pt–C (glassy carbon) pairs (entries 4 and 10). Moreover, it was noticed, that the increase in the electrode surface area negatively influenced the product yield. This can be explained by limited mass transfer from material pores into solution, *i.e.*, with the accumulation of the reaction product in them and its further oxidation. Optimal temperature was estimated for Pt–Pt couple when both excessive heating and cooling decrease the yield of **2a** (entry 10).

The modifying of the supporting electrolyte implied the minimization of bromine concentration in electrochemical cell towards its catalytic quantities but sufficient to preserve the solution conductivity. The catalytic role of bromide anions was shown with the help of cyclic voltammetry (Figure 1). In fact, the addition of Bu_4NBr to a reaction mixture resulted in drastic current drop from 8 to 1 mA in the voltage range of the reaction (3–5 V). Moreover, the yield of **2a** synthesized in the absence of Bu_4NBr was 4 times lower.

The important features that the chosen electrolyte must meet are decent solubility in methanol, electrochemical stability of both anion and cation to prevent side reactions, low nucleophilicity of anion to limit competing in nucleophilic addition with methoxy group of the solvent. Thus, a mixture of sodium methoxide and NH_4Br (5 wt%) was proposed. Indeed, sodium methoxide is easily dissolved in methanol and maintains needed conductivity, while 5% of NH_4Br is enough for catalysis.

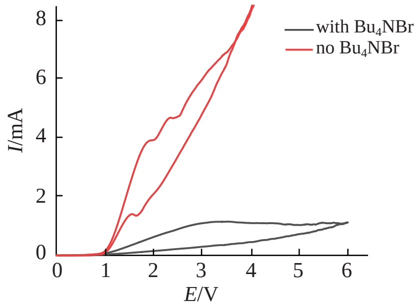
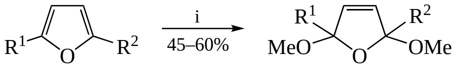


Figure 1 Cyclic voltammetry of reaction mixtures with (black line) and without (red line) Bu_4NBr in MeOH.



1a–d **2a–d**

R^1 = H, R^2 = CO_2Me or CHO: no product

a R^1 = H, R^2 = Me
b R^1 = R^2 = Me
c R^1 = H, R^2 = CH_2OH
d R^1 = R^2 = H

Scheme 2 *Reagents and conditions*: i, undivided cell, Pt–Pt electrodes, MeONa, NH_4Br, MeOH, –20 °C, j = 40 mA cm^{-2}, $Q \approx 1.86$ F mol^{-1}.

Moreover, nucleophilic addition of either methanol or methoxide anion should afford the same product, so no side reactions should occur. Under the given conditions of current density (40 mA cm^{-2}), temperature (–20 °C), supporting electrolyte composition ($MeONa/NH_4Br$ = 95 : 5, w/w), electrode material (Pt–Pt) we managed to increase the yield of **2a** up to 50% (isolated yield). We tried to apply the optimized procedure to a series of substituted furans **1a–d** (Scheme 2).

As it was established with NMR spectroscopy and GC-MS chromatography (see Online Supplementary Materials, Figures S1–S6), in all cases the mixtures of *cis*- and *trans*-isomers of 2,5-DHFs **2a–d** were obtained. The yields of 2,5-DHFs **2a–c** from furans **1a–c** containing electron-donating groups are somewhat higher than that of **2d** from unsubstituted furan **1d**. Furans with electron-withdrawing groups (methyl 2-furoate or furfural) did not give the desired products and underwent full polymerization (the formation of colored precipitates was observed).

In conclusion, the synthesis of valuable substituted 2,5-DHFs from available furan derivatives *via* the modified electrochemical process was developed. Lower current density and temperature are favorable for better yields of products. The proposed supporting electrolyte composition consisting of sodium methoxide and ammonium bromide (5 wt%) provided good results being both effective and cheap.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.033.

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