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The "one-pot" synthesis of 2,5-diformylfuran, a promising synthon for organic materials in the conversion of biomass*

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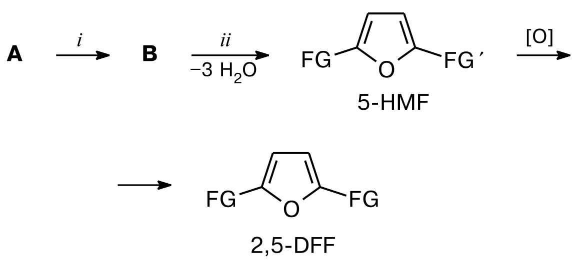
The organic ionic oxidant 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate, [Pip*(O)][BF_4], was found to be compatible with both classical organic solvents and the ionic liquids [BMIm][Cl]/[BMIm][BF_4] (BMIm is 1-butyl-3-methylimidazolium), which are essential in the conversion of cellulose biomass. A unique NMR monitoring procedure developed in our group was used to study the conversion of fructose to 2,5-diformylfuran in ionic liquids. This process can successfully be carried out in a "one-pot" fashion; [Pip*(O)][BF_4] efficiently oxidizes intermediate 5-hydroxymethylfurfural. The reaction is highly selective, giving 2,5-diformylfuran in 95% yield.

Key words: 2,5-diformylfuran, ionic liquids, carbohydrates, biomass, NMR monitoring, 5-hydroxymethylfurfural.

Efficient use of natural resources calls for new methods of turning renewable raw materials into important chemical compounds and materials. For this reason, a study of the conversion of biomass consisting of natural oligo- and polysaccharides (notably, cellulose) is of current interest.[1] The main drawbacks of the biomass-processing plants that are currently operating are their narrow ranges of target products and the formation of environmentally harmful wastes. At present, the strategy of integrated wasteless processing of biomass to individual chemical compounds with certain structures is being actively developed. 2,5-Disubstituted furan derivatives are promising intermediate products for chemical industry in the 21st century. They are used in fine organic synthesis and pharmaceutics as well as for the preparation of polymers, solvents, and liquid biofuel.[2—4] An innovative approach to the chemical recovery of hexose-containing raw materials involves catalytic hydrolysis and dehydration leading to an essential chemical intermediate, *viz.*, 5-hydroxymethylfurfural (5-HMF)[5—7] (Scheme 1).

Scheme 1



A is biomass (oligo- and polysaccharides); **B** is monosaccharides (fructose, glucose, *etc.*).
FG stands for functional group, FG = CHO; FG´ = CH_2OH.

i. Hydrolysis; *ii.* Dehydration.

Imidazolium halides are promising solvents for the synthesis of 5-HMF because cellulose biomass is readily soluble in these ionic liquids, and a number of side reactions (such as isomerization, dehydration, fragmentation, and polymerization) occurring in common organic solvents can be suppressed. The efficiency of ionic liquids for the dehydration of carbohydrates has been confirmed with many catalytic systems based on inorganic acids,[8,9] various metal salts,[9,10] and sulfonated ion-exchange resin (Amberlyst-15).[9,11]

5-Hydroxymethylfurfural is currently a formally recognized platform chemical for a number of industrial processes; its potential for fine organic synthesis is under study.[12,13] Since 5-HMF contains asymmetric functional groups (FG ≠ FG´, see Scheme 1), it needs to be modified before using in the production of some materials. The synthesis of symmetric functional derivatives (FG = FG´) *via* selective or complete oxidation of 5-HMF to carbonyl

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and carboxyl furan-containing products such as furan-2,5-dicarboxylic acid (2,5-FDCA) and 2,5-diformylfuran (2,5-DFF) is of particular interest. These compounds are employed as intermediates in organic synthesis[12] and as monomers in the preparation of some polymer materials.[14,15] The oxidation of 5-HMF to 2,5-FDCA occurs under mild conditions,[12,16] while 2,5-DFF (see Scheme 1) can be obtained using a limited number of oxidants that are not always highly selective. Aerobic homogeneous and heterogeneous methods for the oxidation of 5-HMF to 2,5-DFF with supported transition metals,[17—19] their salts and oxides,[20—23] organic oxidants,[16,24,25] and enzymes[26] have been reported. Some oxidants are effective under anaerobic conditions; however, the yield of the target product is not very high.[27]

The goal of this study was to develop an efficient method for the selective oxidation of 5-HMF to 2,5-DFF with ionic compounds related to the reaction medium (ionic liquids). The efficiency and selectivity of various oxidants in both organic solvents and ionic liquids were studied to develop a "one-pot" procedure for the synthesis of 2,5-DFF from fructose without isolation of intermediate products.

Results and Discussion

First, by varying the solvent and the reaction temperature, we analyzed how efficient are some known systems used for the selective oxidation of alcohols to carbonyl compounds in treatment of 5-HMF. Selected literature data (entries *1—7*) and our experimental results (entries *8—19*) are given in Table 1.

Transition metals and their oxides catalyze the aerobic selective oxidation of 5-HMF to 2,5-DFF under mild conditions, ensuring good yields of the latter (see Table 1, entries *1*, *2*). However, only few documented examples refer to the use of oxidative systems based on transition metals in ionic liquids.[17,27] Heterogeneous oxidants are inappropriate for the "one-pot" synthesis of 2,5-DFF from

Table 1. Oxidation of 5-HMF to 2,5-DFF in different systems[a]

Entry	Oxidant	Reaction conditions	T/°C	τ/h	Conversion of 5-HMF	Yield of 2,5-DFF
					%	
1	Ru/C (see Ref. 17)	O_2, DMF	20	6	—[b]	76
2	MnO_2 (see Ref. 27)	O_2, DMF	20	1	100	97
3	CAN (see Ref. 28)	[EMIm][TfO]	100	6	100	100
4	TEMPO (see Ref. 29)	CAN, $NaNO_2$, TEAB, O_2/H_2O	80	3	12.5	12.4
5	TEMPO (see Ref. 24)	$Ca(ClO)_2/CH_2Cl_2—H_2O$	15	1/6	—[b]	75
6	TEMPO (see Ref. 16)	CuCl, BiPy, O_2/Me_3CN	50	24	97	92
7	TEMPO (see Ref. 25)	O_2, TBN/AcOH	50	2	99[c]	99[c]
8	NBS	CH_2Cl_2	40	2	55	30[c]
9	[Pip*(O)][BF_4]	$CHCl_3$	30	2	50[d]	50[d]
10	[Pip*(O)][BF_4]	$CHCl_3$	50	2	70[d]	70[d]
11	[Pip*(O)][BF_4]	Silica gel (1 equiv.)/$CHCl_3$	30	2	55[d]	55[d]
12	[Pip*(O)][BF_4]	Silica gel[e]/$CHCl_3$	30	2	92[d]	95[d]
13	[Pip*(O)][BF_4]	CH_2Cl_2	30	2	60[d]	60[d]
14	[Pip*(O)][BF_4]	Silica gel/CH_2Cl_2	30	2	98[d]	98[d]
15	[Pip*(O)][BF_4]	[BMIm][Cl]	80	2	95[d]	95[d]
16	[Pip*(O)][BF_4]	Silica gel/[BMIm][Cl]	80	3	70[d]	70[d]
17	[Pip*(O)][BF_4]	Silica gel/ [BMIm][Cl] + $CHCl_3$ (1/0.5)	60	2	75[d]	75[d]
18	[Pip*(O)][BF_4]	Silica gel/ [BMIm][Cl] + $CHCl_3$ (1/1)	60	2	78[d]	78[d]
19	[Pip^*(O)][BF_4]	Silica gel/ [BMIm][Cl] + $CHCl_3$ (1/2)	60	2	90[d]	90[d]

[a] The data for entries *1—7* are taken from the corresponding reference sources. For entries *8—19*, see the Experimental section and the text. The abbreviations used are BMIm for 1-butyl-3-methylimidazolium, EMIm for 3-ethyl-1-methylimidazolium, CAN for cerium(IV) ammonium nitrate, TEMPO for (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, TEAB for tetraethylammonium bromide, TBN for *tert*-butyl nitrite, NBS for *N*-bromosuccinimide, and [Pip*(O)][BF_4] for 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate.

[b] No available data.

[c] According to GC-MS data.

[d] Determined by ^1H NMR spectroscopy in $CDCl_3$.

[e] Hereafter, the weight ratio of silica gel to oxidant is 2 : 1.

carbohydrates in ionic liquids because the reaction medium becomes much more viscous in the presence of such oxidants. Selective oxidation of 5-HMF with Ce^{IV} salts in ionic liquids of the imidazolium series gives 2,5-DFF in quantitative yield, though under drastic conditions (see Table 1, entry *3*).[28] Moreover, ionic liquids decompose under drastic conditions when high concentrations of the oxidant are used.[28] Glucose is oxidized in two steps with not easily accessible Co^{II} phthalocyanine complexes to 2,5-DFF in a solution of [EMIm][Cl]. The conversion of 5-HMF in the first step is >95%; however, further aerobic oxidation gives a mixture of 5-HMF and 2,5-DFF in 22 and 61% yields, respectively.[30]

The use of nitroxyl radicals of the TEMPO series for catalytic oxidation of 5-HMF to 2,5-DFF is well studied.[16,24,25,29] In many cases, the reaction proceeds selectively and provides good yields (see Table 1, entries *4*—*7*). With nitroxyl radicals, which are precursors of *N*-oxoammonium salts, the presence of a cooxidant is required (as a rule, in amounts of 1.1—2 equiv. with respect to the substrate). Alkali and alkaline-earth metal hypochlorites, chlorine, bromine, *N*-bromo- and *N*-chlorosuccinimides, oxygen, *etc.* can function as such cooxidants. However, strong oxidants can make the oxidation of alcohols less selective because of the formation of by-products.[31]

The literature data on the use of *N*-bromosuccinimide for the oxidation of 5-HMF are lacking. The results we obtained suggest that the reaction is not selective, being accompanied by bromination leading to 5-bromomethylfurfural in 25% yield (see Table 1, entry *8*).

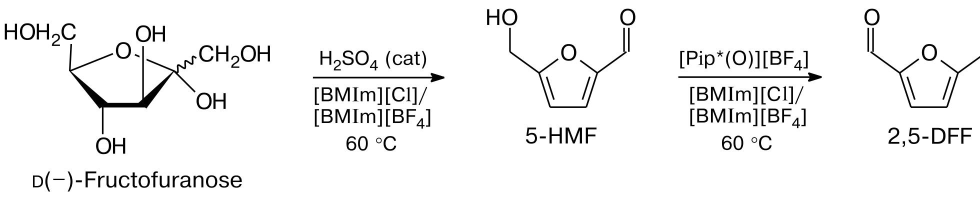
The use of TEMPO-related oxoammonium salts for the oxidation of primary alcohols to carbonyl compounds has been reported earlier.[32—36] Accordingly, we studied the possibility of employing the salt [Pip*(O)][BF_4] for selective oxidation of the primary alcohol group of 5-HMF (see Table 1, entries *9*—*19*). The best results were achieved under the following conditions: the weight ratio of silica gel : substrate : oxidant is 2 : 1 : 1, chlorinated solvents, gentle heating (see Table 1, entries *12*, *14*). Our findings agree with literature data.[37] We also found that the conversion of 5-HMF increases appreciably when at least two equivalents of silica gel have been used. When the reaction mixture was heated to 50 °C in the absence of silica gel, the conversion above 70% could not be reached (see Table 1, entries *10*, *11*).

In the ionic liquid [BMIm][Cl], the oxidation of 5-HMF with the salt [Pip*(O)][BF_4] proceeds with high yields; the complete conversion of 5-HMF to 2,5-DFF at 80 °C takes 2 h (see Table 1, entry *15*). A high selectivity of the reaction was confirmed by NMR spectroscopy that revealed no signals due to by-products. The presence of silica gel decreases the conversion of 5-HMF, probably because of the abruptly increased viscosity of the reaction medium (see Table 1, entry *16*). The use of a mixture of $CHCl_3$ and [BMIm][Cl] in the presence of silica gel also decreases the observed conversion (see Table 1, entries *17*—*19*).

Then we tried a "one-pot" synthesis of 2,5-DFF from D(−)-fructose with [Pip*(O)][BF_4] as an oxidant, involving no isolation of intermediate 5-HMF (Scheme 2). A mixture of the ionic liquids [BMIm][Cl]/[BMIm][BF_4] was used as a reaction medium because these liquids were very efficient in the acid-catalyzed dehydration of fructose to 5-HMF.[9] The high catalytic activity of H_2SO_4 allowed the dehydration of fructose to 5-HMF at 60 °C to be completed in 2 h. Then [Pip*(O)][BF_4] (2 equiv.) was added to the system, and the conversion of 5-HMF was 95%. Using our unique approach,[38] we conducted direct $^{13}C\{^1H\}$ NMR monitoring in the ionic liquid and analyzed the composition of the reaction mixture (Fig. 1). The high-resolution NMR spectra of the reaction system show individual signals of compounds. The conversion of 5-HMF was estimated by comparing the integrated individual signals for the carbonyl groups of 5-HMF and 2,5-DFF at δ 177.0 and 179.4, respectively. The conversion can also be determined from the signals for the C atoms of the furan ring at δ 150.7 and 152.6. It should be noted that the possibility of conducting the NMR monitoring is an important advantage of the system we proposed since immediate analysis of chemical systems in ionic liquids is often a difficult problem.[39]

Simultaneous addition of H_2SO_4 and the oxidant proved to be ineffective: 5-HMF was the only reaction product in this system. Apparently, fructose reacts with the oxidant faster than 5-HMF does. This is confirmed by the literature data: a silicone-embedded nitroxyl radical of the TEMPO series has been employed for the oxidation of α-methylglucoside to 1-*O*-methylglucuronate as well as for the transformation of polysaccharides (amylose, amylopectin, dextrins, chitin, and cellulose) into various carboxy derivatives.[40,41]

Scheme 2



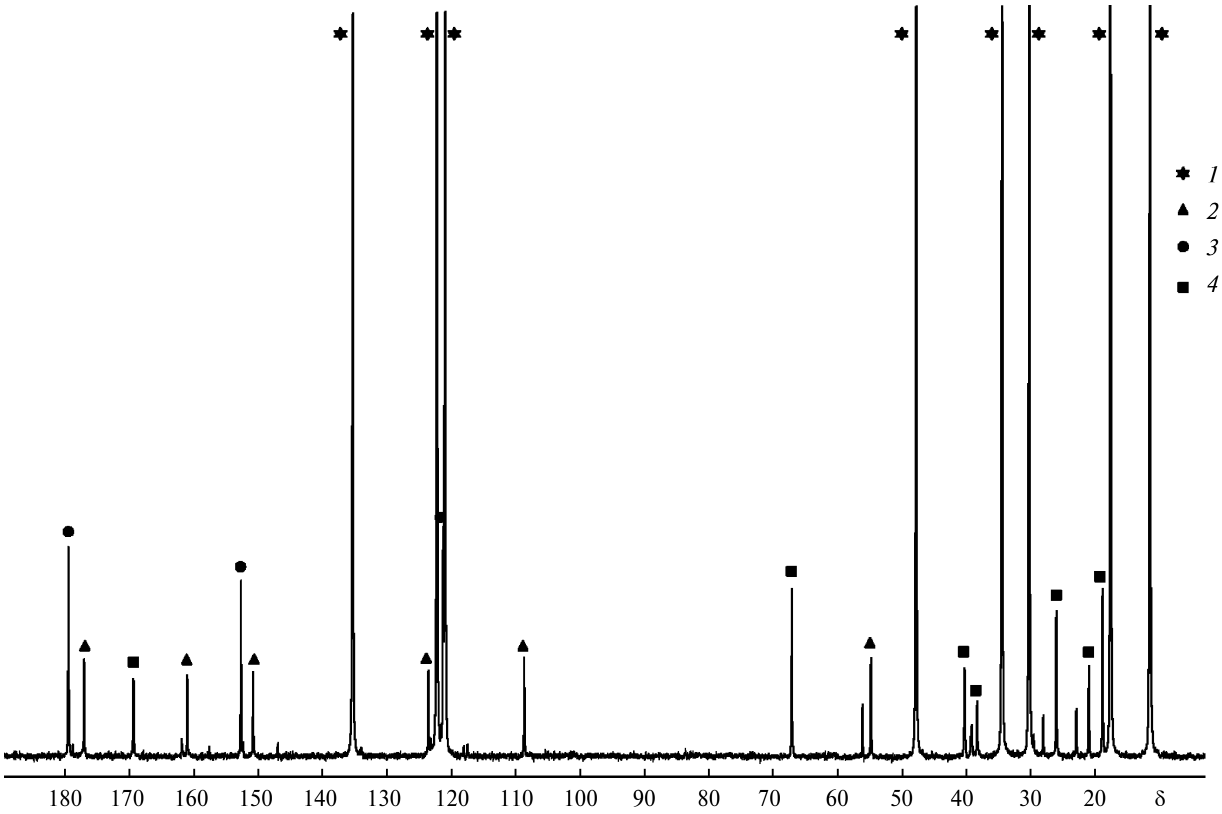


Fig. 1. Direct $^{13}C\{^1H\}$ NMR monitoring of the reaction mixture: [BMIm][Cl]/[BMIm][BF_4] (*1*), 5-HMF (*2*), 2,5-DFF (*3*), and [Pip*(O)][BF_4] (*4*). The recording conditions: 100 MHz, 60 °C, ~70% conversion of 5-HMF.

To sum up, we conducted the two-step "one-pot" synthesis of 2,5-DFF from fructose immediately in an ionic liquid. The use of an ionic oxidant compatible with the ionic liquid is crucial for the success of the reaction. We demonstrated that 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate ([Pip*(O)][BF_4]) is an efficient oxidant that provides the formation of 2,5-DFF as the only product. An important advantage of the novel system is its high selectivity associated with the fact that the hydroxymethyl group is affected only, whereas formyl groups remain intact. In addition, this system allows recording high-resolution NMR spectra immediately in ionic liquid and direct NMR monitoring of the reaction.

Two synthetic procedures are of preparative interest. The first one involves selective oxidation of 5-HMF to 2,5-DFF with a small excess of [Pip*(O)][BF_4] in chlorinated hydrocarbons in the presence of silica gel (~98% yield of the target product). The second one is the "one-pot" synthesis of 2,5-DFF by acid hydrolysis of fructose followed by the oxidation of intermediate 5-HMF with a twofold excess of [Pip*(O)][BF_4] in a mixture of the ionic liquids [BMIm][Cl]/[BMIm][BF_4] (~95% yield of 2,5-DFF).

Note that the direct preparation of functionalized heterocyclic compounds from carbohydrate components of biomass is extremely important in the design of organic and hybrid molecular systems.[42] The synthetic potential of the prepared platform chemicals calls for further detailed investigations.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (400.13 and 100.63 MHz, respectively). The solvent signals served as internal standards. All the spectra were processed with the Bruker Topspin 2.1 program. The oxidation of 5-HMF was monitored in an NMR tube as described earlier.[38] To check the conversion of 5-HMF, the 1D NMR spectra of the system were recorded following the addition of each portion of [Pip*(O)][BF_4] at 60 °C. High-resolution mass spectra (ESI) were recorded on a Bruker micrOTOF II instrument. Nitroxyl radicals and the salt [Pip*(O)][BF_4] were prepared according to a published procedure.[37]

Oxidation of 5-HMF to 2,5-DFF in organic solvents. 5-Hydroxymethylfurfural (0.252 g, 2 mmol) was dissolved in CH_2Cl_2 or $CHCl_3$ (5 mL) in a round-bottomed flask equipped with a magnetic stirring bar. Then silica gel (0.5 g) and [Pip*(O)][BF_4] (0.7 g, 2.5 mmol) were added with stirring. The resulting bright yellow suspension was stirred at 30 °C until it became colorless (2—3 h). The silica gel was filtered off and washed with the solvent (2×10 mL). The combined organic extracts were washed with water (2×3 mL), dried with anhydrous Na_2SO_4, and concentrated. The crude product (0.23 g, 92%) was obtained as light yellow crystals with m.p. 106—109 °C. For further purification, 2,5-DFF was recrystallized from CCl_4 or Et_2O—EtOAc (3 : 1) to give white fine crystals or a white powder. The yield of 2,5-DFF was 82%, m.p. 109—111 °C (*cf.* Ref. 43: m.p. 110 °C). ^{1}H NMR (CDCl$_3$), δ: 9.83 (s, 2 H, CHO); 7.33 (s, 2 H, =CH). ^{13}C NMR (CDCl$_3$), δ: 179.21 (CHO), 154.15 (=C), 119.42 (=CH). MS (ESI), *m/z*: 147.0045 $[M + Na]^+$. $C_6H_4O_3$. Calculated: 147.0053, Δ = 5.4 ppm.

"One-pot" synthesis of 2,5-DFF from fructose in ionic liquids. D(−)-Fructose (0.1 g, 0.56 mmol; Acros), [BMIm][Cl] (0.4 g, 2.29 mmol), and [BMIm][BF$_4$] (0.3 g, 1.55 mmol) were placed in an NMR tube. The resulting mixture was stirred with an RW11 overhead stirrer (IKA) at 60 °C to complete homogenization. Then H_2SO_4 (4 μL, 0.075 mmol) was added as a catalyst, and the reaction mixture was stirred at 60 °C for 2 h. The salt [Pip*(O)][BF$_4$] was added with stirring at 60 °C in four portions (84 mg, 0.28 mmol each) every 1.5 h.

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