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FULL PAPER

One-Pot Transformation of Carbohydrates into Valuable Furan Derivatives

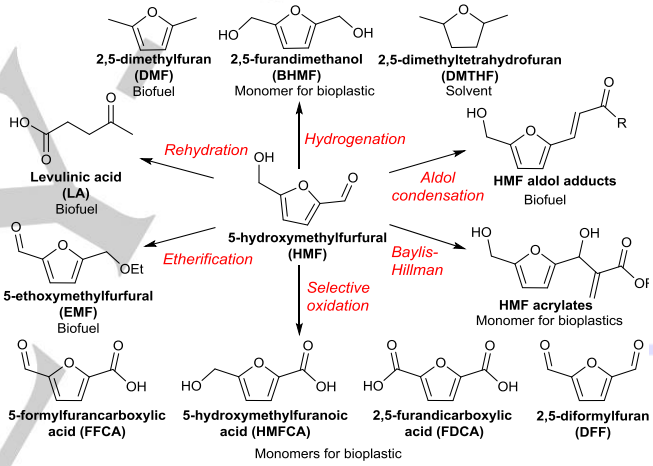
Pauli Wrigstedt,[a] Juha Keskiväli,[a] J. E. Perea-Buceta[a] and Timo Repo*[a]

5-Hydroxymethylfurfural (HMF) constitutes one of the pivotal chemicals to utilize biomass as chemical feedstock. For this approach the vast majority of methods require accessing to pure HMF from biomass before its utilization, thus incorporating one or more purification steps that obstruct industrial implementation. This work describes an operationally simple and versatile method encompassing in a one-pot process both the dehydration of several carbohydrate substrates into HMF and subsequently its direct conversion into various high value-added furan derivatives. To that end, we selected the aldol condensation of HMF with methyl isobutyl ketone (MIBK) as a model reaction. With the optimized conditions of solvent and base catalyst in hand, the one-pot dehydration of fructose and condensation sequence with various ketones afforded the products in good overall yields over two steps. The scope of the process was successfully expanded to more complex carbohydrates, such as glucose, lactose, sucrose, cellobiose and inulin. Moreover, by fine-tuning the reaction conditions, the one-pot methodology using inulin as substrate was found to be highly efficient when applied to various other important reaction types, such as oxidation, reduction, Cannizzaro and Baylis-Hillman reactions, rendering the corresponding furan derivatives in high overall yields.

Introduction

Amidst the growing global environmental concerns, there is a tremendous interest to gradually shift from traditional fossil fuel-derived feedstocks towards more sustainable and renewable biomass. In this sense, 5-hydroxymethylfurfural (HMF) has emerged as one of the main platform chemicals to bridge the connection between fossil- and biofuel resources. Therefore, numerous homo- and heterogeneous catalytic systems have been extensively investigated for its production through dehydration of carbohydrates.[1]

Additionally, a number of catalytic routes have been recently developed to transform HMF into solvents, biofuels, building blocks for bioplastics and commodity chemicals.[1b, 1d, 2] The most notable of these (Scheme 1) encompass the reduction of HMF to 2,5-bis(hydroxylmethyl)furan (BHMF), its oxidation to 2,5-furandicarboxylic acid (FDCA) or 2,5-diformylfuran (DFF), its hydrogenation to dimethylfuran (DMF) or dimethyltetrahydrofuran (DMTHF), its rehydration to levulinic acid and its aldol condensation to furnish biofuel precursors.[3] Furthermore, well-known processes such as the Cannizzaro or the Baylis-Hillman reaction have been also studied.[4] However, most of these transformations have been performed using HMF in pure form rather than producing it directly from hexoses to subsequently utilize it in a single one-pot reaction.[5] To date, the direct one-pot transformation of carbohydrates into chemicals through HMF mostly involve acid-catalyzed etherification (i.e. to produce ethoxymethylfurfural, EMF), oxidation to FDCA and reduction to DMF, DMTHF or BHMF.[5] However, these processes typically utilize fructose as substrate and examples of reactions employing more complex carbohydrates are rare.[1b, 1d, 5]



Scheme 1. HMF as a platform chemical for the production of valuable furanic compounds.

The relatively high cost of HMF, and problems associated to its stability and purification,[1b] constitute major challenges for its implementation in large-scale biorefinery applications. Additionally, the dehydration of carbohydrates into HMF under acidic conditions is often accompanied by a series of side reactions, such as HMF hydrolysis and self-condensation reactions,[6] which decrease the efficiency of the processes. An interesting alternative to overcome these problems is to convert HMF to 5-chloromethylfurfural (CMF) directly from carbohydrates.[7] Due to the sensitivity of CMF to moisture, several methods have been developed to convert CMF into stable products, such as the conversion to 5-acetoxyfurfural,[1b, 8] which, in turn, has been shown to be an amenable platform chemical for various processes.[9] However, this strategy requires an extra synthetic step to access the desired end products, and, from a processing viewpoint, the development of a highly efficient catalytic systems enabling the one-pot conversion of sugars directly into the end products would be highly desirable.

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Furthermore, the synthesis of CMF involves drastic conditions such as the use of large stoichiometric amounts of concentrated HCl that do not comply with the desirable requirements of sustainability at large industrial scale.[7b]

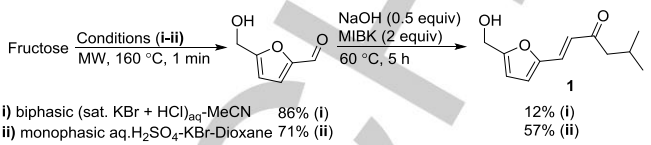
In the context of our current research to valorize biomass as chemical feedstock,[3c, 10] we describe herein the development of one-pot transformation of carbohydrates through HMF to various furan derivatives. Our strategy involved the optimization of the reaction conditions for fructose using the aldol condensation with methyl isobutyl ketone (MIBK) as model system, after which the methodology was successfully implemented to more complex carbohydrate substrates as well as to various reaction types, such as reduction, oxidation, Cannizzaro and Baylis-Hillman reactions.

Results and discussion

Initial experiments

To date, a plethora of homo- and heterogeneous catalytic methods for the generation of HMF from fructose have been reported.[1] We began our investigation to develop a sequential one-pot fructose dehydration and aldol condensation methodology by selecting a practical and high-yielding microwave-enhanced biphasic $(KBr+HCl)_{aq}$-MeCN system (Scheme 2, **i**).[10b] Alkalimetal halide salts, such as NaCl, KBr or KCl, serve a dual role in this type of biphasic systems. First, their use as saturated solutions ensures the continuous extraction of HMF to the organic phase during the reaction.[11] This limits the formation of water-promoted byproducts, such as levulinic acid and humins,[6a] and results in higher HMF yields and selectivities.[12] Moreover, alkalimetal halides catalyze the dehydration of fructose in both aqueous and organic media.[10a, 13] This positive catalytic effect on the HMF yields has been attributed to the anions rather than cations in solution and is reported to decrease in the order Br > I > Cl in organic solvents,[13b] and Br > Cl > I in aqueous biphasic systems.[10a]

For the second step, we applied typical aldol condensation conditions (Scheme 2). First the reaction media was basified with NaOH, after which the condensation partner MIBK was added and the resulting biphasic mixture heated at 60 ℃ for 5 hours. Under these conditions, the first dehydration step gave HMF in very good 86% yield, but low HMF conversion (25%) and aldol adduct **1** yield (12%) were obtained in the second step. The low conversion was ascribed to the biphasic system, in which the reagents were heterogeneously distributed in immiscible phases, consequently preventing the deprotonation of MIBK by NaOH at an appropriate rate. This assumption was supported by the fact that water miscible acetone reacts readily with HMF under similar conditions.[3b] We addressed this by switching from a biphasic to a monophasic reaction setup applying aq. H_2SO_4-KBr-organic solvent system (Scheme 2, **ii**).[14] 1,4-dioxane was chosen as model co-solvent due to its water miscibility (small amount of water is essential for dissolving fructose) and compatibility towards slightly basic and acidic conditions. The combined dehydration and condensation reaction was performed under the same conditions as with the biphasic system (Scheme 2), with the exception of using 1 equiv of KBr instead of saturated solution to avoid phase separation. Even though the dehydration step gave HMF in lower yields than the biphasic system (71% vs 86%), the aldol adduct **1** was now obtained in promising 57% yield.



Scheme 2. Initial conditions for the one-pot two-step conversion of fructose to HMF-MIBK aldol adduct **1**.

Optimization of the fructose dehydration step

At this stage, we adopted a strategy to optimize separately the fructose dehydration step, using an aqueous H_2SO_4-KBr-dioxane monophasic system. First, we investigated in more detail the effect of KBr and H_2SO_4 on the fructose dehydration step. The screening of the added amount of KBr (10, 20, 30, 50 and 100 mol-%) and H_2SO_4 (0.017M = 4.5 mol%, 0.035 M = 9 mol% and 0.07 M = 18 mol%) identified 30 mol-% of KBr and 0.017 M H_2SO_4 as the optimal combination, affording HMF in 84% yield with quantitative conversion of fructose in 1 min at 150 ℃ under MW heating. The use of higher than 50 mol-% of KBr led to a small decrease in HMF yield, indicating that KBr also enhances the HMF decomposition. Nevertheless, the optimization studies revealed the remarkable catalytic effect of KBr on the reaction in the presence of H_2SO_4. The fructose conversion and HMF yields, obtained with or without the presence of KBr, together with the initial fructose consumption and HMF formation rates are illustrated in Figure 1. As expected, without the presence of KBr, the initial rates for both fructose consumption and HMF yields increased by increasing the acid concentration gradually from 0.017 M to 0.07 M. In comparison to 0.017 M H_2SO_4 only case, the addition of 30 mol-% of KBr accelerated the initial fructose consumption rate by twofold. The drastic catalytic influence of KBr on the reaction was manifested in the HMF formation rate, which soared to 16-fold compared to the reaction without KBr (0.017 M H_2SO_4 vs 0.017 M H_2SO_4 + KBr). Even a threefold increase in the initial HMF formation rate was observed in comparison to the reaction with the highest acid concentration of 0.07 M H_2SO_4. As the initial reaction rates of fructose consumption and HMF formation with KBr+0.017 M H_2SO_4 are closer to each other (0.30 vs 0.223 M/s, 1.3-fold) compared to 0.017 M H_2SO_4 only (0.14 vs. 0.014 M/s, tenfold), it is obvious that KBr greatly enhance the fructose dehydration by accelerating the conversion of intermediate products to HMF. Despite our attempts, we were not able to detect any intermediates by HPLC analysis, indicating that they are unstable (short-lived) under the applied conditions.

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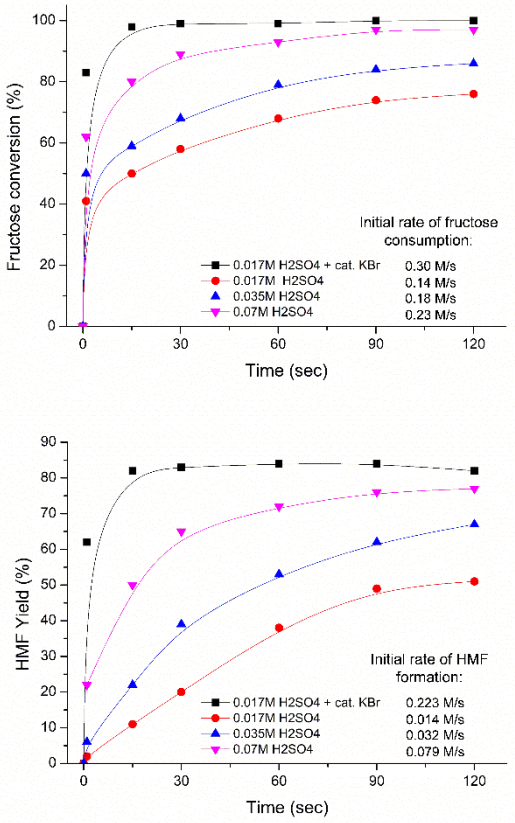
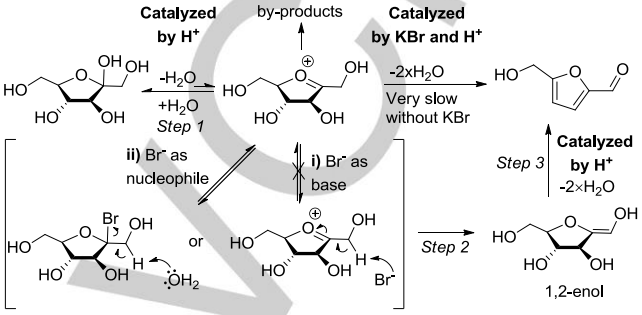


Figure 1. Impact of KBr in the fructose dehydration step in the presence of H_2SO_4. Fructose conversion (above) and HMF yield (below). *Conditions:* 150 mg fructose, 30 mol-% KBr in H_2SO_4 (aq)-dioxane (0.3-2.1 mL), MW 150 ˚C, 1-120 s.

From a mechanistic point of view, the catalytic effect of halides is not fully established, particularly in aqueous solutions. According to our results above, the catalytic amplification promoted by bromides (or any other halide) occurs after the initial Brønsted acid (H_2SO_4) catalysed dehydration at C-2 in fructose,[1b, 15] forming a highly reactive fructofuranosyl oxocarbenium ion (step 1, Scheme 3). This ion can spontaneously deprotonate at C-1 to form an 1,2-enol (step 2),[15] which then doubly dehydrates, driven by aromatization, to form HMF (step 3).[16] In organic solvents, it was proposed that halides can catalyze the reaction following two possible mechanisms; they act either as a base or a nucleophile, thus facilitating the formation of the 1,2-enol (routes **i** and **ii**, Scheme 3).[13c] In our aqueous system, however, the role of bromide as base (route **i**) can be ruled out by the fact that water is significantly more basic (pKa of H_3O^+ = -1.7) than bromide (pKa of HBr = -8.8).[17] Additionally, the fructofuranosyl oxocarbenium ion is known to be attacked readily by alcohols[18] and fluorides.[19] Consequently, it is evident that in aqueous solutions the dramatic catalytic influence of halides originates from their nucleophilic attack to the C-2 of the fructofuranosyl oxocarbenium ion (route **ii**, Scheme 3). The formed 2-halo-fructofuranose then experiences elimination with water as base to form the 1,2-enol, which then rapidly undergoes two *β*-elimination to form HMF. The plausible explanation for the superior performance of bromides over chlorides and iodides is that bromide is more suitable leaving group (appropriate stability) to promote the *β*-elimination over the oxocarbenium formation of the 2-halo-fructofuranose, which leads to the crucial 1,2-enol intermediate.



Scheme 3. The catalytic routes **i** and **ii** proposed to occur in organic solvents after the initial dehydration of C-2 (reference 13c). In aqueous solutions route **i** can be ruled out as H_2O (excess) is significantly more basic than Br^- (30 mol-%).

Once the optimized amounts of KBr and H_2SO_4 were established (0.017 M H_2SO_4 ~5 mol-%, 30 mol-% KBr), we screened a series of green (γ-valerolactone, EtOH, *i*-PrOH)[20] and water miscible (THF, EtOH, *i*-PrOH, dioxane, MeCN and DMF) solvents for the fructose dehydration step (Figure 2). High-performing DMSO[21] and ionic liquid solvents[1a] were excluded from this study due to the incompatibility of DMSO towards the applied conditions[22] and relatively expensive and operationally tricky ionic liquids. In addition to 1,4-dioxane, high HMF yields were obtained in MeCN (82%) and *i*-PrOH (80%), albeit longer reaction time was required with the latter as a result of slower fructose conversion rates. The reactions in those solvents were highly selective, resulting in only low levels of by-products, such as levulinic acid, formic acid and insoluble polymeric products (visible humins), often formed concurrently with HMF.[1b] Conversely, poor HMF selectivity was observed using EtOH, presumably due to the competitive formation of 5-ethoxymethylfurfural under acidic conditions.[23] Surprisingly, other polar aprotic solvents such as DMF, γ-valerolactone (GVL) or THF were ineffective, giving HMF in very low yields and selectivities. These results imply that those solvents suppress the H_2SO_4-catalyzed fructose dehydration. This may explain the exceptionally high yields of glucose obtained in cellobiose and biomass hydrolysis using the H_2SO_4-GVL system in place of H_2SO_4-dioxane.[24] It is worth noting that, in comparison to MW irradiation, the conversion rates of fructose in 1,4-dioxane, MeCN or *i*-PrOH under conventional heating were considerably slower and resulted in substantially lower HMF yields of 81%, 72% and 52%, respectively (see Table S2 in Supporting Information).

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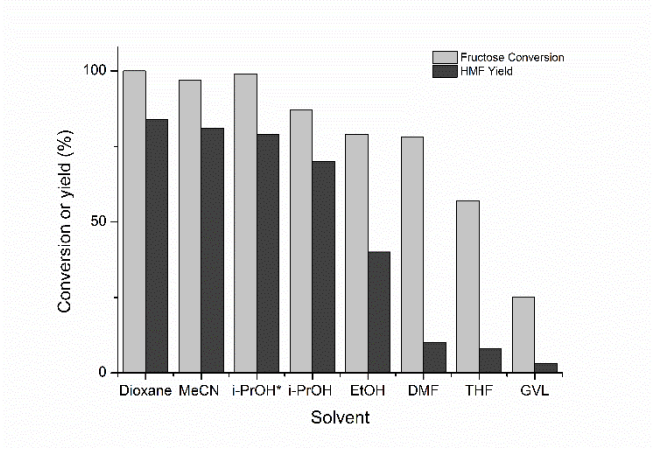

Figure 2. The effect of solvents in the dehydration of fructose to HMF. *Conditions:* 150 mg fructose, 30 mol% KBr in 0.125 M H_2SO_4-solvent (0.3-2.1 mL), MW 150℃, 120 s. *Reaction time 180 s.

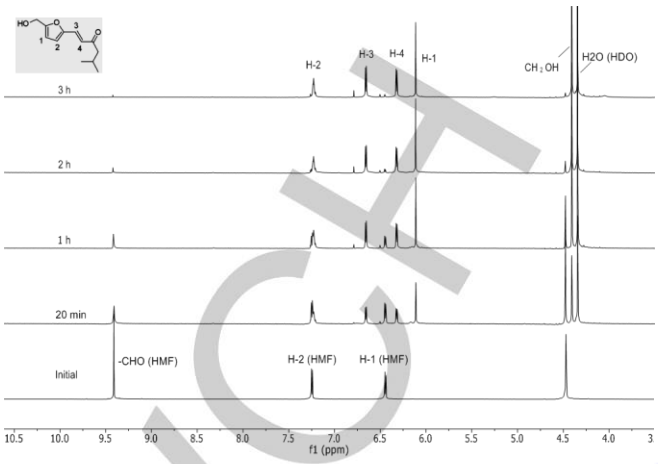

Figure 3. In situ ^{1}H NMR spectra for the aldol condensation of HMF with MIBK in CD_3CN-D_2O-NaOD. *Conditions:* 15 mg HMF, 21 µL MIBK (2 equiv), 5 µL (30% NaOD), 0.6 mL CD_3CN, 0.07 mL D_2O, 1 mg K_2SO4 and 2 mg KBr, 20 min to 3 h, 55℃. Initial spectrum recorded before the addition of NaOD.

One-pot dehydration and aldol condensation sequence using fructose

To gain detailed insight into the aldol condensation of HMF with MIBK, we followed the progress of the reaction by ^{1}H NMR spectroscopy, utilizing commercial HMF with NaOD as a base and a mixture of CD_3CN-D_2O as solvent. To simulate the reaction conditions used in the first step, equivalent amounts of K_2SO_4 (from H_2SO_4) and KBr were added to the reaction. As Figure 3 illustrates, the reaction proceeded rather cleanly and virtually full conversion was achieved after 3 h. Further experimentation showed that maintaining the reaction temperature in the range of 40 to 65 ℃ had no notable effect on products yields, albeit the reaction was accelerated at higher temperature, which is a common feature in aldol condensation reactions. However, lower product yields were recorded at temperatures higher than 65℃. The ^{1}H and ^{13}C NMR spectra, measured after simple extraction of the reaction mixture with EtOAc, showed no presence of organic impurities in the crude products (See crude ^{1}H and ^{13}C NMR spectra of **1** in Supporting Information). It is well-known that Cannizzaro reactions can take place under the applied conditions,[25] resulting in HMF disproportionation to give equimolar amounts of 5-(hydroxymethyl)furan-2-carboxylic acid (HMFCA) and 2,5-bis(hydroxylmethyl)furan (BHMF), the former of which is soluble in basic water and thus, not detectable on the crude ^{1}H and ^{13}C NMR spectra (extraction with EtOAc). However, the HPLC analysis of the control reaction conducted in the absence of MIBK (commercial HMF and 50 mol% NaOH in H_2O-MeCN, 3 h at 55 ˚C), found only traces of HMFCA present in the aqueous phase after extraction, thus confirming that the Cannizzaro reaction under such mildly basic conditions was negligible.

With the range of suitable solvents (1,4-dioxane, MeCN and *i*-PrOH) and general conditions of the monophasic fructose dehydration and aldol condensation steps in hand, we next explored the effect of various bases, including NaOH, KOH, K_2CO_3, Cs_2CO_3, piperidine and *tert*-BuOK, and various Lewis acids, such as $MgAlO_4$, $Fe(NO_3)_3$, $Eu(OTf)_3$ or $InCl_3$, [3a, 26] on the aldol condensation step using MIBK as a model condensation partner. The reactions were conducted in one-pot fashion, in which the reaction time of the first step depended on the solvent (Table 1). In accordance with previous report,[3c] a strong base was required for the deprotonation of MIBK, regardless of the applied solvent. Thus, only NaOH, KOH and *t*-BuOK were applicable to the reaction, each of them producing **1** in similar yields ranging from 68-70% (in 1,4-dioxane). No reaction occurred using weaker bases or Lewis acids, even at higher temperature (110℃) or with extended reaction time (15 h). Curiously, the used solvent did not affect the outcome of the aldol condensation, since the differences observed in **1** yields were related to the obtained yields of HMF with different solvents in the first reaction step (Figure 2). Additionally, using higher amount of base or MIBK did not further increase the **1** yield, which, in turn, was only improved by 3% using commercial HMF (entry 1 vs entry 4, Table 1). Pleasingly, other ketones such as 2-butanone and acetone were successfully subjected to the reaction sequence giving the corresponding aldol adducts in 59% (2:1 mixture of isomers, *i.e.,*1- or 3-aldol addition adducts) and 51% yield, respectively.

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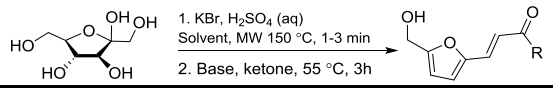
Table 1. Influence of different bases and solvents on the aldol condensation step.[a]



Entry	Ketone [b]	Base [c]	Organic solvent [d]	Yield [e] (%)
1	MIBK	NaOH	1,4-dioxane	70[f]
2	MIBK	NaOH	MeCN	68
3	MIBK	NaOH	*i*-PrOH	67
4	MIBK	NaOH	1,4-dioxane	73[g]
5	MIBK	KOH	1,4-dioxane	68
9	MIBK	*t*-BuOK	1,4-dioxane	70
10	2-butanone	NaOH	1,4-dioxane	61
11	2-butanone	NaOH	*i*-PrOH	59
11	Acetone	NaOH	1,4-dioxane	51
12	Acetophenone	NaOH	1,4-dioxane	-

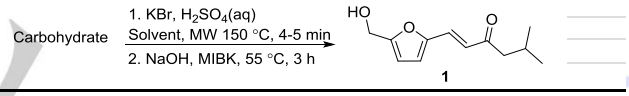
[a] *Conditions:* 0.83 mmol fructose, 10 mol% $CrCl_3 \times 6H_2O$ if used, 30 mol% KBr in 0.125 M H_2SO_4-dioxane (0.3 mL-2.1 mL); [b] 2.4 mmol of ketone; [c] 50 mol% of base; [d] Reaction times in the first step; 60 s with 1,4-dioxane, 120 s with MeCN and 180 sec with *i*-PrOH; [e] Overall yield over two steps determined by GC-FID; [f] isolated yield of 58% after column chromatography; [g] Commercial HMF.

Dehydration and aldol condensation sequence using other carbohydrates

Most of the direct one-pot carbohydrate transformations to chemicals through HMF employ fructose as substrate and reports dealing with the compatibility of these processes with more complex carbohydrates are rare.[5] Therefore, we aimed to extend the one-pot dehydration-condensation process to glucose, lactose, cellobiose, sucrose and inulin. It is well-known that the synthesis of HMF from glucose or other glucose-containing carbohydrates (sucrose, lactose and cellobiose) requires a catalyst that is able to isomerize glucose to fructose (aldose-to-ketose isomerization) during the reaction.[27] Several homogeneous Lewis acid catalysts, such as $SnCl_4 \times 5H_2O$, $AlCl_3 \times 6H_2O$ and $CrCl_3 \times 6H_2O$,[1a, 1b] have been identified to efficiently catalyze this transformation, out of which $CrCl_3 \times 6H_2O$ has been shown to perform best under aqueous conditions.[10] Therefore, we employed $CrCl_3 \times 6H_2O$ on the trials where glucose was present (the reaction was optimized using glucose as a model compound; see Table S4 in Supporting Information). It is worth noting that, unlike Cr^{VI}, which is highly toxic, Cr^{III} is very stable and essential for the normal metabolism of carbohydrates, lipids, and fats in humans.[28] The reactions were conducted using the KBr-H_2SO_4-*i*-PrOH system and MIBK as ketone partner. However, we slightly modified the reaction conditions by using extended reaction times for the first dehydration step and a larger amount of base for the second step when $CrCl_3 \times 6H_2O$ was utilized ($CrCl_3 \times 6H_2O$ forms acidic solutions in water, pH ~ 2)[29].

From the results shown on Figure 4, all of the carbohydrates tested were compatible with the reaction conditions and gave the HMF-MIBK condensation product **1**. The reaction performed notably well with fructan inulin in all the applicable solvents and afforded **1** in close to equal yield to that obtained from fructose. Additionally, the high HMF yield obtained from inulin (75-78% depending on solvent) is comparable to those obtained in ionic liquids[30] and aqueous biphasic systems.[31] However, a low **1** yield of 37% was recorded using sucrose as substrate in the absence of an isomerization catalyst. The addition of $CrCl_3 \times 6H_2O$ catalyst improved the **1** yield up to 52% due to the enhanced glucose-to-fructose isomerization. The system was less effective in terms of **1** yield when glucose or glucose-containing lactose or cellobiose were utilized as substrates, giving **1** in 41%, 30% and 41% yields respectively. Clearly, this was linked to the first reaction step, which gave HMF in lower yields than the reactions starting from fructose. However, the presence of $CrCl_3 \times 6H_2O$ during the aldol condensation step had no significant effect on the reaction outcome and only a slight loss of approximately 5% in **1** selectivity was observed (comparison of HMF and **1** yields with or without catalyst), thus underscoring the robustness of the aldol condensation step. Appreciably, the reaction could be scaled up to gram-scale using inulin as substrate (from 0.83 mmol to 6.7 mmol, eightfold) with only a small decrease in the **1** yield from 65% to 60%, albeit a slightly longer reaction time for both steps (5 min, 4 h) was required.

Table 2. One-pot transformation of various carbohydrates to **1**.[a]



Entry	Carbohydrate	Solvent	HMF Yield (%)[b]	**1** Yield (%)[c]
1	Inulin	1,4-dioxane	78	65
2	Inulin	MeCN	75	62
3	Inulin	*i*-PrOH	75	63
4	Glucose + Cr(III)	*i*-PrOH	55	41
5	Sucrose	*i*-PrOH	45	37
6	Sucrose + Cr(III)	*i*-PrOH	67	52
7	Cellobiose + Cr(III)	*i*-PrOH	56	41
8	Lactose + Cr(III)	*i*-PrOH	39	30
9[d]	Inulin	1,4-dioxane	74	60

[a] *Conditions:* 0.83 mmol carbohydrate, 10 mol% $CrCl_3 \times 6H_2O$ if used, 30 mol-% KBr in 0.125 M H_2SO_4-dioxane (0.3 mL-2.1 mL), reaction times in the first step; 4 min with 1,4-dioxane and 5 min with MeCN and *i*-PrOH; [b] Determined by HPLC; [c] Determined by GC-FID and correspond to the overall yields over two steps [d] 1.2 g inulin, 30 mol-% KBr in 0.25 M H_2SO_4-dioxane (1.2 mL-8.0 mL), MW 150 ℃, 5 min.

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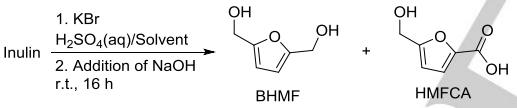
One-pot transformation of inulin into furan-based chemicals

The presence of alcohol and aldehyde functional groups in HMF makes it a versatile platform chemical for the syntheses of a variety of bio-based value-added products, as shown in Scheme 1. As these transformations have been mostly performed using pure HMF rather than produced directly from hexoses in a single one-pot reaction,[5] we next asked whether the one-pot dehydration and functionalization sequence described herein might be applicable to other transformations than aldol condensation, using inulin as substrate. Accordingly, the compatibility of various reaction types for the direct one-pot conversion of inulin to furan derivatives were investigated, including the selective oxidation of HMF using Pt/C[32] and Ru/C,[33] the reduction of HMF to BHMF by $NaBH_4$,[9] the Baylis-Hillman coupling of HMF with methyl acrylate[4a] and the Cannizzaro reaction.[25] An overview of these reactions is depicted in Scheme 5.

One-pot inulin dehydration and Cannizzaro reaction sequence.

The Cannizzaro reaction is a base-induced redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols. When applied to HMF, the Cannizzaro reaction yields an equimolar mixture of BHMF and HMFCA, both of which are equally important biobased chemicals. BHMF find applications in the manufacture of polyurethane foams,[34] crown ethers[35] and polyesters,[1b] while HMFCA serves as a component for novel bioplastics, such as polyesters,[36] and as precursor to prepare 2,5-furandicarboxylic acid.

Table 3. One-pot inulin dehydration and subsequent Cannizzaro reaction.[a]



Solvent	NaOH	Y_{BHMF} (%)[b]	Y_{HMFCA} (%) [c]	Y_{HMF} (%)
i-PrOH	4 M (aq)	21	20	8
i-PrOH	Powder	30	31	1
MeCN	Powder	30	30	1
1,4-dioxane	Powder	29	30	3

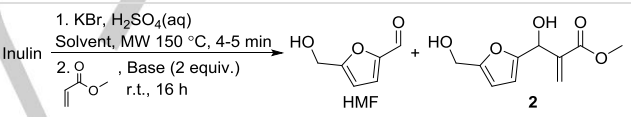
[a] *Conditions:* 0.83 mmol inulin, 30 mol-% KBr in 0.125 M H_2SO_4-dioxane (0.3 mL-2.1 mL), MW 150 ℃, reaction times in the first step; 3 min with 1,4-dioxane and 5 min with MeCN and *i*-PrOH; 4 equiv of NaOH; [b] BHMF purified according to Ref. 25 [c] Yields determined by HPLC and correspond to the overall yields over two steps.

The treatment of HMF with NaOH (4 equiv) in 1,4-dioxane, using our one-pot protocol starting from inulin (Table 3), afforded both BHMF and HMFCA in good overall yields of 30% and 31%, respectively. The combined product yields corresponds to 81% yield from HMF (Inulin to HMF in 75% yield, see Table 2), which are comparable to those obtained from pure HMF.[25, 37] Likewise with aldol condensation, the reaction proceeded well regardless of the solvent used. However, better yields were obtained when NaOH was added as a powder instead of as a 4 M solution, a fact suggesting that the reaction decelerates significantly by increasing the water content (dilution of NaOH concentration). In addition to the Cannizzaro reaction, the one-pot inulin dehydration and reduction sequence using $NaBH_4$ in *i*-PrOH as co-solvent gave BHMF in a good overall yield of 67% (Scheme 5).

One-pot inulin dehydration and Baylis-Hillman reaction sequence.

The Baylis–Hillman reaction is one of the most important C-C bond-forming processes in modern organic synthesis.[38] This process involves reacting an aldehyde with an activated alkene in the presence of a tertiary amine base to give a densely functionalized product. The reaction exhibits a highly favorable atom economical character as every atom present in the substrates is found in the products. Furthermore, the Baylis–Hillman reaction is compatible with HMF in aqueous media,[4] which increases its attractiveness from the point of view of sustainable chemistry.[39] As an example, the Baylis-Hillman adducts of HMF could be utilized for the manufacture of bio-based acrylate thermoplastics.[40]

Table 4. One-pot inulin dehydration and subsequent Baylis-Hillman reaction with methyl acrylate.[a]



Entry	Solvent	Base[b]	Relative yields (%)[c] **2**	HMF	**2** yield (%)[d]
1	1,4-dioxane	DBU	-	100	n.d.
2	1,4-dioxane	DBN	-	100	n.d.
3	1,4-dioxane	DMAP	20	80	n.d.
4	1,4-dioxane	DABCO	91	9	58
5	*i*-PrOH	DABCO	77	23	48
6	MeCN	DABCO	49	51	32
7[e]	1,4-dioxane	DABCO	96	4	60

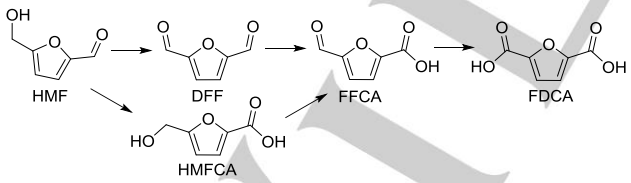
[a] *Conditions:* 0.83 mmol inulin, 30 mol-% KBr in 0.125 M H_2SO_4-dioxane (0.3 mL-2.1 mL), reaction times in the first step; 3 min with 1,4-dioxane and 5 min with MeCN and *i*-PrOH; [b] 2 equiv of base; [c] Determined by ^{1}H NMR from the crude products; [d] isolated yield after column chromatography; [e] 24 h reaction time

The integrated inulin dehydration and Baylis-Hillman reaction of HMF with methyl acrylate was studied in different conditions of solvent and base catalyst and the results are detailed in Table 4. Of the catalysts studied, only DABCO (1,4-Diazabicyclo[2.2.2]octane) was found to be compatible with the applied conditions (2 equiv of DABCO and 3 equiv of methyl acrylate, r.t., 16 hours)[41]. With other tertiary amines, such as DBN (1,5-Diazabicyclo[4.3.0]non-5-ene) or DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene),[38a, 42] no Baylis-Hillman adduct was formed, while the reaction occurred using DMAP (4-dimethylaminopyridine),[43] but extremely sluggishly. Even with DABCO, the reaction was found to proceed quite slowly, as is

often observed for Baylis-Hillman reactions. Conversely to Cannizzaro and aldol condensation reactions, the rate of the Baylis-Hillman reaction was affected by the used organic co-solvent (relative yields of **2** and HMF in Table 4). In terms of reaction rate the binary solvent system 1,4-dioxane/H_2O performed better than *i*-PrOH/H_2O or MeCN/H_2O, and afforded the Baylis-Hillman adduct **2** in a good yield of 58% over two steps, which was raised up to 60% by increasing the reaction time to 24 h. However, heating the reaction (50 ℃) resulted in a decrease of product yield and selectivity.

One-pot inulin dehydration and oxidation to FDCA by Pt/C.

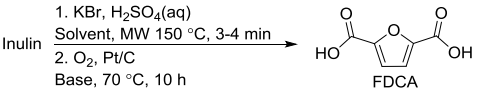
2,5-furandicarboxylic acid (FDCA) has been identified as one of the most promising building blocks for the production of value-added chemicals derived from biomass.[44] Recently, FDCA has evolved as a promising renewable substitute for petroleum-derived terephthalic acid, which is used in the manufacture of polyethylene terephthalate (PET) and polybutyleneterephthalate (PBT) plastics,[45] or as a precursor to adipic acid, one of the two monomers used in nylon 6,6.[46] The preferred route for the production of FDCA involves the catalytic transformation of biomass-derived carbohydrates to HMF, followed by catalytic oxidation (Scheme 4).[47] Various systems using Pt-,[32a] Pd-,[48] Ru[49] or Au-based[50] heterogeneous catalysts have been reported to catalyze the oxidation of pure HMF to FDCA in nearly quantitative yields under neutral (mainly Au)[50a] or basic aqueous conditions. Direct synthetic routes to FDCA from fructose, that combine a dehydration and oxidation steps in one-pot, have been reported using Pt−Bi/C in combination with solid acid,[51] Co(acac)−SiO2 as bifunctional catalyst[52] and Pt/C with NaOH in *i*-PrOH[53] resulting in FCDA yields of 25%, 71% and 51%, respectively. To the best of our knowledge, no literature reports exist which describe the direct one-pot transformation of inulin to FDCA. In our studies, the second HMF oxidation step was performed using Pt/C as oxidation catalyst due to its well-known versatility and efficiency.[1b, 32b, 48, 54] The effect of various bases, such as NaOH, Na_2CO_3 and $NaHCO_3$, on the oxidation outcome was simultaneously investigated using either 1,4-dioxane or MeCN as the organic co-solvent (Table 5).



Scheme 4. HMF oxidation routes to FDCA and intermediates.

The screen of base and co-solvent identified $NaHCO_3$ and MeCN as the best combination which afforded FCDA in 52% yield (10 hours at 70 ℃, Table 5). The application of stronger bases, *i.e.* NaOH or Na_2CO_3, under the same conditions rendered lower FDCA yields and selectivities (carbon balance) regardless of the organic co-solvent. This can be partly explained by HMF degradation and side reactions, such as the Cannizzaro reaction and HMF rehydration and cross-polymerization, which are known to occur at elevated temperatures under strongly alkaline conditions.[55] In all cases, intermediate products 5-hydroxymethylfuranoic acid (HMFCA) and 5-formylfuran carboxylic acid (FFCA) were detected after the reaction, the distribution of which depended on the base or solvent employed (see Table S5 in Supporting Information). With $NaHCO_3$ as base the main product of the reaction was FDCA, accompanied by HMFCA and small amounts of FFCA, while with Na_2CO_3 and NaOH the major products were FFCA and HMFCA, respectively. The presence of those intermediates suggested that the reaction did not go to completion after 10 hours of reaction time. However, with all bases, the extension of the reaction time up to 20 h had only marginal effect on the product distribution, which indicates that the Pt/C catalyst deactivation occurs in a relatively early stage of the reaction. Gratifyingly, with $NaHCO_3$ as base, the evaporation of the organic co-solvent (MeCN)[56] before the second oxidation step leveraged the FDCA yield from 52% to 70% (94% yield if calculated from HMF) with full conversion of HMF and, HMFCA and FFCA intermediates. The same result was achieved by isolating the crude HMF after the first dehydration step by extraction and evaporation of solvents, followed by oxidation using Pt/C in $NaHCO_3$. This demonstrated that, with respect to pure water, the presence of an organic co-solvent significantly hampered the reaction. This negative impact was attributed to either strong adsorption of the formed FDCA salt or other intermediates to the platinum surface (salts less soluble in the organic solvents)[32b, 57] or coordination of the organic co-solvent to the platinum center, resulting in the deceleration of the reaction and the premature deactivation of the Pt/C catalyst.

Table 5. One-pot inulin dehydration to HMF and subsequent oxidation to 2,5-furandicarboxylic acid.



Entry	Solvent	Base	C_{HMF}(%)[b]	Y_{FDCA} (%)[c]
1	1,4-dioxane	NaOH	98	21
2	MeCN	NaOH	99	25
3	1,4-dioxane	Na_2CO_3	54	2
4	MeCN	Na_2CO_3	58	4
5	1,4-dioxane	$NaHCO_3$	97	41
6	MeCN	$NaHCO_3$	96	52
7	MeCN[d]	$NaHCO_3$	>99	70
8	Water[e]	$NaHCO_3$	>99	71

[a] *Conditions:* 0.83 mmol inulin, 30 mol% KBr, 0.3 mL 0.0125 M H_2SO_4-solvent (0.3 mL-2.1 mL); reaction time 3 min with dioxane and 4 min with MeCN; p(O_2)= 8 bar, 2.5 mol% Pt/C, 3 equiv of base; [b] HMF conversion determined by HPLC; [c] overall yields over two steps, determined by HPLC; [d] Performed in one-pot by evaporating MeCN before the second step; [e] Performed in $NaHCO_3$ solution using crude HMF, isolated after the first step by extraction and evaporation of solvents.

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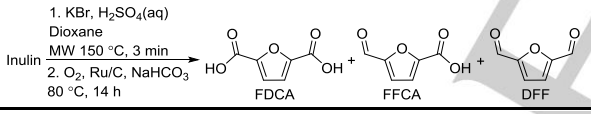
Unfortunately, recycling of the Pt/C catalyst by filtering and washing with water after the reaction resulted in decrease in the FDCA yields to 21% and 9% after the second and third run, respectively (see detailed product distribution on Figure S2 in Supporting Information). Thus, regeneration of the activity of Pt/C catalyst after the reaction still remains a challenge.

One-pot inulin dehydration and oxidation to furan derivatives by Ru/C.

Ru-based heterogenous catalysts on various supports have been reported to catalyze the oxidation of HMF selectively to DFF, FFCA or FDCA in organic solvents[33, 58] or water[49, 58-59] under neutral or basic conditions. In parallel to our studies on the direct one-pot inulin transformation to FDCA by Pt/C, we performed similar experiments using Ru/C as an oxidation catalyst, in the presence of $NaHCO_3$ (Table 6). Inspired by the work of Ebitani and co-workers, who showed that Ru on hydrotalcite can be used in the one-pot synthesis of DFF from fructose[60] and raffinose[61], we aimed to optimize our one-pot inulin transformation process to DFF, which is a valuable bio-based precursor for pharmaceuticals, furanic biopolymers, antifungal agents and furan-urea resins.[62] However, shortly after beginning our studies it turned out that the presence of water, which is essential to our system, caused overoxidation to FFCA (Scheme 4),[33] resulting in a mixture of DFF, FFCA and FDCA (2nd step: 5 mol% Ru/C, 3 equiv $NaHCO_3$, 80 ℃, 14 h, 1,4-dioxane as co-solvent). Attempts to overcome this problem by altering temperature, organic co-solvent (MeCN) or the initial pH of the reaction failed and relatively low yields of DFF were obtained (maximum 25%, entry 4, Table 6).

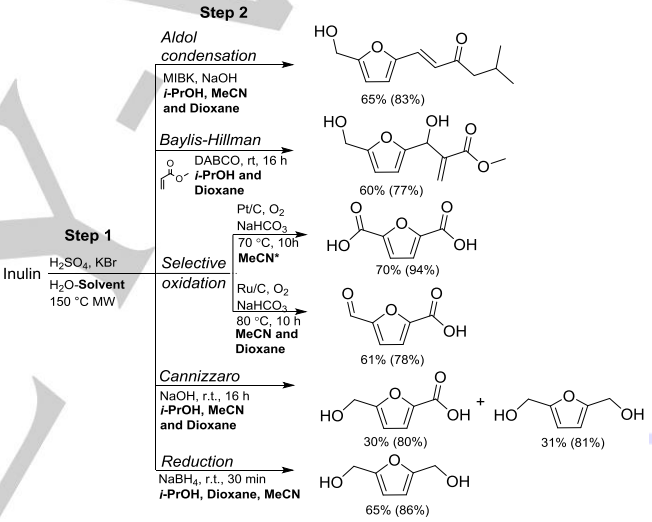
Table 6. One-pot inulin dehydration to HMF and subsequent oxidation by Ru/C.[a]



Entry	pH[b]	C_{HMF} (%)	Y_{FDCA} (%)	Y_{FFCA} (%)	Y_{DFF} (%)
1[c]	8-9	65	trace	34	12
2	7-8	>99	14	56	-
3	6-7	>99	8	43	20
4	5-6	58	3	18	25
5[d]	<3	15	-	3	8
6[e]	7-8	>99	7	61	-
7[f]	7-8	>99	44	22	-

[a] *Conditions:* 0.83 mmol inulin, 30 mol% KBr, 0.3 mL 0.0125 M H_2SO_4-dioxane (0.3 mL-2.1 mL; $p(O_2)$= 8 bar, 2.5 mol% Ru/C; yields corresponds to the overall yields over two steps (HPLC); [b] Initial pH, adjusted with $NaHCO_3$; [c] Sat. aq. $NaHCO_3$ was used [d] without addition of $NaHCO_3$; [e] Reaction time 8 h [f] 3 h 140 C

In spite of the setback in the selective formation of DFF, those studies unveiled the significant impact of the initial reaction pH on the Ru/C activity and the reaction outcome. In terms of Ru/C activity, the optimal initial pH range was found to be narrow between 7 and 8, while at pH lower than 6 or higher than 8 the reaction was very slow. Similar behavior was observed previously in the aqueous oxidation of HMF to DFF or FDCA by Ru on various supports,[58] whereas the addition of hydrotalcite provided appropriate basicity (pH = 8-10) improving conversions and product yields.[63] At slightly basic conditions (pH 7-8) the reaction was highly selective affording FFCA in good 56% overall yield over two steps, accompanied by 12% yield of FDCA and full conversion of HMF. Shortening the reaction time from 14 to 10 hours increased the FFCA yield to 61% due to the diminished exposure time to oxidation. As expected, increase in the reaction temperature from 80 ℃ to 140 ℃ accelerated the FFCA oxidation rate and leveraged the FDCA yield to 44%.[49, 59] These results emphasize the utility of Ru/C as a convenient catalyst for the oxidation of HMF, as the products distribution can be tuned, even with crude HMF, by simply adjusting the reaction conditions, such as initial pH, temperature and reaction time.



Scheme 5. Overview of the direct one pot two-step transformations of inulin through HMF into value-added products conducted in this study. Applicable solvents on bold. Yields are overall yields over two steps and the yields of the second step on brackets (calculated from HMF). * MeCN was evaporated before the second step.

Conclusions

This work illustrates that the carbohydrate dehydration to HMF and its further derivatization by a one-pot reaction strategy is a powerful approach to generate value-added furan derivatives. We have demonstrated that HMF in crude form, obtained in sufficient purity by using straightforward microwave-enhanced aqueous dehydration of various carbohydrates, is amenable to various transformations, such as the base-catalyzed aldol condensation with ketones and the Cannizzaro and Baylis-Hillman reactions as well as the oxidation by Pt/C or Ru/C and reduction by $NaBH_4$, in a single one-pot reaction. Most strikingly, fructose-containing inulin, which is preferred over fructose in the synthesis of HMF due to its non-digestible nature, was found to

be compatible with all the reaction types investigated, and provided the respective furan derivatives in very good yields. This was especially manifested in the one-pot oxidation of inulin to 2,5-furandicarboxylic acid with Pt/C as catalyst, which proceeded in very good 70% overall yield over two steps (94% if calculated from HMF). In terms of product yields, the major limitation of the process was the first dehydration step since the second step, regardless of the reaction type, proceeded in very similar yields compared to those of reported for pure HMF in similar reaction conditions. In this sense, the efficiency of the process could be improved simply by improving the carbohydrate dehydration step. This could be achieved by optimizing the reaction conditions for other solvent systems, such as ionic liquids or purely organic media, which are known to be efficient in carbohydrate dehydration to HMF. Collectively the results presented in this study highlight the potential of transforming carbohydrates to high value-added furan derivatives in a one-pot manner without resorting to purification of HMF intermediate, thus bridging the gap between the large scale exploitation of biomass and the sustainable production of commodity chemical and fuels.

Experimental Section

General

All solvents, bases, carbohydrates, Pt/C, Ru/C and $CrCl_3 \times 6H_2O$ were purchased from commercial sources and used without further purification unless otherwise noted. All the reactions were carried out in 2–5 mL glass vials using a Biotage Initiator microwave reactor (2.45 GHz magnetron). The instrument uses one IR sensor to measure temperature of the reaction mixture and adjusts the heating power accordingly. The absorption level was set to "very high" and the reaction mixture was stirred with magnetic stirring at 600 rpm.

HMF, DFF, HMFCA, FFCA and FDCA, glucose and fructose yields were determined with High Pressure Liquid Chromatography (HPLC). HPLC runs were performed using Agilent 1200 HPLC system equipped with a Phenomenex Rezex ROA (300×7.8 mm) column. Sulfuric acid (0.25 mM) in water was used as an eluent at 40 ℃ with a flow rate 0.35 mL min^{-1}. HMF, DFF, HMFCA, FFCA and FDCA were detected using UV-detector, whereas fructose and glucose were analyzed using refractive index (RID) detector. The exact yields were calculated from calibration curves prepared for all the compounds from commercially available reagents. The yields of the aldol condensation product **1** were determined by a gas chromatograph equipped with a flame ionization detector (GC-FID). The GC-FID runs were performed using Agilent Technologies 6890N Network GC System fitted with Agilent HP-INNOWAX column (length 30 m, internal diameter 0.25 mm and stationary phase thickness 0.25 µm). The calibration curves were plotted using standard samples with different concentrations of pure **1** (column chromatography, EtOAc: $CHCl_3$ 1:4, R_f = 0.50). ^{1}H NMR and ^{13}C NMR spectra were acquired at 27 °C using 300 MHz (300 MHz ^{1}H-frequency and 75 MHz ^{13}C-frequency) spectrometer. Chemical shifts are reported in ppm, and the ppm scale was referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$; 7.26 ppm for 1H and 77.16 ppm for 13C, acetone in acetone-d_6; 2.05 ppm for ^{1}H and 29.84 ppm for ^{13}C). Coupling constants are reported in Hz. ^{13}C NMR experiments were performed using APT pulse sequence (^{13}C {^{1}H} proton decoupling).

Procedure for the one-pot fructose dehydration and aldol condensation sequence (Figures 2 and 3 and Table 1)

To a 2-5 ml microwave vial with a magnetic stirring bar containing fructose (0.15g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol %) was added 0.3 mL of 0.125 M H_2SO_4. After dissolution of fructose, 2.1 mL of the organic solvent (1.4-dioxane, MeCN, *i*-PrOH, γ-valerolactone, DMF, THF or EtOH) was added, the vial was closed with aluminum/silicone crimp cap and the solution was heated at 150 °C in the microwave reactor (Biotage Initiator). After required time (2 min, except with 1,4-dioxane 1 min and with *i*-PrOH 3 min), the vial was immediately cooled down to room temperature, whereupon 0.4 mL of 1 M NaOH (0.4 mmol) and 0.30 mL of methyl isobutyl ketone, 0.18 mL of acetone or 0.21 mL of 2-butanone (2.4 mmol) were added and the solution was heated at 55 °C for three hours under oil bath. Then, EtOAc (25 mL) and brine (10 mL) were added, the organic layer separated and dried over Na_2SO_4. The product yield was determined from this solution by GC-FID (diluted to 50 mL) using acetophenone as an internal standard. Additionally, in the case of fructose in 1,4-dioxane, after evaporation of the solvents, the purification by column chromatography afforded HMF-MIBK adduct **1** (EtOAc:$CHCl_3$ 1:4, R_f = 0.5, colorless oil) in 58% yield, HMF-2-butanone adduct (EtOAc:hexane 1:1, R_f = 0.25, light green oil) in 61% yield as a mixture of two isomers (2:1 ratio, ^{1}H NMR) and HMF-acetone adduct (EtOAc:hexane 1.5:1, R_f = 0.30, colorless oil) in 51% yield. *1-(5-(hydroxymethyl)furan-2-yl)-5-methylhex-1-en-3-one (**1**)*; ^{1}H NMR (300 MHz, chloroform-d) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.98 (br. s, 1H), 2.09-2.32 (m, 1H), 2.46 (d, *J* = 7.0 Hz, 2H), 4.65 (s, 2H), 6.38 (d, *J* = 3.3 Hz, 1H), 6.60 (d, J = 3.4 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 7.28 (d, *J* = 15.8 Hz, 1H). ^{13}C NMR (75 MHz, chloroform-d) δ 22.8, 25.5, 50.8, 57.8, 110.6, 116.6, 123.8, 128.5, 151.2, 156.7, 200.0. *HMF-2-butanone adducts: Major isomer 1-(5-(hydroxymethyl)furan-2-yl)pent-1-en-3-one:* ^{1}H NMR (300 MHz, chloroform-*d*) δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.50 (br. s, 1H), 2.60 (q, *J* = 7.3 Hz, 2H), 4.64 (s, 2H), 6.36 (d, *J* = 3.2 Hz, 1H), 6.58 (d, *J* = 3.3 Hz), 6.62 (d, *J* = 16.0 Hz, 1H), 7.26 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 8.4, 34.7, 57.7, 110.5, 116.6, 123.1, 128.5, 151.1, 156.9, 200.8. *Minor isomer 4-(5-(hydroxymethyl)furan-2-yl)-3-methylbut-3-en-2-one:* ^{1}H NMR (300 MHz, chloroform-*d*) δ 2.10 (s, 3H), 2.38 (s, 3H), 2.50 (br, 1H), 4.62 (s, 2H), 6.43 (d, *J* = 3.4 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 7.25 (s, 1H); ^{13}C NMR (75 MHz, chloroform-*d*) δ 13.0, 25.6, 57.7, 110.4, 116.3, 126.9, 134.2, 151.7, 156.3, 199.5. *HMF-acetone adduct: 4-(5-(hydroxymethyl)furan-2-yl)but-3-en-2-one;* ^{1}H NMR (300 MHz chloroform-d) δ 2.30 (S, 3H), 2.48 (br. s, 1H), 4.63 (s, 2H), 6.38 (d, *J* = 3.4 Hz, 1H), 6.56-6.62 (m, 2H), 7.22 (d, *J* = 15.7 Hz, 1H). ^{13}C NMR (75 MHz, chloroform-d) ^{13}C NMR (75 MHz, chloroform-d) δ 28.1, 57.7, 110.5, 116.8, 124.2, 129.5, 150.8, 157.2, 198.1.

Procedure for the one-pot glucose, cellobiose, lactose or sucrose dehydration and aldol condensation with MIBK (Table 2)

To a 2-5 ml microwave vial with a magnetic stirring bar containing the desired carbohydrate (0.83 mmol), potassium bromide (30 mg, 0.25 mmol, 30 mol%) and $CrCl_3 \times 6H_2O$ (22.4 mg, 10 mol%) was added 0.3 mL of 0.125 M H_2SO_4. Then, 2.1 mL of desired organic solvent (1.4-dioxane, MeCN or *i*-PrOH,) was added, the vial was closed with aluminum/silicone crimp cap and the solution was heated at 150 °C in the microwave reactor. After required time (4 min with 1,4-dioxane, 5 min with MeCN and *i*-PrOH), the vial was immediately cooled down to room temperature, whereupon 1.0 mL of 1 M NaOH (1 mmol) and 0.3 mL of methyl isobutyl ketone were added and the solution was heated at 55 °C for three hours under oil bath. Then, EtOAc (25 mL) and brine (10 mL) were added, the organic layer separated and dried over Na_2SO_4. The product yields were determined from this solution by GC-FID (diluted to 50 mL).

Procedure for the one-pot inulin dehydration and aldol condensation with MIBK (Table 2)

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136 g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol%) was added 0.3 mL of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of the desired organic solvent (1.4-dioxane, MeCN or *i*-PrOH) was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C (3 min with 1.4-dioxane, 4 min with MeCN and 5 min with *i*-PrOH) in the microwave reactor. After the required time, the vial was immediately cooled down to room temperature, whereupon 0.4 mL of 1 M NaOH and 0.3 mL of methyl isobutyl ketone were added and the solution was heated at 55 °C for three hours under oil bath. Then, EtOAc (25 mL) and brine (10 mL) were added, the organic layer separated and dried over Na_2SO_4. The product yields in different solvents were determined from this solution by GC-FID (diluted to 50 mL).

Procedure for the one-pot inulin dehydration and Cannizzaro reaction sequence (Table 3)

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol %) was added 0.3 mL of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of the desired organic solvent (1.4-dioxane, MeCN or *i*-PrOH) was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C (3 min with 1.4-dioxane, 4 min with MeCN and 5 min with *i*-PrOH) in the microwave reactor. After the required time, the vial was immediately cooled down to room temperature, whereupon 133 mg powdered NaOH (3.3 mmol, 4 equiv) was added and the mixture was stirred at r.t. for 16 hours. Then, 1 M NaOH (10 mL) and 15 mL of EtOAc were added. The organic layer was separated and the aqueous layer was further extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness to give a dark color solid, which was washed with Et_2O/hexane to afford pure 2,5-furandimethanol (BHMF) as a light yellow solid in 30% yield.[25] The hydroxymethylfuranoic acid (HMFCA) yield (31%) was determined from the basic aqueous layer (diluted to 50 mL by water) by HPLC analysis. Data for *furan-2,5-diyldimethanol (BHMF):* ^{1}H NMR (300 MHz, acetone-d_6) δ 4.08 (br. s, 2H), 4.47 (s, 4H), 6.18 (s, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 57.2, 108.2, 155.8.

Procedure for the one-pot inulin dehydration and reduction to BHMF by $NaBH_4$ (Scheme 5).

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136 g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol-%) was added 0.3 mL solution of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of *i*-PrOH was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C for 5 min in the microwave reactor (Biotage Initiator). Then, the vial was immediately cooled down to room temperature followed by the addition of sodium borohydride in small portions (38 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 30 min, whereupon the solution was neutralized by a careful addition of 0.5 M H_2SO_4. Then, EtOAc (20 mL) and brine (10 mL) were added, the organic layer was separated and the aqueous layer was further extracted with EtOAc (3×10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated to dryness to afford crude product, which was purified by column chromatography (EtOAc:$CHCl_3$ 1:1) to give BHMF as white solid in 67% yield (68 mg, 0.53 mmol). The ^{1}H and ^{13}C NMR data of the product are in accordance with the NMR data of BHMF obtained from Cannizzaro reaction.

Procedure for the one-pot inulin dehydration and Baylis-Hillman reaction sequence (Table 4)

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136 g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol-%) was added 0.3 mL solution of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of the desired solvent (*i*-PrOH, 1,4-dioxane or MeCN) was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C (3 min with 1.4-dioxane, 4 min with MeCN and 5 min with *i*-PrOH) in the microwave reactor. Then, the vial was immediately cooled down to room temperature followed by the addition of required amount (1.67 mmol, 2 equiv) of base (DABCO, DBN, DBU or DMAP) and methyl acrylate (0.23 mL, 2.5 mmol). The reaction mixture was stirred at room temperature for either 16 h or 24 h, whereupon, EtOAc (20 mL), brine (10 mL) and water (4 mL) were added, the organic layer was separated and the aqueous layer was further extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification by column chromatography (EtOAc:hexane 2:1, R_f = 0.3) in the case of 1,4-dioxane as solvent and DABCO as a base (24 hours) gave the product as colourless oil in 60% yield (101 mg, 0.51 mmol). *Methyl 2-(hydroxy(5-(hydroxymethyl)furan-2-yl)methyl)acrylate*: ^{1}H NMR (300 MHz, chloroform-d) δ 1.90 (br. s, 1H) 3.17 (br. s, 1H), 3.77 (s, 3H), 4.57 (s, 2H), 5.57 (br. s, 1H), 5.97 (q, *J* = 1.1 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 6.39 (q, *J* = 0.8 Hz, 1H). ^{13}C NMR (75 MHz, chloroform-d) δ 52.2, 57.4, 67.0, 67.2, 108.1, 108.7, 127.0, 139.5, 154.1, 154.3, 166.6.

Procedure for the one-pot inulin dehydration and oxidation to FDCA by Pt/C (Table 5)

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136 g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol-%) was added 0.3 mL solution of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of the desired solvent (1,4-dioxane or MeCN) was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C (3 min with 1.4-dioxane or 4 min with MeCN) in the microwave reactor (Biotage Initiator). Then, the vial was immediately cooled down to room temperature followed by the addition of 3.0 mL of aqueous base solution (2.4 mmol, $NaHCO_3$, Na_2CO_3 or NaOH) and 80 mg of 5%-Pt/C (2.5 mol%).***** The vial was closed using a septa with an oxygen inlet (a needle through the septa) and loaded into the reactor which was closed and pressurised with *p*=8 bar oxygen, after purging three times to remove air. The reaction mixture was heated at 70℃ for 10 h, whereupon the reactor was cooled to room temperature followed by the addition of 10 mL of 1 M NaOH and stirring for 3 min. The catalyst was filtered off and water was added to make the total volume of 50 mL. The yields of HMF, DFF, HMFCA, FFCA and FDCA were determined from this solution by HPLC analysis.

***** The best FDCA yield was obtained when MeCN was evaporated before the second step by air flow. Thus, after addition of 2.0 mL of sat.aq.$NaHCO_3$ (~3 equiv) two phases emerged and MeCN was evaporated from the top by airflow under stirring.

Procedure for the one-pot inulin dehydration and oxidation with Ru/C (Table 6)

To a 2-5 ml microwave vial with a magnetic stirring bar containing inulin (0.136 g, 0.83 mmol) and potassium bromide (30 mg, 0.25 mmol, 30 mol-%) was added 0.3 mL solution of 0.125 M H_2SO_4. The mixture was stirred for 1 min, whereupon 2.1 mL of the desired solvent (1,4-dioxane or MeCN) was added, the vial closed with aluminum/silicone crimp cap and the mixture was heated at 150 °C (3 min with 1.4-dioxane or 4 min with

MeCN) in the microwave reactor. Then, the vial was immediately cooled down to room temperature followed by the addition of required amount of $NaHCO_3$ to reach the desired initial pH value (dropwise addition of 5%. $NaHCO_3$; see Table 6) and 42 mg of 5% Ru/C (2.5 mol%). The vial was closed using a septa with an oxygen inlet (a needle through the septa) and loaded into the reactor which was closed and pressurised with *p*=8 bar oxygen, after purging three times to remove air. The reaction mixture was heated at 80 ℃ or 140 ℃ for the required time (2, 10, 14 or 20 h; see Table 6), whereupon the reactor was cooled to room temperature followed by the addition of 10 mL of 2 M NaOH and stirring for 3 min. The catalyst was filtered off and water was added to make the total volume of 50 mL. The HMF, DFF, HMFCA, FFCA and FDCA yields were determined from this solution by HPLC analysis as described above.

Acknowledgements ((optional))

Acknowledgements Text.

Keywords: 5-hydroxymethylfurfural • Biomass • Renewable Resources • Sustainable Chemistry • Carbohydrates

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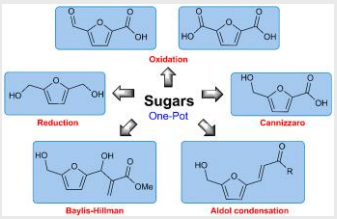

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