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COMMUNICATION

Highly efficient dehydration of carbohydrates to 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural (HMF) and levulinic acid by biphasic continuous flow processing†

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Using a continuous flow reactor, the dehydration of D-fructose and other carbohydrates to 5-(chloromethyl)-furfural (1) is achieved in reaction times as short as 60 s. The biphasic flow process allows for high-yielding multigram scale production of CMF (1) which is obtained with excellent purity after a simple extractive work-up. Efficient conversion of D-fructose into 5-(hydroxymethyl)furfural (2) and levulinic acid (6) is also demonstrated using flow reactor techniques.

The conversion of biological feed stock into functional chemical intermediates and renewable fuels plays an increasingly important role in the context of today's efforts to make chemistry more sustainable and to address the global issue of fossil fuel depletion.[1] For example, the dehydration of carbohydrates readily leads to substituted furans, levulinic acid derivatives, and other functional small molecules. While these transformations have been known for decades, only recently has their impact been fully recognised.[2] We were interested to study the dehydration reactions of sugars under continuous flow conditions, as micro- and mesoscale flow reactors can offer increased efficiency and safety compared to conventional chemical reactors, combined with lower costs and environmental impact of chemical production.[3] Another notable advantage of flow reactors is their considerably smaller footprint compared to conventional batch reactors – an important factor for production of chemical intermediates on scale.

Herein we report a new highly efficient methodology for the dehydration of feed stock carbohydrates to the value-added furan derivatives 5-(chloromethyl)furfural "CMF" **1**[4] and 5-(hydroxymethyl)furfural "HMF" **2**[5] as well as levulinic acid "LA" **6** by biphasic continuous flow reactor processing.

The dehydration of sucrose, D-fructose and D-glucose to CMF **1** in continuous flow using a biphasic solvent system is presented in Table 1. The carbohydrates were dissolved in aqueous hydrochloric acid, and the solution was pumped into the flow reactor (Vapourtec®),[6] where it was mixed with either dichloromethane (CH_2Cl_2) or 1,2-dichloroethane (DCE), prior to entering a heated flow coil (PFA tubing, volume 10 mL, 1 mm inner diameter). Under these biphasic conditions, the aqueous and the organic phase enter the flow reactor in defined alternating segments. A back pressure regulator (8 bar) was connected to the reactor outlet. When a 0.12 M solution of sucrose in 32% HCl aq. was processed using CH_2Cl_2 as the organic solvent, and at 100 °C for 2.5 min (Table 1, entry 1), CMF **1** was isolated in 51% yield after work-up, and with excellent purity. The crude product contained no HMF **2**, while unreacted sugar remained in the aqueous phase. Reaction of D-fructose and D-glucose under identical conditions (entries 2 and 3) led to CMF **1** in 80% and 15% yield, respectively, showing that under these conditions D-fructose reacts *ca.* five times faster than D-glucose.

The reaction mixtures obtained from sucrose, D-fructose and D-glucose after a reaction time of 2.5 min (entries 1–3) contained *ca.* 1 weight% of carbon particles, which were easily removed by filtration through a short plug of silica gel. However, when sucrose and D-glucose were processed for longer periods of time or at higher temperatures to improve conversion, greater amounts of carbon formed through product decomposition, which eventually led to reactor blockage. To address this limitation in the process so as to allow large scale processing and in a truly continuous fashion, a particle filter was incorporated into the flow stream (Scheme 1). The filter consisted of a glass column (Omnifit®),[7] without the usual teflon frit in its upper end piece, and filled with a short bed of sand. Overhead space above the sand bed would allow particles to sediment gently, rather than being forced into a dense filter plug which would lead to pressure increase. Hence, this simple device, connected to the outlet of the reactor coil, and placed before the back pressure regulator, enabled effective in-line filtration of the otherwise problematic carbon particles.

The process was subsequently optimized for carbohydrate concentration, reaction time and yield (entries 4–8). Acid concentration of 32% HCl aq. was retained, as experiments with more dilute HCl produced mixtures of CMF **1** with HMF **2**.[8] D-Glucose could be converted into CMF **1** in 58% yield when

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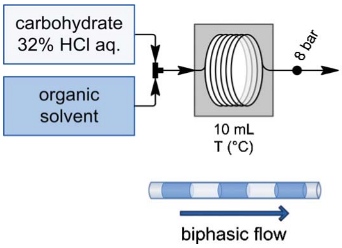
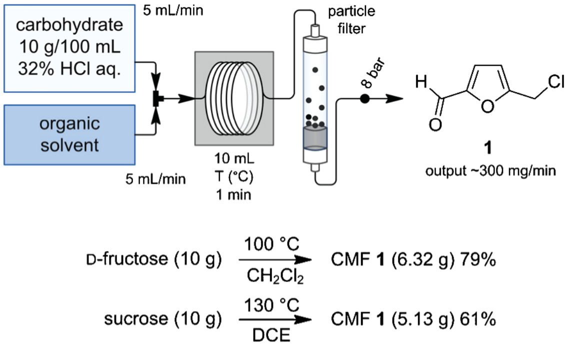
Table 1 Conversion of carbohydrates into CMF **1** by biphasic continuous flow processing



Entry	Sugar	g/10 mL (conc.)[a]	Solvent	T/°C	Flow rate (mL min^{-1})	rt[b] (min)	Yield (%)
1	Sucrose	0.2 (0.12 M)	CH_2Cl_2	100	2 × 2	2.5	51
2	D-Fructose	0.2 (0.11 M)	CH_2Cl_2	100	2 × 2	2.5	80
3	D-Glucose	0.2 (0.11 M)	CH_2Cl_2	100	2 × 2	2.5	15
4	D-Glucose	0.2 (0.11 M)	CH_2Cl_2	100	2 × 0.5	10	47[c]
5	D-Glucose	0.2 (0.11 M)	DCE	120	2 × 1	5	58[c]
6	D-Fructose	0.5 (0.28 M)	CH_2Cl_2	100	2 × 2	2.5	69
7	D-Fructose	1 (0.56 M)	CH_2Cl_2	100	2 × 3	1.67	81
8	D-Fructose	1 (0.56 M)	CH_2Cl_2	100	2 × 5	1	76

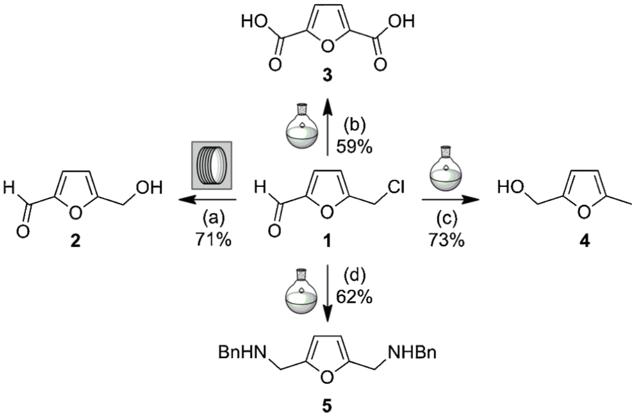
[a] Reactions were run using 10 mL solutions of the carbohydrates in 32% HCl aq. [b] rt = residence time. [c] Reaction was run with particle filter.



Scheme 1 Continuous flow conversion of sucrose and D-fructose into CMF **1** on a 10 gram scale.

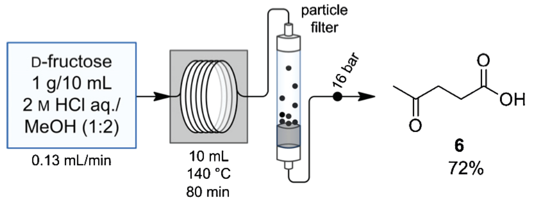
reacted at 120 °C for 5 min, and using the particle filter (entry 5). In case of D-fructose, the concentration could be increased to 1 g per 10 mL of aqueous solvent (0.56 M), and reaction times as short as 60 s were sufficient to achieve conversion into **1** in *ca.* 80% yield (entries 6–8).[9] As shown in Scheme 1, we also performed the dehydration of D-fructose and sucrose on a 10 gram scale. Under optimum conditions, 6.32 g of **1** (79% yield) were produced from 10 g of D-fructose, in only 20 min of total process time. Likewise, 10 g of sucrose were converted into 5.13 g of **1** (61% yield) using DCE as the organic solvent and at 130 °C. Employing these procedures, a single flow channel would thus produce an output of *ca.* 300 mg of product **1** per minute.

CMF **1** is a valuable small molecule for synthesis,[10] and Scheme 2 shows some examples of new useful transformations of **1** we developed, *e.g.* the aqueous hydrolysis of **1** to yield HMF **2** (performed in a flow reactor),[11] the oxidation of **1** leading to furan dicarboxylic acid **3**, the reduction of **1** with sodium borohydride (under phase transfer conditions)[12] to afford (5-methylfuran-2-yl)methanol **4**, and bis-amination of **1** to the symmetrical furan diamine **5** by a one-pot substitution-reductive amination procedure, respectively.



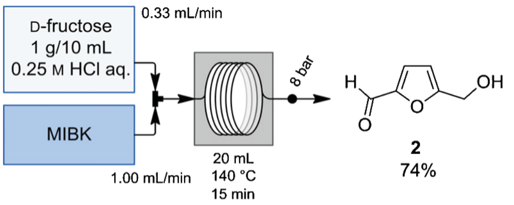
Scheme 2 Reactions of CMF **1** in batch and continuous flow. Conditions: (a) **1** 0.5 M in THF, H_2O, flow-heating, 100 °C, 2.5 min. (b) 69% HNO_3 aq., 80 °C, 24 h. (c) $NaBH_4$, $Bu_3PC_{16}H_{33}{}^+Br^-$, TBME/$H_2O$, 5 °C to rt, 2 h. (d) (i) Et_3N, $BnNH_2$, 4 Å MS, DCE, rt, 16 h. (ii) $NaBH(OAc)_3$, HOAc, rt, 16 h.

The aqueous hydrolysis of **1** to HMF **2** in continuous flow (Scheme 2) was only moderately selective as **2** was accompanied by 20% of levulinic acid (LA) **6**.[11] LA **6** itself is a valuable platform chemical,[2d] and it can be accessed directly from D-fructose as shown in Scheme 3. A 10% aqueous solution of carbohydrate in a 1 : 2 mixture of 2 M HCl aq. and methanol was heated to 140 °C for 80 min in a flow reactor, to produce levulinic acid **6** in 72% yield (along with 11% of isolated HMF **2**).[13]



Scheme 3 Continuous flow dehydration of D-fructose to LA **6**.

As the formation of HMF **2** by hydrolysis of CMF **1** proceeded with only moderate selectivity under flow conditions, we turned our attention to its direct preparation from D-fructose. The production of HMF **2** from biological feedstock has been extensively investigated,[2,5] as one of its important applications is the heterogeneous hydrogenation leading to the biofuel 2,5-dimethylfuran (DMF).[5c,e,f] Previous work has shown that, analogously to the formation of CMF **1** from sugars, the selectivity of this dehydration is increased by employing biphasic solvent systems; HMF **2** is readily extracted into the organic phase as it forms, preventing it from reacting further to LA **6**. High boiling solvents like DMSO[5d,14] or dimethylacetamide[5e] have been employed in the process, as well as speciality solvents like ionic liquids[5b] and Lewis acid additives.[5b,f] Instead, we have used here the simple biphasic solvent system of 0.25 M aqueous HCl and methyl isobutyl ketone (MIBK).[5a] The dehydration of D-fructose to HMF **2** was readily achieved with good selectivity and high yield under these reaction conditions (Scheme 4), and no formation of carbon particles occurred when a 10% aqueous solution of the carbohydrate was used. The best results were obtained when the organic phase was mixed into the flow stream with a flow rate 3 × higher than the aqueous solution of the carbohydrate. Heating the resulting flow stream to 140 °C for 15 min gave, after work-up and filtration through silica, 74% of isolated HMF **2** (the crude product contained HMF **2** and LA **6** in a ratio of 87 : 13 with less than 3% of other side products).[14]



Scheme 4 Biphasic continuous flow dehydration of D-fructose to HMF **2**.

Conclusions

We have developed efficient and practicable procedures for the dehydration of carbohydrates to the value-added products 5-(chloromethyl)furfural **1**, 5-(hydroxymethyl)furfural **2** and levulinic acid **6** under biphasic continuous flow conditions. The flow reactor-assisted conversion of D-fructose, D-glucose and sucrose into CMF **1** is superior to previously published procedures[4h,i] in terms of overall efficiency: a reaction time of 60 s is sufficient to produce **1** with 80% isolated yield from D-fructose and 60% yield from sucrose. Likewise, the biphasic continuous flow protocol for the conversion of D-fructose into HMF **2** proceeds with high isolated yield, in a reaction time of only 15 min, and avoids high boiling solvents like DMSO[5d,14] or other additives like Lewis acids,[5b,f] or special phase modifiers.[5a] In summary, this study has shown that by using flow reactor processing, carbohydrates can readily be converted into the important platform chemicals **1**, **2** and **6** with good efficiency and a high state of purity. This was achieved using inexpensive reagent systems, in short reaction times and with simple work-up procedures.

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6 Vapourtec® R2/R4 systems were used, see www.vapourtec.co.uk and Supporting Information for detail.

7 For detail, see www.omnifit.com and Supporting Information.

8 Use of 4 M HCl aq. led to the formation of **1** and **2** in 1 : 1 ratio.

9 No unreacted carbohydrate was isolated after these reactions.

10 For examples, see: (*a*) M. K. Jogia, V. Vakamoce and R. T. Weavers, *Aust. J. Chem.*, 1985, **38**, 1009; (*b*) L. L. Klein and M. S. Shanklin, *J. Org. Chem.*, 1988, **53**, 5202; (*c*) T. K. Chakraborty, S. Tapadar and S. K. Kiran, *Tetrahedron Lett.*, 2002, **43**, 1317; (*d*) B. Das, S. Rudra, A. Yadav, A. Ray, A. V. S. R. Rao, A. S. S. V. Srinavas, A. Soni, S. Saini, S. Shukla, M. Pandya, P. Bhateja, S. Malhotra, T. Mathur, S. K. Arora, A. Rattan and A. Mehta, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4261.

11 The batch mode hydrolysis of CMF **1** to HMF **2** has been reported previously, see ref. 4 (i), with a yield of 86% of **2** and 10% of LA **6**. However, we could not obtain a comparable result by flow reactor processing despite extensive optimization.

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13 The overall yield of the reaction reflects the formation of carbon particulates which occurs in batch experiments to the same extend. Conducting the reaction in flow at higher temperatures would lead to shorter reaction time, but would generate more carbon particles and also require steel tubing. PFA tubing has a lower pressure rating (140 °C at 16 bar are close to the material's stability limit), but the advantage of transparency of the flow channel and a lesser propensity for blockages.

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