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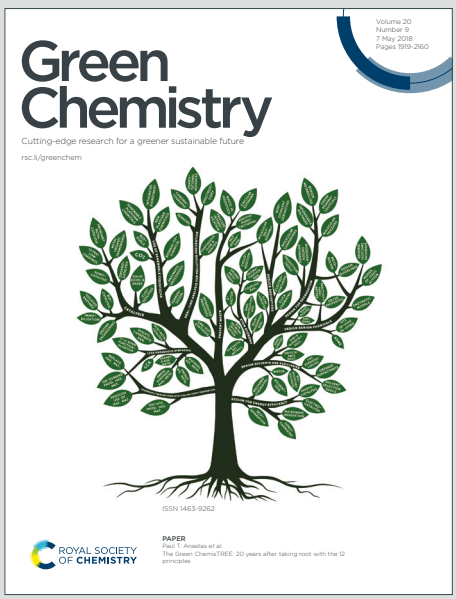

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COMMUNICATION

Scalable Synthesis of Hydroxymethyl alkylfuranoates as Stable 2,5-Furandicarboxylic acid Precursors

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Hydroxymethyl furanoic acid and derivatives thereof have been synthesized in high yields and purity from gluconolactone. The reaction sequence allow recovery of reagents, use of bio-friendly chemicals and solvents, and can easily be up-scaled. Reactions on >100 gram scale can be purified by a single purification, such as a destillation or precipitation. Overall yield is above 50%.

Introduction

The conversion of abundant carbohydrates into platform chemicals has received immense attention in the last two decades.[1–4] Glucose or related carbohydrates, such as fructose, have been the main interest as these can be derived from cellulose, which is the most abundant bio-polymer and by far the cheapest source. Converting carbohydrates to chemicals, to substitute fossil-based sources, involves dehydration reactions as a central process. Simple acid mediated dehydration of glucose and fructose has been known for more than a century to produce short chain acids[5] and furane compounds (Figure 1). Where hydroxymethyl furfural (HMF) has received the most attention as a potential platform chemical.[6–10] One reason for this is its conversion to furane dicarboxylic acid (FDCA, **1**), when oxidized.[11–13] This can substitute phthalic acids in the industrial production of polymers. Countless methods have therefore been published on HMF synthesis, notably many starting from fructose as it is more reactive and easier to convert. However, less relevant for an industrial production, where glucose or sucrose, or even better, cellulose would be preferred.[4,8,14] Despite this the synthesis of HMF from fructose has been the method of choice for several chemical companies developing FDCA syntheses.[15] Beside the more valuable fructose as preferred starting material, HMF itself also cause extensive problems in large-scale production. The presence of an aldehyde and a hydroxyl group makes it particularly reactive towards polymerisation. This leading to the formation of humins that remains problematic, both in preparation and storage.[16,17] Development of methods for direct one-pot oxidation to FDCA has to some extent reduced this problem.[18–20] An alternative approach for the synthesis of FDCA precursors and related furanoates, would use an already oxidized glucose derivative. Surprisingly, few have investigated this option. The cheapest and simplest oxidation product of glucose is gluconic acid, where the aldehyde has been oxidised to the acid. This can be done enzymatically or chemically and is already performed on multiple ton scale, making it almost as cheap as glucose.[21,22] The corresponding lactone, gluconolactone, has therefore received some attention in valorising biomass.[23] Baumann et al.[24] have recently demonstrated that cyclopentanone derivative can be synthesized from gluconolactone in flow. To our knowledge, no examples of the direct synthesis of furanoates from aldonolactones have been published. In this communication, we describe a simple method for the conversion of gluconolactone into alkylfuranoates, such as hydroxymethyl methylfuranoate (HMMF, **2**) and hydroxymethyl furanoic acid (HMFA, **3**). Furthermore, examples of derivative synthesis are presented as well.

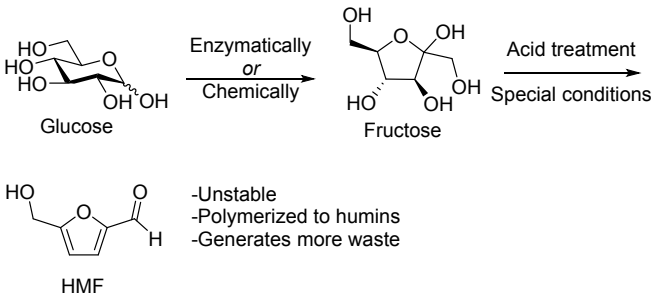

Figure 1. Generalized outline for the conversion of glucose and fructose to HMF, an often tedious and messy production.

Results and discussion

To allow for selective functionalisation of gluconolactone, the first step in the synthesis is full acetylation. Aside from being a protective group, the acetylation also serves for the activation

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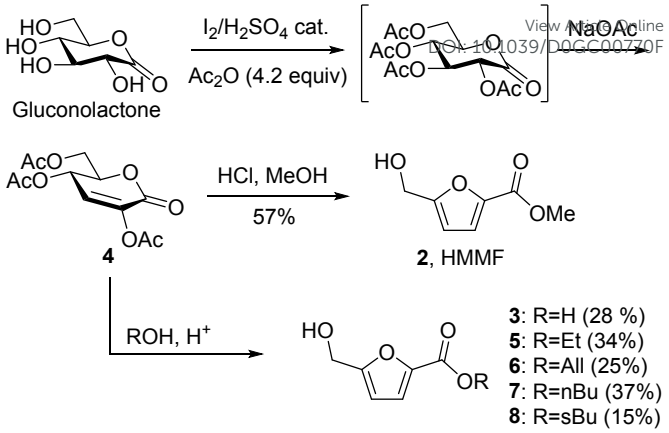
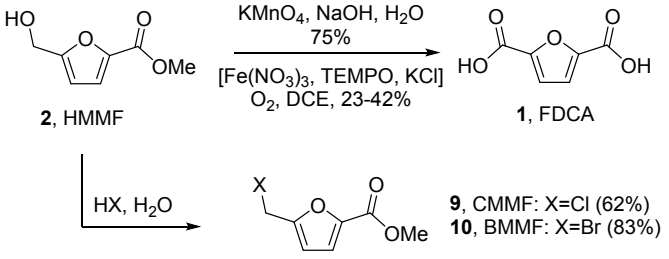
of the 3-O, which is required for the subsequent elimination. While acetylation of the 2-O lowers the pK_a of 2-H. Besides being the simplest and cheapest dual function protective group, the acetyl is an acetic acid derived group, which is a non-hazardous and an unrestricted chemical. Acetylation of carbohydrates is one of the most common reactions in carbohydrate chemistry, and quantitative yields are normally obtained, using standard conditions, i.e. excess Ac_2O in pyridine. Keeping large-scale synthesis in mind, we optimized the conditions in terms of reagent quantity, recovery, handling and yield. Acid catalysed esterification in neat Ac_2O was the most efficient method and advantageously avoiding amine bases, such as pyridine. The amount of Ac_2O required could be lowered to 4.2 equivalent before the yield was affected (Scheme 1). Several strong acid catalysts were screened, e.g. iodine could be used in very low amounts (0.15-0.087 mol%) with full conversion. Iodine is however not compatible with stainless steel equipment commonly used in industries and hence exchanged for H_2SO_4 or a solid phase acid like Amberlite IR-120. This gave equally high yields and clean conversion. In terms of price and handling H_2SO_4 was the preferred acid. The following β-elimination was directly performed by addition of base to the reaction mixture. Several groups have previously studied this reaction. A major issue is the double elimination, when gluconolactone is acetylated using base catalysed acetylation.[25,26] Pedersen optimized the reaction conditions to selectively give the mono-elimination of purified acetylated gluconolactone applying triethylamine in CH_2Cl_2.[27] These conditions were not suitable for our purpose and we therefore aimed to find more industrially and environmentally friendly conditions. After some investigation, NaOAc in stoichiometric amounts or even in a catalytic amount dissolved in AcOH was found to smoothly eliminate the 3-OAc in high yields. NaOAc is a food additive, environmentally friendly and a very cheap base. On prolonged reaction times the double elimination took place as well. Besides generating acetic acid as the only by-product, a further advantage was the ease of NaOAc recovery by filtration, when used in stoichiometric amounts. The crude elimination product **4** in MeOH was then treated with a catalytic amount of acid, typically from adding AcCl, to acidify the solution (See supporting information Table 1). When full conversion was observed by TLC analysis the mixture could be directly purified by fractional distillation, returning the MeOH and pure HMMF in 56% overall yield from gluconolactone on a >100 g scale. The methyl ester is particularly stable under these conditions and could be stored for months without notably decomposition. Similarly, other ester derivatives could be obtained just by changing the alcohol used as solvent. In this way the ethyl **5**, allyl **6**, n-butyl **7** and s-butyl **8** esters were synthesized, and purified by chromatography. The corresponding carboxylic acid HMFA **3** could easily be produced in one-pot, by addition of either dilute HCl or H_2SO_4 in water, followed by crystallization. Generally, when other alcohols than methanol was used, we observed a higher degree of side-product formation. In all reaction the major side-product was a 2-*H*-pyranone derivative like the double elimination product following β-elimination.



Scheme 1. Synthesis of HMMF and other ester-derivates directly from gluconolactone in 3 steps, one-pot and one purification.

With access to a variety furanoates, derived in a few simple steps from gluconolactone, we studied some further transformations demonstrating their versatility as potential platform chemical. During the synthesis of HMMF applying HCl or HBr as the acid catalysts, small amounts of the chloromethyl methyl furanoate (CMMF) and bromomethyl methyl-furanoate (BMMF) were observed. As these compounds are potentially valuable alkylating agents, their syntheses (Scheme 2) were further investigated. Starting from HMMF, HCl (5 equiv., 37% in water) or HBr (5 equiv., 47% in water) was used as the halide source giving reasonable yields of CMMF **9** and BMMF **10** (62% and 83% respectively).

As previously mentioned, HMMF and HMFA are observed intermediates in the oxidation of HMF, readily undergoing further oxidized to FCDA.[18,20] An old method is treating HMMF with $KMnO_4$ in basic water, oxidizing the hydroxymethyl to the carboxylic acid and hydrolysed the methyl ester giving FDCA **1** in one step and 75% isolated yield as an off-white precipitate after acidification. Several other oxidizing agents can be used and have already been studied for the conversion of HMF into FDCA,[18–20] where HMMF and HMFA have been observed as intermediates.[28] More modern methods include iron catalysed aerobic oxidations.[29] This protocol gave 23 % of a mixture between the mono-methyl ester and FDCA, without optimization. However, performing this oxidation on five gram HMMF **2,** we were able to isolate 42 % yield of a similar mixture.



Scheme 2. HMMF is a versatile starting material that is easily oxidized to the dicarboxylic acid or converted to its methyl halide.

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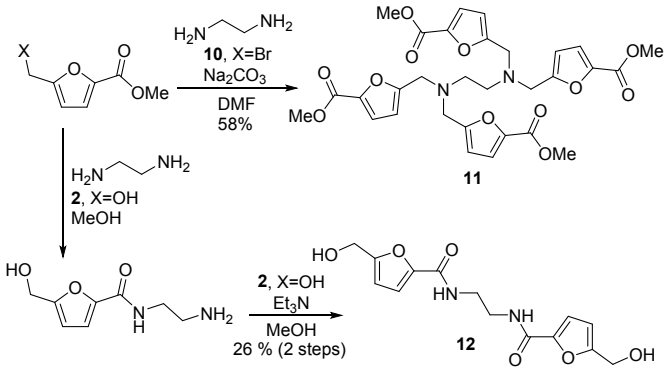

Scheme 3. Both BMMF and HMMF were converted into two potential building blocks for polymerization reaction by simple transformations with ethylenediamine.

We were able to synthesise a furane analogue of the widely used ethylenediaminetetraacetic acid (EDTA). Reacting BMMF with ethylenediamine formed the tetramethyl ester **11** in 58 % yield (Scheme 3).

One major downside to HMMF **2** and HMFA **3** is their dual functionality, a well-known problem in polymerizations. To circumvent this, most polymerization reactions use an A/B type protocol with two components, each exposing one type of functionality. Hence the interest into the dicarboxylic acid FDCA. However, reacting HMMF **2** sequentially with ethylenediamine provided the diamide **12** in 26 % yield, which fulfil the criteria exposing one type of functionality.

NMR studies

To gain insight into the transformation of gluconolactone into HMMF, time-resolved NMR-spectroscopy was used to monitor the reactions in deuterated solvents. Conversion of peracetylated gluconolactone to **4** was performed in an NMR tube containing AcOD-*d3* and NaOAc at 50°C in an ultra-sonic bath to agitate the mixture. At specific times the NMR tube was removed, cooled to rt and proton NMR recorded.

Plotting the data revealed this reaction to be first order in respect to gluconolactone (See supporting information Figure S1). The time-resolved NMR furthermore revealed that the transformation to **4** is very clean. Prolonging the reaction time revealed the formation of two new products from **4**. One of them being the double eliminated product **14** (Scheme S2). Both compounds followed zero order kinetics, whereas **4** decreased with first order kinetics (See supporting information Figure S2).

In another experiment we observed the formation of HMMF from **4**, using MeOD-*d4* as the solvent and AcCl as a source of dry HCl . The conversion of starting material followed first order kinetics, whereas the formation of HMMF was more complicated, due to the formation of several intermediates in equilibrium, including the formation of a side-product, which was observed by the time-resolved NMR (See supporting information Figure S3). The observed side-product corresponded the spectra of the double-eliminated product **14**, 2-*H*-pyranone, observed in first step of the HMMF synthesis. The formation of this side-product is complicated, as with HMMF it most likely goes through several intermediates in equilibria. Based on the NMR-experiment the pyranone side product is enough to account for most of the loss of yield in the conversion reactions of compound **4**.

Conclusions

In conclusion a highly efficient and scalable method for synthesizing hydroxymethyl furanoate derivatives from cellulose-derived biomass has been developed. This can be performed in a one-pot reaction allowing for good compliance with a broad range of reaction vessels. Most importantly, this method bypasses the unstable HMF as intermediate on the way to the industrially interesting FDCA. The key intermediate, HMMF or its acid HMFA, are both stable, storable and can be prepared in high yield from gluconolactone. The reaction sequence allow for recovery and recycling of reagents and solvents, and the final products are isolated by one single final purification.

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Conflicts of interest

MJP and CMP have filed a patent application containing part of this publication PCT WO2019/170204 A1.

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