Production of biobased HMF derivatives by reductive amination†

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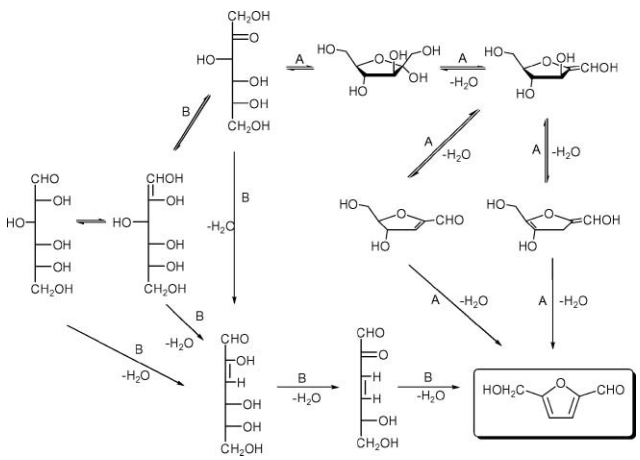
5-(Hydroxymethyl)furfural (HMF) has recently attracted a significant amount of revived attention as a renewable building block for conversion to a wide range of useful derivatives. A simple procedure for the conversion of HMF to (5-alkyl- and 5-arylaminomethyl-furan-2-yl)methanol has now been developed. Reactions were conducted without the use of a catalyst and under very mild conditions. As a proof of concept, a small library of derivatives was produced from HMF and several aliphatic and aromatic amines in high yields and requiring only minimal purification. This route presents a novel way for the production of furan-based renewable building blocks.

Introduction

With the upcoming depletion of petrochemical reserves on Earth, the chemical community is focussing on renewable resources to find or improve procedures for their conversion to useful chemicals. 5-(Hydroxymethyl)furfural (HMF) is one of the renewable building blocks with a high potential for further chemical modifications and it has recently attracted much attention by a number of research groups. An extensive review on HMF production was published by Kuster;[1] two reviews by Lewkowski[2] and Cottier and Descotes[3] incorporated both HMF production and chemistry.

HMF is obtained by acid-catalysed dehydration of hexoses, mainly fructose. Two mechanisms for HMF formation have been suggested: the cyclic A and alicyclic route B (Scheme 1). Aldoses mostly give lower yields of HMF under the same conditions than ketohexoses since an alkaline medium is required for the formation of the enol and for their further conversion to HMF. Under the conditions that work well for ketohexoses, aldoses form a stable pyranose ring and the enolisation rate is low.[1]



Scheme 1 Proposed routes of HMF formation from glucose and fructose.[1]

Agents promoting the dehydration reaction include various organic and inorganic protic acids, Lewis acids, different salts, but also heterogeneous catalysts such as ion-exchange resins and zeolites (ref. 2 and references therein). Some novel work on HMF production includes the use of different ionic liquids as promoting media for the dehydration,[4-12] the use of supercritical solvents,[13-15] two-phase optimized solvent systems,[16-19] or microwave heating.[20,21] However, in most of the published procedures that claim an improved HMF production, its separation and final purification still remain an issue. HMF is not easy to extract since the distribution coefficient between the organic and the aqueous phase is not very favourable; in accordance, the yield of HMF in the above cited work is mostly reported in solution as analysed by HPLC of both phases. In some work,[5,10,11] batch extraction was reported to be 100% efficient, however these results were not reproducible in our lab. High vacuum distillation is another option but this technique is rather energy demanding. Furthermore, under the conditions needed for its production, HMF tends to further degrade to levulinic and formic acid and other side products and to polymerize to soluble and insoluble humins. These undesirable reactions are observed primarily in aqueous medium and in concentrated solutions, and eventually cause problems during HMF purification[22] as well as during its handling and storage. The difficulties in isolating and in manipulating this interesting molecule are the major obstacles in its large-scale production and conversion.

An interesting concept of HMF isolation from the reaction mixtures is based on the formation of derivatives: a production process patented by Avantium (NL) starts from glucose and continues to HMF ethers and esters in a continuous process.[23,24] The authors suggested the use of the obtained derivatives as starting materials for the production of polymers and fuel additives. Apart from these structures, there is a range of molecules that can easily be produced from HMF and have applications in the chemical and in other industries. For example,

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2,5-furandicarboxylic acid can be successfully used as a substitute for petrochemically produced terephthalic and isophthalic acid in the production of polymers;[25,26] 2,5-di(hydroxymethyl)furan is already used in the production of polyurethane foams.[25] 2,5-Furandicarboxaldehyde is a starting material for the production of 2,5-di(hydroxymethyl)furan and of the Schiff bases used in further conversions.[25] Novel vinyl-based polymers made from HMF have recently been reported,[27] and 2,5-dimethylfuran, a potential fuel additive with very promising features has recently attracted much attention.[28,29]

In addition to this, 2-alkyl- and 2-arylaminomethylfurans are known for their wide range of pharmacological activities: they are used in medicinal chemistry as antihistaminics,[30-32] glutamate modulators,[33] glycine antagonists,[34] muscarinic agonists,[35] renin inhibitors,[36] antifungal agents,[37] kinase inhibitors[38,39] *etc.* These structures are generally produced from furfural; however, the production procedures usually include long reaction times and rather drastic temperature/pressure conditions.[40,41] The reason for this is the deactivating effect of the C_2 carbaldehyde group that makes the addition to the C_5 position of the furan ring fairly difficult.

One example of obtaining these compounds from HMF was published by Gupta *et al.*[42] Using a template directed approach and solid-phase catalysis, a library of similar heterocyclic compounds was synthesized starting from resin-immobilized HMF. In an automated synthesizer, more than fifty compounds were produced with purities of 70–92% but in rather modest yields.

Production of similar compounds from HMF was mentioned in two patents.[33,39] However, production processes involved prolonged heating in several organic solvents, addition of several equivalents of resin and/or extensive purification by preparative HPLC.

We hereby report a very simple protocol for the production of 5-aminomethyl-2-furfuryl alcohols using HMF as starting material. By using this facile and straightforward method, a small library of compounds containing a hydroxymethyl and an aminomethyl moiety on the furan ring was produced (Fig. 1).

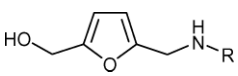
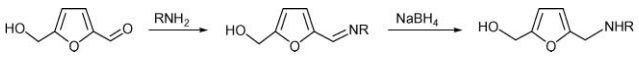


Fig. 1

Surprisingly and to the best of our knowledge, most of these simple structures were never described before. These amines can serve as starting materials for a wide range of conversions[43] and be particularly useful in the above mentioned production of pharmaceuticals. This method is also based on a renewable molecule (HMF instead of furfural) but, (a) it does not necessarily involve any particular conditions of pressure, temperature or catalyst, (b) it is based on readily available reagents and reaction media and (c) demands a minimal work-up. Water, ethanol and methanol were used as reaction media and they worked well without the addition of catalysts. Beside the starting materials, a reasonably mild and cheap reducing agent (sodium borohydride) was used. Mild conditions of room temperature and atmospheric pressure were initially applied and minimal purification of the product was necessary (additional purification was performed routinely but simple extraction and solvent evaporation already gave a product purity >95%).

Results and discussion

Our work was based on a one-pot, two-step reductive amination, thus without the purification of the intermediate imines (Scheme 2). By the choice of reaction media we have attempted to increase the sustainability of this process. Water is the most abundant, the cheapest and environmentally most benign solvent,[44] whereas ethanol and methanol can be obtained in a sustainable way by biomass fermentation.[45,46] Of course, a somewhat negative aspect of using water as reaction medium is the difficult and costly purification, which may lead to additional costs.



Scheme 2 Schematic production route of the HMF based amines.

The mild reaction conditions are essential to prevent breakdown of HMF and to obtain a reasonable yield of the end product.

Reductive amination is a widely used tool in organic synthesis and is mostly performed in two steps: the production of aldimines followed by the *in situ* reduction with sodium borohydride.[47]

Schiff bases of aromatic aldehydes are easily obtained by condensation with amines. The chemistry of this process involves the elimination of water from an intermediate amino alcohol. Water elimination is thus usually aided by various means, such as magnesium or calcium sulfate,[48] molecular sieves[49] or azeotropic distillation with a suitable organic solvent.[50] On the contrary, Simion *et al.*[51] reported a simple procedure for the reaction between various aldehydes and amines to form a range of imines in aqueous medium. Reactions were conducted in the absence of a catalyst during short reaction times at room temperature and gave excellent purities and generally good yields of the resulting imines.

Following this approach, a number of reactions were performed using aqueous solutions of HMF to yield several imines. The imines are then reduced to the corresponding amines with sodium borohydride in a one-pot reaction. Generally this procedure gave very good results in reactions with aliphatic amines (Table 1). Complete conversion to the imines was obtained within several hours and the imine reduction was generally completed after one hour.

However, conversions of aromatic imines did not proceed easily in aqueous medium: conversions up to 50% were observed after several days. Therefore, other reaction media were tested. Methanol was suitable for several reasons: it is a good solvent for both starting materials, a preferred solvent for reductions with borohydride and is easily produced in a sustainable way from renewable materials. Unfortunately, reactions in dry methanol with aromatic amines also gave poor results, similar to the reactions in water. On the other hand, the required reaction times of aliphatic amines with HMF were drastically improved: *e.g.* imine formation from allylamine and HMF took 45 minutes

Table 1 Overview of the reductive aminations

Entry	R	Solvent	Reaction time step 1	Reaction time step 2	Yield	Chromatographical purification
1		H_2O	5h	1h	92%	MeOH–CH_2Cl_2 10/90 R_f 0.42
2		H_2O	4h	1h	80%	MeOH–CH_2Cl_2 10/90 R_f 0.12
3		H_2O	4h	1h	97%	MeOH–CH_2Cl_2 10/90 R_f 0.55
4		H_2O	4h	1h	77%	EtOAc–PE 5/95 R_f 0.45
5		H_2O	6h	1h	82%	MeOH–CH_2Cl_2 10/90 R_f 0.24
6		H_2O	6h	1h	88%	MeOH–CH_2Cl_2 10/90 R_f 0.26
6′		MeOH	2h	30′	94%	see above
7		MeOH	1h	1h	99%	MeOH–CH_2Cl_2 10/90 R_f 0.30
2′		MeOH	45′	30′	93%	see above
8		EtOH	30h	1h	96%	MeOH–CH_2Cl_2 2/98 R_f 0.36
9		EtOH	30h	1h	86%	MeOH–CH_2Cl_2 2/98 R_f 0.22
4′		EtOH	2h	1h	96%	see above
5′		EtOH	1.5h	1h	92%	see above
10		EtOH	50h	1h	83%	MeOH–CH_2Cl_2 2/98 R_f 0.18
11		EtOH	50h	1h	91%	MeOH–CH_2Cl_2 2/98 R_f 0.30
10′		EtOH	30h	1h	83%	MeOH–CH_2Cl_2 2/98 R_f 0.18
12		EtOH	50h	1h	97%	MeOH–CH_2Cl_2 10/90 R_f 0.61

in methanol whereas reaction in water needed 4 hours for completion (entries 2 and 2′, Table 1).

Dry ethanol was the next solvent of choice. Ethanol is, similar to methanol, a good solvent for the starting materials and reagents (sodium borohydride has a limited solubility of 4 g/100 ml at 20 °C, which was still enough to perform the reactions). Acting as a water scavenger, ethanol is also assumed to increase the rate of imine formation. The reactions were repeated with aliphatic amines in ethanol as reaction medium, which again resulted in a decrease of the required reaction time: a couple of hours required for formation of the imines (entries 4′ and 5′, Table 1). Aromatic amines, however, demanded longer reaction times (up to 50 hours, entries 9-12, Table 1). Addition of molecular sieves was tested to improve the efficiency of the reaction *i.e.* to shorten the reaction time; molecular sieves of 4 Å in entries 4′ and 8, and 3 Å in entry 10′, Table 1. This approach was moderately successful as it was estimated that the reaction time was enhanced already by the solvent change and that the addition of the sieves did not have a significant influence on the reaction with an aliphatic amine (entry 4′ compared to entry 5′). By comparison of entries 8 and 9, it can also be seen that the addition of sieves did not significantly influence the reaction performance. On the other hand, in entries 10 and 10′, addition of the sieves proved to substantially reduce the reaction time from 50 to 30 hours.

Using this procedure, a small library was produced and is presented in Table 1. Reactions were followed on TLC and ^{1}H-NMR and the identity of the final products was confirmed by LC-MS, ^{1}H- and ^{13}C-NMR, IR spectroscopy and elemental analysis where possible.

For comparison, tetrahydrofuran was also tested as a medium for the reaction with aromatic amines but the conversion to the imine was poor compared to ethanol (up to 40% *vs.* >99% conversion).

Table 2 Reactions conducted under conventional and microwave heating

Entry	R	Solvent	Time	Temperature	Heat source	Conversion to imines
5a		H_2O	5′	50 °C	Microwave	100%
5b		H_2O	15′	50 °C	Conventional	100%
6a		H_2O	15′	50 °C	Conventional	100%
11a		EtOH	1.5 h	40 °C	Microwave	50%
11b		EtOH	6h	100 °C	Microwave	65%
11b		EtOH	6h+24 h	100→–20 °C	Microwave→none	85%
11c		H_2O	2h	100→200 °C	Microwave	70%
12a		EtOH	20′	40 °C	Microwave	65%
12a		EtOH	1 h	40→100 °C	Microwave	70%
12b		EtOH	72 h	–20 °C	None	80%

In the first step of the reaction (the imine formation), a significant difference in the reactivity of amines was noticed. A decreasing reactivity order can be determined: aliphatic amines > aromatic amines with electron donating groups > aromatic amines > aromatic amines with electron withdrawing groups (the experiments with aromatic amines containing NO_2 and Cl substituents did not yield more than 30% conversion compared to the corresponding imines in 24 h and therefore the further procedure was abandoned).

In an additional attempt to reduce the reaction time necessary for imine formation, reactions were conducted under microwave heating, as microwaves were shown to enhance this type of reaction[52,53] (Table 2).

Reactions were followed by ^{1}H-NMR and HPLC. It was noted that microwave heating indeed resulted in a drastic improvement of the iminations with aliphatic amines (down to 5 minutes at 50 °C, entry 5a). However, conventional heating gave similar results—complete conversion to imines in a matter of minutes (entries 5b and 6a). On the other hand, mild microwave heating did not give such positive results in trials with aromatic amines (entry 11a). Nevertheless, the pressurised vessel in the microwave synthesizer allowed reactions at temperatures higher than the boiling point of the solvent. Reactions performed at 100 °C (in water and ethanol) and 200 °C (in water) resulted in improved conversions (entries 11b and 11c). It is noted that, due to the high absorbing nature of ethanol, the energy required to reach this temperature (100 °C) was only 1-2 W during the reaction. For reactions in water, temperatures of 100 °C were achieved and retained by the use of 10-20 W power. Maximal power of the reaction setup (200 W) was used only during heating of the reactions to 200 °C in water.

Microwave heating did improve the reaction rate of the imine formation; however, using the times mentioned in Table 2, no complete conversions were observed. Moreover, under the prolonged heating, HMF tends to degrade to humic substances (these were noticed as black insoluble accumulations in the reaction mixture).

It is also important to notice the formation of imines on simple standing at –20 °C in the freezer for prolonged periods. In entry 11b, a 6 hours microwave irradiated reaction was kept for 24 hours in the freezer which resulted in an additional conversion to imine, up to 85% (estimated by HPLC). Similarly, in entry 12b, a significant conversion was noted without any prior heating, on standing at –20 °C during 72 hours. Obviously, the reaction time is a very important factor in these conversions, apart from the reaction temperature.

Considering the production issues elaborated in the first part of the article and following some unpublished work previously performed in our lab, the feasibility of performing the reductive amination *in situ* from HMF precursors was tested. Motivated by the fact that HMF can be produced in acidic media from hexoses, preliminary experiments were performed on HMF in acidic media (aqueous solutions acidified by citric or levulinic acid to a pH of 2–4). Under these conditions, conversion to the imine took a longer time (85% conversion in 5 hours for a test reaction with benzylamine) but was successful. Unfortunately, when the production of HMF from fructose in acidic aqueous media was followed by a one-pot conversion to the imine, the

resulting reaction mixture contained many side-products which made the purification difficult and led to a significantly lower yield.

Conclusions

A simple and convenient procedure was developed for the production of several novel as well as known aminomethylfurans starting from HMF, a promising renewable building block. This procedure can be utilised to produce a number of building blocks for the chemical and pharmaceutical industry. Use of water as the reaction medium, as well as the biobased solvents ethanol and methanol improves the sustainability of the reaction. Conventional and microwave heating resulted in an increase of the reaction rate but increased the energy demand of the process. In most cases a simple extraction provided derivatives of sufficient purity. The formation of these derivatives from sugars (precursors of HMF) was unfortunately not successful.

Experimental section

Methanol was dried over molecular sieves (4 Å) and fractionally distilled. Ethanol was dried over CaO, refluxed and fractionally distilled.

The reaction materials, including organic solvents for the reactions or for the work-up were purchased from Sigma-Aldrich and Acros Organics and used as such, except for these mentioned above.

Microwave-assisted reactions were performed on a CEM Discover BenchMate synthesizer with a IR temperature sensor. High-resolution ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Jeol JNM-EX 300 NMR spectrometer. HPLC analysis of the reaction mixtures and the final products was performed on an Agilent 1200 series HPLC equipped with a UV/Vis DAD detector at 254 and 280 nm, on a Zorbax Eclipse XBD-C18 4.6 × 150 × 5 µm RP column. Low-resolution mass spectra were recorded with an Agilent 1100 Series VS (ES = 4000 V) mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. All compounds were analysed in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points of the solid compounds were measured with a Büchi 540 apparatus and have not been corrected. Elemental analysis was performed on a Perkin-Elmer 2400 Elemental Analyzer. Additional purification of the reaction mixtures was performed by column chromatography in a glass column on silica gel (Acros, particle size 0.035–0.070 mm, pore diameter *ca.* 6 nm).

Procedure in water

In a 50 ml round-bottom reaction flask, 300 mg of HMF (2.3 mmol) and 1.1 eq of primary amine were stirred in 10 ml of deionised water at room temperature. Conversions were complete within several hours. After the imine formation, 1.5 eq of sodium borohydride were added to the reaction mixture and the reaction mixture was stirred for an hour. The resulting amine was extracted with 3 × 15 ml of diethyl ether. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. This procedure gave purities of 95% of the resulting amines (determined by ^{1}H-NMR). Additional purification was performed by column chromatography, resulting in high yields of isolated material in all cases.

Procedures in methanol and ethanol

In a 50 ml round-bottom flask, 1.1 eq of primary amine was added to ~300 mg of HMF (2.3 mmol) in 10 ml of alcohol, and the reaction mixture was stirred under a nitrogen flow at room temperature (exact values are reported in Table 1). In entries 4′ and 8, ~1 g of molecular sieves 4 Å was added to the reaction mixture. In entry 10′, ~1 g of molecular sieves 3 Å was added to the reaction mixture. After the reaction was complete, the resulting imine was reduced by addition of 1.5 eq of sodium borohydride for generally one hour. The alcohol was then evaporated and to the resulting dry mixture 1 ml of water was added. The final product was extracted with 2 × 15 ml of dichloromethane. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. This procedure gave purities over 95% of the resulting amines (determined by ^{1}H-NMR). The products were additionally purified by column chromatography and characterised.

Reactions performed under microwave heating

In a 10 mL sealed vessel 1.1 eq of primary amine was added to ~150 mg of HMF (~1.16 mmol) in 5 ml of solvent (water or ethanol). Reactions were followed by HPLC and ^{1}H-NMR.

Reactions performed under conventional heating

In a 25 ml round-bottom flask, 1.1 eq of primary amine was added to ~150 mg of HMF (1.16 mmol) in 5 ml of solvent (water or ethanol). Reaction mixtures were heated in an oil bath and followed by HPLC and ^{1}H-NMR.

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