Invited paper

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Synthetic approaches to 2,5-bis(hydroxymethyl)furan (BHMF): a stable bio-based diol

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Abstract: Biorefinery is defined as a sustainable process where biomass is converted in a spectrum of marketable products and fuels. In this view, C6 furan-based compounds, usually referred as furanics, have been extensively investigated as aromatic promising building blocks from renewables. 5-Hydroxymethylfurfural (HMF) and 2,5-furan dicarboxylic acid (FDCA) are well known examples of furanics whose syntheses and applications have been extensively reviewed in the literature. Herein for the first time it is reported a comprehensive overview on the synthetic procedures to another bio-derived furan compounds, i.e. 2,5-bis(hydroxymethyl)furan (BHMF), a stable bio-based diol with numerous applications as monomer for bio-materials and fuels. Advantages and limitations of the different synthetic approaches are addressed, as well as possible future developments to render this compound part of the biorefinery market.

Keywords: 2019 IUPAC-Zhejiang NHU International Award; bio-based diol; bio-based platform chemicals; biorefinery; furanics; green chemistry.

Introduction

The ever-increasing threats to our ecosystem by petroleum-based derived compounds, materials, and fuels in combination with the current oil-reserve depletion have inspired numerous scientists to focus on biorefinery with the ultimate intent to substitute petrorefinery chemicals with biomass alternatives. In this view C6 furan-based compounds (Fig. 1), also called furanics, have been extensively investigated in the last 10 years as promising building blocks from renewables [1, 2].

Among furanics, 5-hydroxymethylfurfural (HMF) **1** has received considerable attention [3]. This compound can be synthetized in different yields depending on the reaction conditions and starting material employed (cellulose or simple C6 sugars such as fructose and glucose) [4, 5]. HMF is a versatile substrate that incorporates hydroxyl, furan, and aldehyde units all of which can be easily further modified (Fig. 1) [6]. However, there are some well-known limitations that prevent this furan-base structure to be exploited at its full potential, i.e., high cost, stability issues – partially solved by the addition of small amount of a stabilizer – and high sensitivity towards acids, bases and oxygen [7].

As a result, 2,5-furan dicarboxylic acid (FDCA) **4** [8, 9], HMF oxidized derivative, is nowadays considered a more marketable compound in consideration of its greater stability and potential applications as bio-alternative of petroleum-derived terephthalic acid in the production of sustainable polymers, such as poly (ethylene 2,5-furandicarboxylate) (PEF) [10].

Article note: A collection of peer-reviewed articles by the winners of the 2019 IUPAC-Zhejiang NHU International Award for Advancements in Green Chemistry.

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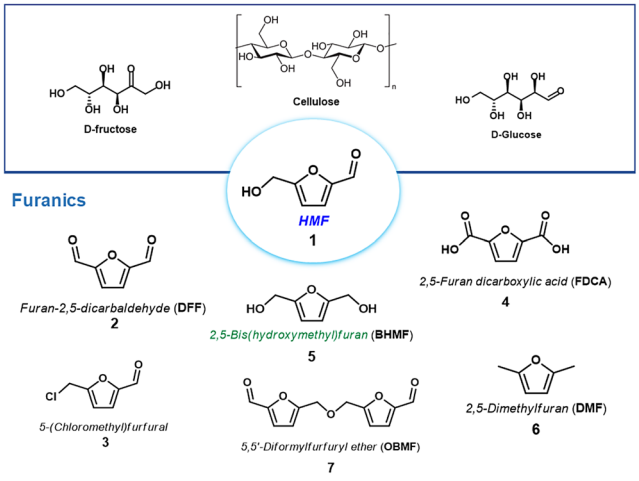


Fig. 1: Examples of furanic compounds (**2-7**) derived from HMF **1**.

More recently, 2,5-bis(hydroxymethyl)furan (BHMF) **5**, another HMF derivative, is gaining increasing attention. This compound, mainly prepared via HMF reduction, has started to be widely investigated as chemical intermediate [11–22], bio-fuel precursors [23–33] and monomer for polymers [34–41] or macromolecules [42–44].

In this review, it is reported for the first time a comprehensive summary of BHMF synthetic approaches so far developed; easy access to the pure product and scalable procedures are highlighted.

BHMF synthetic approaches

Table 1 reports the list of the synthetic procedures published in either scientific journals or patents for the preparation of 2,5-bis(hydroxymethyl)furan; amount of the starting material, reaction conditions, catalyst recycling and product yield are outlined.

BHMF synthetic approaches can be divided into five main categories: (i) metal catalyzed selective hydrogenation (#1–17; Table 1); (ii) hydrogen transfer reaction (#18–22; Table 1); (iii) Cannizaro reaction (#23–25; Table 1); (iv) integrated approaches starting from simple (poly)carbohydrates (#26–32; Table 1) and (v) miscellaneous syntheses (#33–34; Table 1). In consideration of their simplicity, HMF hydrogenation via commercially available reducing agents (mainly $NaBH_4$) [45–56] will not be discussed unless included in an integrated approach.

BHMF via metal catalyzed selective hydrogenation reaction

Numerous metal-based catalytic systems have been investigated for the synthesis of BHMF via selective hydrogenation reaction; in most of the cases studied HMF was the preferred substrate (Scheme 1).

Although the majority of the catalytic systems utilized are heterogenous, some efficient homogeneous systems have also been described. As an example, a homogenous ruthenium pincer complex – generally employed as hydrogen-transfer catalyst – was demonstrated to be capable of converting HMF into BHMF in quantitative yield [47]. In the best-found reaction condition 0.01 mol% (100 ppm) of the ruthenium catalyst (Scheme 1) was used; BHMF was isolated after quick filtration on a silica gel pad.

Recently the first hydrogenation of esters employing a homogenous manganese pincer complex was also reported. This catalytic system enabled the high yielding reduction of FDCA diethyl ester, namely diethyl 2,5-furan dicarboxate, to BHMF in 99 %, although the reported isolated yield was only 58 % [48].

Heterogeneous catalysts were the preferred choice for the selective HMF hydrogenation reaction as they can be more easily recovered from the reaction mixture and eventually recycled. In this view, Dumesic and co-

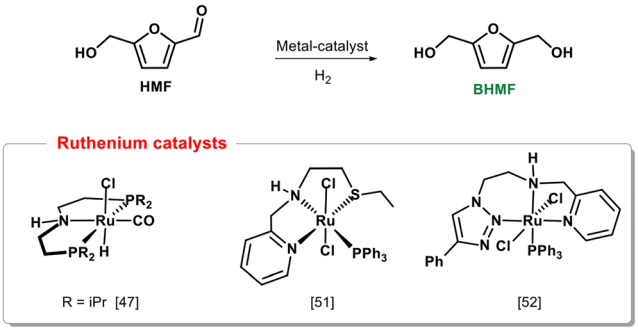
Table 1: BHMF main synthetic procedures.

	Entry	Starting material	Reaction condition	BHMF yield	Cat. recycling	Refs.
Metal-catalyzed selective hydrogenation	1	HMF (1.0 g)	Ru-pincer cat (2 mol%), NaOEt, EtOH, H_2 30 bar, 25 °C.[a]	99 %		[47]
	2	FDCA (0.15 g)	Manganese pincer complex (3 mol%), H_2 30 bar, 1,4-dioxane, 24 h, 110 °C.	99 % (58 %)[b]		[48]
	3	HMF (0.4 g)	Ru supported on Mg–Zr (200 mg), H_2 30 bar; H_2O/BuOH; 130 °C; 2 h.	94 %		[49]
	4	HMF (0.5 g)	5 wt% Ru/C (1 wt%), H_2 30 bar, T = 50 °C 4 h.	93 %	3 runs	[50]
	5	HMF (1.0 g)	$Ru(NNS^{Et})(PPH_3)Cl_2$ (0.5 mol%); KOBut, iPrOH, H_2, 30 bar, 80 °C.[a]	93 %		[51]
	6	HMF (0.25 g)	$RuCl_2(NNN)(PPh_3)$ (0.05 mol%), KOtBu, H_2 10 bar THF, 80 °C.[a]	52 %		[52]
	7	HMF (0.1 g)	$Ru(methylally)_2COD$ (1%), Bispyridine, H_2 10 bar, toluene,120 °C, 16 h.[c]	98 %		[53]
	8	HMF (0.2 g)	Cu-Ni/γ-Al_2O_3 (0.5 g), H_2 30 bar, THF, 130 °C, THF, 6 h.	61 %	3 runs	[54]
	9	HMF (1.0 g)	CuZnO (0.3 g), Dioxane, H_2 30 bar, 220 °C; 0.5 h.	92 %	5 runs	[55]
	10	HMF (1 wt% in water)	Flow 0.05 mL min^{-1}, RANEY® Cu, 90 °C, H_2 90 bar.[d]	79 %		[56]
	11	HMF (0.5 g)	10% Pd/C, H_2O, 1 bar H_2, 60 °C.	46 %		[57]
	12	HMF (0.15 g)	Pd/C (5 wt%); H_2 50 bar, 20 h, 80 °C.	71 %		[58]
	13	HMF (0.13 g)	Pt/Al_2O_3 (0.25 mol%), H_2 15 bar, EtOH, r.t., 18 h.	85 %		[59]
	14	HMF (0.5 g)	Pt/MCM-41 (20 wt% ratio), H_2 8 bar; H_2O, 35 °C, 2 h.	98 %	6 runs	[60]
	15	HMF (0.13 g)	Au/SiO_2 (0.01 mmol), 2,4,6-trimethylpyridine, H_2 6 bar, iPrOH, 100 °C, 24 h.	99 %	5 runs	[61]
	16	HMF (63 mg)	Co@C catalyst (HMF/cat mol ratio 3.1), 110 °C, H_2 20 bar.[e]	99 %	2 runs	[62]
	17	HMF (0.2 g)	$NiRe_2$ (10 mg), H_2 50 bar, H_2O, BuOH, 40 °C, 4 h.	72 %		[63]
Hydrogen transfer	18	DFF (30 mg)	$Ru(PPh_3)_3Cl_2$ (0.025 mmol), HCOOH, Toluene, 90 °C, 2 h.	99 %		[64]
	19	HMF (5.0 g)	Ru pincer complex (HMF/Cat 20 000), NaOiPr, iPrOH 82 °C, 10 min.	90 %		[65]
	20	HMF (0.1 g)	$ZrSi_3$ (100 mg), iBuOH, N_2, 120 °C.	86 %	[f]	[66]
	21	HMF (0.12 g)	Hf–LigS catalyst (100 mg) iPrOH, 100 °C, 1 h.	90 %	10 runs	[67]
	22	HMF	Au-Cu/CeO_2, 2-butanol via continuous gas phase apparatus.	n.r.		[68]
Cannizaro react.	23	HMF (12.0 g)	NaOH, H_2O, 18 h.	85 %		[69]
	24	Acetoxymethylfurfural ([a] 0.47 g; [b] 1.2 g)	1) $NaBH_4$, MeOH; 2) NaOH 5N.	(a) 92 % (b) 86 %		[70]
	25	HMF (0.1 g)	NaOH aq., H_2O, solution, $Na_2S_2O_4$.	96 %		[71]
Integrated approaches	26	D-fructose (0.18 g)	1) [BMIm]Cl 130 °C 20 min; 2) H_2O, 5% Ir/TiO (0.05 g), H_2 60 bar, 50 °C 3 h.	71 %		[72]

Table 1: (continued)

	Entry	Starting material	Reaction condition	BHMF yield	Cat. recycling	Refs.
	27	D-fructose (10.0 g)	1) Amberlyst-15 (1 g), TEAB, DMC; 2) $NaBH_4$ (1.2 eq.), THF, r.t., 12 h.	66 %		[73]
	28	Inulin (0.13 g)	1) KBr (30 mol%), H_2SO_4; MW 150 °C 3 min; 2) $NaBH_4$. iPrOH.	64 %	2 runs	[74]
	29	D-fructose (0.25 g)	Cp*Ir(TsDPEN) (0.5 mol%); HCOOH, NaOH, THF, 40 °C.[g]	99 %		[75]
	30	D-fructose (15 g)	Cu(60)–SiO_2 catalyst (0.5 g), BuOH, 15 bar H_2, 100 °C, 4 h.	86 %	5 runs	[76]
	31	D-fructose (0.28 g)	USY@ZrCP (0.05 g), 2-PrOH, reflux 6 h.	83 %[h]	6 runs	[77]
	32	D-fructose (0.3 g)	1) NbP (D-fructose/Cat weight ratio = 4), H_2O, MIBK, 160 °C, 3 h; 2) 20CA (20 mol% Cu-Al_2O_3), H_2 130 bar.	58 %	4 runs	[78]
Miscell.	33	Furfuryl alcohol (11.3 g)	*n*-BuLi (2.2 eq.); HCOH; THF −78 °C.	96 %		[79]
	34	DFF (0.12 g)	PhSiH 2, 5 mol% Cs_2CO_3, MeTHF, 25 °C; then EtOH, 80 °C, 2 h.	87 %		[80]

[a]Catalyst structure depicted in Scheme 1; [b]Isolated yield; [c]COD = Cyclooctadiene; [d]Continuous-flow hydrogenation reactor was an H-CUBE® model; [e]Co@C catalyst was prepared by hydrothermal decomposition of a Co-EDTA complex at 450 °C; [f]Recyclability of the catalyst is mentioned although no evidence are reported. [g]TsDPEN = N-tosyl-1,2-diphenylethylenediamine; [h]Yield refers to 2,5-bis(isopropoxymethyl)furan.



Scheme 1: Selective hydrogenation catalyzed by Ruthenium pincer catalysts.

workers investigated a water/butanol biphasic system where ruthenium supported on carbon (or on various oxides) was used as catalyst. Although the scope of this investigation was the fully reduced compound 2,5-dihydroxymethyltetrahydrofuran (DHMTHF), formation of BHMF **5** in high yield was observed at low reaction time (2 h) in the presence of ruthenium supported on magnesia–zirconia (Mg–Zr) [49]. The reactions were conducted at 130 °C and in a rather small scale.

Commercial catalyst, Ru/C (1 wt%) also demonstrated to be effective in the hydrogenation of HMF dissolved in an aqueous solution (2–3 wt%) [50]. Interestingly it was showed that by tuning the reaction temperature it was possible to achieve either BHMF or the fully reduced DHMTHF in good yields (93 and 95 %, respectively).

Similar ruthenium (pincer) catalysts also showed a good to excellent efficiency in HMF conversion to BHMF [51–53]. Chemical structures of representative Ru-pincer catalysts are depicted in Scheme 1; specific reaction conditions and related BHMF yields are outlined in Table 1.

Copper-based catalysts have been extensively investigated for reduction of the HMF aldehydic group. A series of alumina-supported copper-nickel catalysts was reported by Parikh et al. These catalytic systems were prepared by impregnation method, fully characterized and the role of Cu/Ni ratio on the hydrogenation of HMF

(and furfural) was studied in details [54]. HMF conversion reached the maximum value (70 %) when Cu-Ni/γ-Al_2O_3(Cu/Ni = 1) was employed as catalyst at 130 °C in the presence of hydrogen; BHMF selectivity was ca 88.4 %. This result was attributed to the effect of the highly dispersed Cu species although it was observed that the Cu-Ni catalytic system also caused some decarbonylation of HMF as traces of furfuryl alcohol were also visible in the reaction mixture. The reaction temperature was determinant in driving the selectivity; at lower temperature (130 °C), BHMF **5** was the major product, meanwhile, at higher temperature (200 °C) further hydrogenolysis occurred leading to the formation dimethyl furan (DMF) **6**.

In another study, a new CuZnO catalystd – prepared via the wet impregnation method – showed an excellent efficiency in reducing HMF to BHMF in 93 % yield although the energy demand was quite high, i.e., the reaction was carried out at 220 °C [55].

An interesting HMF hydrogenation was reported using a continuous-flow hydrogenation reactor (H-CUBE®) in combination with commercially available cartridge catalysts including heterogeneous RANEY® catalysts (Ni, Cu) [56]. The reactions were performed using aqueous solutions of HMF (1wt%) as feeding solution in mild reaction condition (90 °C, 90 bar H_2). Among the cartridge catalysts used RANEY® Cu showed a good efficiency in converting HMF to BHMF (conv. 94 %; selectivity 84 %). The final scope of this investigation was to develop a one-step procedure to achieve 2,5-bis(hydroxymethyl)tetrahydrofuran directly from HMF.

Several studies reported in the literature also showed the possibility of very simple HMF hydrogenation procedure using Pd/C in water or alcohol media; BHMF yields ranged from mediocre to good [57, 58].

Precious metal catalytic systems showed high efficiency in BHMF preparation. In particular, Pt (or Pt/Sn) supported on Al_2O_3 [59] and Pt/MCM-41 [60] under hydrogen pressure, allowed a quick reduction of HMF to BHMF in 85 and 98 % yield respectively. When Pt/MCM-41 was used as catalyst, the reaction was conducted in aqueous media and the conditions were very mild (35 °C, H_2 8 bar, 2 h) although no information was reported for the isolation of BHMF as pure product from the reaction mixture.

Some studies have been also reported on gold catalysts; several bio-based aldehydes, included HMF, have been reduced employing Au nanoparticles in the presence of a Lewis bases (2,4,6-trimethylpyridine); conversion and selectivity toward this diol were almost quantitative (99 %) [61]. In the same study it was demonstrated that a gold catalyst embedded in N-doped carbon (Au@N-doped carbon/TiO_2) was a very efficient reducing catalyst as it could be recycled up to five times.

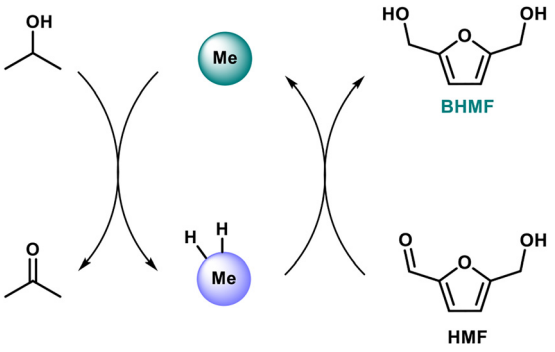
Monodisperse metallic Co nanoparticles with a thin carbon shell (Co@C) showed high activity in the conversion of HMF to BHMF [62]. Interestingly the scope of this investigation was to couple HMF reduction with an enzymatic esterification by lipase to produce biobased plasticizers as candidate substitutes of phthalates.

Finally, Hensen and co-workers [63] reported an interesting approach to HMF reduction using as catalytic system nickel–rhenium supported on TiO_2. To overcome HMF stability issue, mainly due to the aldehyde group, the authors developed an approach based upon the protection of the formyl group with 1,3-propanediol. Hydrogenation was then carried out using the novel catalytic system Ni–Re supported on TiO_2. The reduction was performed in aqueous media and mild temperature (40 °C); careful control of the pH allowed both deprotection and hydrogenation leading to BHMF in high yield (72 %).

BHMF via metal catalyzed hydrogen-transfer reaction

Another metal-catalyzed approach to BHMF is based upon intermolecular hydrogen-transfer reaction where unsaturated bonds are reduced by a combination of hydrogen donors and an appropriate (metal) catalyst via Meerwein–Ponndorf–Verley (MPV) reduction (Scheme 2) [81].

In these procedures, alcohols are generally used as hydrogen donors, although in one of the first example reported for BHMF synthesis, formic acid was used instead, furan-2,5-dicarbaldehyde (DFF) **2** was the starting material and $Ru(Ph_3)_3Cl_2$ the selected catalyst [64]. In this case the hydridic lability of the C-H bond in formic acid was ascribed to the stability of carbon dioxide formed as consequence of the oxidation reaction that takes place simultaneously to DFF **2** quantitative reduction to BHMF (99 % yield).



Scheme 2: Catalytic cycle for transfer hydrogenation of HMF with a generic alcohol.

Similarly, Baratta and co-workers reported a robust ruthenium-based pincer complex that showed a remarkable transfer hydrogenation ability for several bio-based carbonyl compounds. Reactions were conducted using 2-propanol as hydrogen donor at reflux temperature (*ca* 80 °C) in the presence of a base (NaOiPr or K_2CO_3) [65]. In this condition HMF **1** was reduced to the corresponding alcohol in few minutes using an HMF:Ru *ratio* of 20.000. The reduction was carried out also using DFF **2** as starting compounds although in this case a larger amount of catalyst was required (DFF: catalyst *ratio* was 1.000) and the reduction was complete after 1 h.

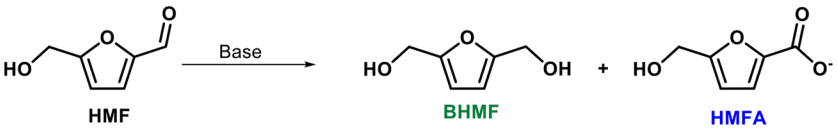
Zr/Si mixed oxides, prepared by a simple sol–gel method, were tested for transfer hydrogenation and etherification cascade processes under mild conditions [66]. The zirconia–silica catalytic systems were prepared by a sol–gel procedure where a solution (30 % in HCl) of zirconyl chloride ($ZrOCl_2$), diluted in deionized water was added dropwise to an aqueous solution of ammonia to obtain hydrous zirconia. Thus, tetraethylorthosilicate (TEOS) in a water/propanol solution was added to hydrous zirconia. The Zr/Si supports were prepared with different nominal amounts of silica (0, 3, 10, 30, and 50 wt%) named accordingly ZrO_2, $ZrSi_3$, $ZrSi_{10}$, $ZrSi_{30}$ and $ZrSi_{50}$. The role of Lewis and Brønsted acid sites was crucial for the product distribution. Previous investigations reported that Lewis acid sites promote hydrogen-transfer by MPV mechanism, while Brønsted acidity favors the hydroxyl etherification reaction. In this view when ZrO_2 or $ZrSi_3$ catalytic systems have been tested, the transfer hydrogenation leading to BHMF was the only reaction observed due to the lack of Brønsted acid sites. Conversion of HMF was for both Zr-catalysts *ca* 90 % and selectivity almost quantitative.

Qi and co-workers reported a new catalytic system prepared by coordination of metal ions (Hf^{4+}, Zr^{4+}, Fe^{3+}, Al^{3+}, Zn^{2+}) with lignosulfonate, a waste material from the paper industry. The so-formed inorganic-biopolymer hybrids (M–LigS) incorporate strong Lewis acid–base couple sites and moderate Brønsted acidic sites, the latter are due to the sulfonic groups. HMF hydrogen-transfer reaction was conducted in the presence of 2-propanol under mild reaction conditions (100 °C in 2 h) and resulted particularly effective when the hafnium–lignosulfonate nanohybrids was employed as catalyst [67]. Furthermore, the Hf–LigS could be reused up to 10 times without minimal change in the catalyst activity.

Another interesting BHMF synthesis was carried out via continuous gas phase HMF hydrogenation process employing 2-butanol as hydrogen donor in the presence of an Au-Cu/CeO_2 catalytic system [68]. The reduction was carried out in a fixed bed vertical continuous flow glass reactor at room temperature. It has been reported that hydrogen utilization of the system was very efficient although data on selectivity/yield were not indicated.

BHMF via Canizzaro reaction

An old-fashion yet interesting synthetic approach to BHMF is by Cannizzaro reaction, an aldehyde base-induced disproportionation reaction. In this procedure a molecule of aldehyde acts as a hydride donor while a second aldehyde is the acceptor; as a result, a carboxylic acid salt, i.e., 5-hydroxymethylfuranoic acid (HMFA), and an alcohol (BHMF) form simultaneously as products (Scheme 3). Since both these HMF derivatives are interesting monomers for biorefinery exploitation, Cannizzaro reaction is a rather convenient approach.



Scheme 3: BHMF via Cannizaro reaction.

In a typical reported procedure to a solution of HMF dissolved in water at 0 °C was added NaOH and the mixture was stirred while reaching room temperature [69]. After 18 h BHMF can be extracted with an organic solvent (ethyl acetate) and the residual carboxylate was recrystallized in ethanol. The BHMF:HMFA product distribution was 1:1 which is standard *ratio* for Cannizaro reaction. Similar results were achieved using acetoxymethylfurfural as starting material [70].

In an interesting additional study, it was demonstrated that to improve BHMF and HMFA isolated yields, a small amount sodium dithionite ($Na_2S_2O_4$) can be added to the starting HMF mixture as this salt showed to be a good stabilizer that slowed down HMF degradation to humin [71]. As a result isolated yields of HMFA and BHMF was improved of ca 10 % for each compound.

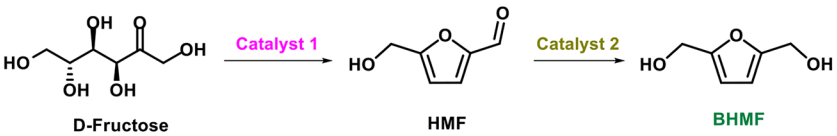
BHMF from (poly)carbohydrates via integrated approaches

The most interesting approach to BHMF, in terms of market value, would be the direct conversion of (poly) carbohydrates into this bio-based diol. Several works in this direction were reported in the literature. A simplistic yet effective approach is by two step reaction encompassing D-fructose dehydration to HMF followed by its reduction to BHMF (Scheme 4). In this view Zhang and co-workers employed commercially available ionic liquid 1-butyl-3-methylimidazolium chloride [BMIm]Cl as solvent and catalyst for the conversion of D-fructose into HMF in autoclave at 130 °C. After 20 min, the reaction was quenched with water and a metal catalyst was added to the mixture under H_2 pressure for HMF reduction to BHMF. Among the catalytic system investigated Ir/TiO_2 resulted the most effective one with an BHMF isolated yield of 71 % [72].

In a similar approach, D-fructose was first converted into HMF via a biphasic system composed by tetraethyl ammonium bromide (TEABr), employed to aid sugar dissolution, and dimethyl carbonate (DMC), used as HMF extracting solvent, in the presence of Amberlyst-15 as the acidic catalyst. Once the dehydration reaction was completed (5 h), HMF was quickly recovered by DMC evaporation and thus reduced via sodium borohydride in the presence of THF allowing the isolation of pure BHMF in 66 % yield (calculated starting from D-fructose). The reaction was scaled up to 20 g of D-fructose without affecting the diol yield [73].

Repo and co-workers reported an integrated approach to BHMF starting from inulin, a naturally occurring polysaccharides mainly composed by fructose. The first dehydration step was conducted using an aqueous H_2SO_4/KBr/dioxane system at 150 °C via microwave; thus, reduction of HMF was conducted either via Cannizaro reaction or employing $NaBH_4$. To the best of our knowledge this is – so far – one of the few procedures to employ a polysaccharide as starting material for a two-step BHMF synthesis [74].

In another methodology D-fructose conversion to BHMF was achieved employing formic acid as the catalyst for the dehydration step and subsequentially as H_2 donor for the HMF reduction in the presence of an iridium catalytic system. Interestingly the high concentration of formic acid (10 mol%), needed for HMF synthesis, was incompatible with the metal catalyst to operate the reduction step efficiently. However, when part of the formic acid was neutralized with NaOH or Et_3N, hydrogenation to BHMF took place in only 2 h and in the presence of 0.05 mol% of the Ir-catalytic system [75].



Scheme 4: Two-step conversion of D-fructose into BHMF.

A quick two-step process starting from D-fructose was developed via sugar dehydration to HMF employing Amberlyst-15 and butanol, then the resulting solution was directly subject to reduction employing a Cu(50)–SiO_2 nanocomposite. This catalytic system showed to be highly stable as no Cu leaching was detected [76].

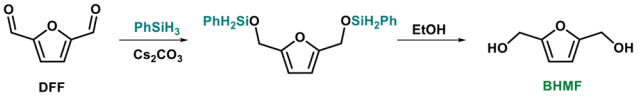
Recently, it was investigated a procedure to achieve 2,5-bis(isopropoxymethyl)furan (BPMF – a promising biofuel additive) by combining D-fructose dehydratation to HMF, catalytic transfer hydrogenation to BHMF and etherification reaction. Despite not being the focus of this review, the proposed synthetic strategy represents a very interesting integrated approach to a BHMF derivative comprising three subsequent reactions. In a first instance the authors demonstrated that Zr-based coordination polymer (ZrCP) was highly efficient catalyst for the transfer hydrogenation of HMF to BHMF. ZrCP was prepared by the coordination of Zr(IV) species and 2-methylimidazole (2-MeIM) at room temperature. The HMF reduction reaction was conducted in isopropanol at 120 °C resulting in quantitative conversion of the substrate and 95 % selectivity toward BHMF [77]. Starting from these promising results, a multifunctional USY@ZrCP catalyst was prepared assembling ZrCP with USY zeolite. This catalytic system incorporated strong Lewis acid sites, as well as Bronsted acid sites, which enabled a highly efficient one-pot conversion of fructose to BPMF by combining dehydration of fructose, MPV reduction to BHMF and its consequent etherification to BPMF with high yield (82.6 %) in short reaction time, i.e., only 6 h.

In another study, a family of copper-alumina catalysts prepared via solvent-free solid-state grinding showed to be efficient in the selective hydrogenation of HMF to BHMF [78]. Thus, an integrated process was developed for the conversion of D-fructose, D-glucose, sucrose, cellobiose, starch and microcrystalline cellulose into BHMF. The process is a two-step reaction where niobium phosphate (NbP) was used for the D-fructose dehydration to achieve HMF and the new copper-alumina catalyst was used for the reduction step to BHMF. Depending on the mono, di, and polysaccharides employed yields range from 25 to 48 %.

BHMF: miscellaneous approaches

In order to give a complete overview of BHMF possible synthetic procedures, two miscellaneous approaches should be also mentioned. In 2011 the group of Lautens published a work focusing on the preparation of bicyclo-[2.2.2]lactones via rhodium-catalyzed enantioselective approach where BHMF was one of the building blocks used. High yielding synthesis of this bio-diol was achieved by carbonyl addition into the furfural structure using paraformaldehyde in the presence of butyl lithium [79].

In 2018 Meier and co-workers developed a methodology for the reduction of dicarbonyl compounds combining relatively unexpensive Cs_2CO_3 with a hydrosilane that acts as a hydride donor. This reduction, conducted at room temperature, was efficient on numerous substrates including the furan-2,5-dicarbaldehyde (DFF) **2** that led to BHMF with 87 % (Scheme 5) [80].



Scheme 5: BHMF via sylil-mediated reduction.

Conclusion and future perspectives

2,5-Bis(hydroxymethyl)furan (BHMF) is receiving increasing attention as bio-based diol among the furanic family, sharing the spotlight with the so called “sleeping giant” HMF, and terephthalic substituted FDCA. As a result, in the last 10 years numerous synthetic procedures have been developed for the high yielding synthetises of this bio-based diol. Despite the evident efforts made by the scientific community, there are still some issues that must be addressed to render this diol more marketable. In fact, most of the above reported procedures operate in small scale (0.1–1.0 g), meanwhile continuous-flow approach for large scale production

of BHMF is still at an exploratory level. Furthermore, most synthetic procedure focuses on the reaction mechanism or on the catalyst activity without isolating the product from the reaction mixture or indicating a purification procedure.

In this view, to develop a marketable upcoming for this compound, future works should address (i) multigrams scale synthetic approach either in batch with a recyclable catalytic system or in continuous-flow, (ii) BHMF isolation and purification, the latter particular important for polymers preparations. Finally, integrated procedures where D-fructose or even better D-glucose are employed as starting materials should be preferred on a simpler HMF reduction.

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