

5-Hydroxymethylfurfural (HMF) in Organic Synthesis: A Review of its Recent Applications Towards Fine Chemicals

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Weigang Fan, Charlie Verrier, Yves Queneau, Florence Popowycz. 5-Hydroxymethylfurfural (HMF) in Organic Synthesis: A Review of its Recent Applications Towards Fine Chemicals. Current Organic Synthesis, 2019, 16 (4), pp.583-614. 10.2174/1570179416666190412164738 . hal-02193105

HAL Id: hal-02193105
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5-Hydroxymethylfurfural (HMF) in organic synthesis: a review of its recent applications towards fine chemicals

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Abstract: 5-Hydroxymethylfurfural (HMF) is a platform molecule produced from renewable carbohydrate sources such as fructose, glucose, sucrose, cellulose or inulin. Its interest as building block for accessing chemicals of industrial relevance such as monomers or biofuels has resulted in intense research on cleaner and more efficient processes for its manufacture. Its increased availability has also attracted many studies exploring its use towards value-added fine chemicals, thus widening the scope of its applications. The aim of this review is to bring an updated overview on the use of 5-HMF in fine organic synthesis, to the exclusion of already well documented platform molecules and intermediates such as 2,5-diformylfuran, 2,5-furandicarboxylic acid, 2,5-dihydroxymethylfuran, 2,5-dimethylfuran and so on.

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1. Introduction

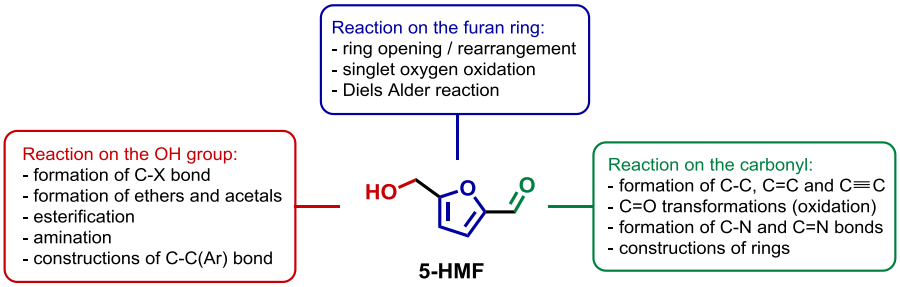
The exploitation of biomass-derived platform molecules is an increasingly developed strategy for replacing building blocks arising from petrochemicals. However, their use can be limited due to low-tonnage productions and rather high prices. In the past decades, the obvious interest of bio-based platform molecules for developing

novel chemicals, notably in the field of polymer chemistry, has generated intensive efforts for improving their manufacture processes, therefore increasing their availability due to higher scale industrial production and lower cost. A consequence of this increased availability has been a renewed interest of the chemical community to apply these bio-based building blocks in strategies towards fine chemicals also.

Among platform molecules, 5-hydroxymethylfurfural (5-HMF) appears as one of the most promising. This apparently simple molecule, obtained by dehydration of hexoses (as monosaccharides or included in oligo- or polysaccharides), incorporates an aldehyde group at the C2 position, a hydroxymethyl group at the C5 position, as well as a reactive furan ring, offering a wide range of possible functionalizations and chemical transformations. Whereas the first reports related to the formation and uses of 5-HMF appeared at the end of the 19th century, it is only in the past decades that this area has entered a boom stage, consistently with the increasing awareness of environmental concerns in the chemical community and the development of biobased chemistry. A specific character of HMF is its relative limited stability, which is a drawback both at the level of its manufacture and of its utilizations. This sensitivity to both heat and acids leads to the occurrence of degradation and undesired reactions such as dimerization or oligomerization.[1-3] Taking into account the high potential of 5-HMF, some methods aiming at improving its stability start to appear, such as the recently reported use of sodium dithionite.[4]

Several comprehensive recent reviews by Afonso,[5] de Vries[6-7] and Ananikov,[8] extensively cover the synthesis and manufacture of HMF, and/or its catalytic conversion to simple molecules such as 2,5-diformylfuran (DFF) or 2,5-difurandicarboxylic acid (FDCA). They illustrate most immediate industrial relevance and economic interests of HMF and, in a less detailed manner, its applications towards fine chemicals. The purpose of the present review article, as a complementary account to the extensive reviews previously published, is to provide an exhaustive and updated overview describing the synthetic methodologies developed around 5-HMF chemistry, in the context of fine chemicals synthesis, including multi-step and total synthesis. It illustrates the importance of the HMF scaffold as a building block in all areas of synthetic organic chemistry.

The review is organized with respect to the different chemical functions present in HMF and their reactivity. First, transformations of the aldehydic moiety of 5-HMF will be discussed, then the transformations of the hydroxymethyl group, and the modifications of the furan ring (Scheme 1). Finally, multistep and multi-functionalization sequences involving 5-HMF are shown, giving a complete exemplification of the incorporation of this platform molecule into complex chemical architectures.



Scheme 1. Overview of 5-HMF chemistry

2. Reactions on the carbonyl group

Aldehydes are essential building blocks in organic synthesis. Their high electrophilicity makes them appropriate partners for reactions with a variety of nucleophiles, allowing the formation of single, double or triple carbon-carbon bonds, but also the construction of carbon-heteroatom bonds through condensation reactions. Consequently, most of the direct transformations of 5-HMF toward high value-added chemicals take advantage of its aromatic aldehyde group.

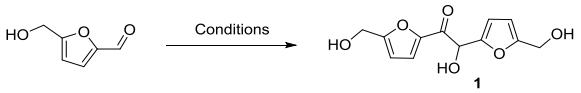
2.1 Carbon-carbon bond formation reactions

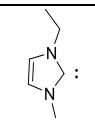
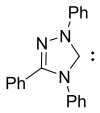
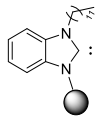
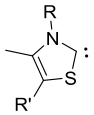
Carbon-carbon bonds are among the strongest bonds of organic chemistry, and their construction constitutes the basis of most synthetic routes toward organic molecules. Many strategies have been developed to generate new C-C bonds using the aldehydic moiety of 5-HMF, offering accesses to new bio-based compounds with various properties.

2.1.1 Formation of C-C bonds

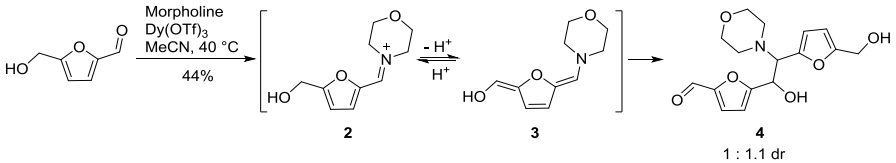
The benzoin condensation is an efficient method to upgrade HMF to C_{12} furoins as potential fuel intermediates. During the course of a study on the degradation of HMF in ionic liquids such as 1-ethyl-3-methylimidazolium acetate ([EMIM]OAc), Chen found that 1-ethyl-3-methylimidazolin-2-ylidene carbene could catalyze the self-condensation of HMF to form 5,5'-dihydroxymethylfuroin **1** with high conversion and selectivity (Table 1).[9] Since this pioneering work, several NHC catalysts derived from ILs and discrete catalysts proved their efficiency for the benzoin condensation of HMF.[10-14] Benzaldehyde lyase could also be used as a biocatalyst for this umpolung condensation.[15] However, under those conditions, a partial spontaneous oxidation to the corresponding diketone was observed.

Table 1. Organocatalysts and biocatalyst for HMF benzoin condensation



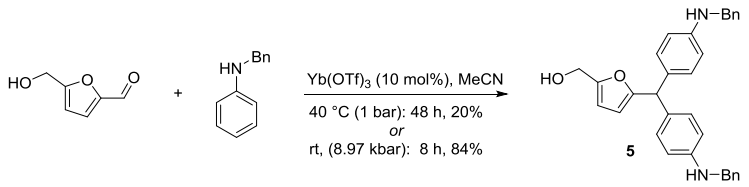
Entry	Catalyst	Conditions	Yield	Ref
1		[EMIM]OAc, 80 °C or 5 mol% [EMIM]Cl, DBU, THF, 80 °C	50% (isolated) or 97% (HPLC)	[9]
2	 TPT	0.1-5 mol% TPT, neat or in THF, 60 °C	87-95% (isolated)	[9-11]
3		10 mol% Silica-g-[BI]-C_{12} azolium salt, DBU, THF, 25 °C, 6 h	94% (NMR)	[12]
4		Thiazolium derived ILs, Et_3N, 120 °C	97-98% (NMR)	[13-14]
5	Benzaldehyde lyase	potassium phosphate buffer /DMSO, rt	70% conversion	[15]

Afonso and coworkers reported the preparation of a highly functionalized furan skeleton *via* a novel reaction pathway from 5-HMF or *O*-protected HMF and a secondary amine.[16] HMF could react with morpholine to provide the iminium intermediate **2**, which is in equilibrium with the trienamine **3** under acidic catalysis (Scheme 2). The two intermediates reacted together, releasing a molecule of amine to yield the coupling product **4**.



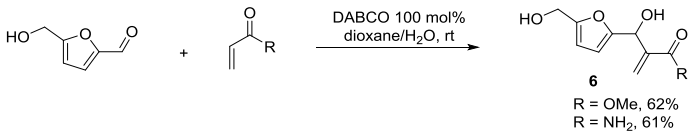
Scheme 2. Homo-bis-vinylogous Mannich-type reaction on 5-HMF

The synthesis of the symmetric triarylmethane **5** was achieved by reaction of a secondary aniline on 5-HMF in the presence of $Yb(OTf)_3$ as acidic catalyst, following a double Friedel-Crafts pathway (Scheme 3).[17] The scope of the reaction was successfully extended to *O*-substituted hydroxymethylfurfurals. The reaction was found to be significantly accelerated by applying high pressure, especially in the case of less reactive anilines. The authors considered that the first Friedel−Crafts reaction proceeded first *via* the addition of the aniline onto the iminium ion formed by condensation of the secondary aniline on the aldehyde. Then a second Friedel−Crafts reaction took place in a non-concerted mechanism suggesting a secondary carbocation as the transient intermediate for this step.



Scheme 3. Synthesis of symmetric triarylmethanes *via* Friedel-Crafts mechanism

A last type of C-C bond forming reaction with carbonyl derivatives exploiting the Morita-Baylis-Hillman reaction has been reported. The use of electron-deficient alkenes such as methyl acrylate[18] and acrylamide[19] in combination with DABCO in a dioxane/water mixture at room temperature gave access to the conjugated compounds **6** (Scheme 4). Our group more recently extended this reactivity to other solvent mixtures, including bio-based solvent, and to glycosylated derivatives of HMF.[20-21]



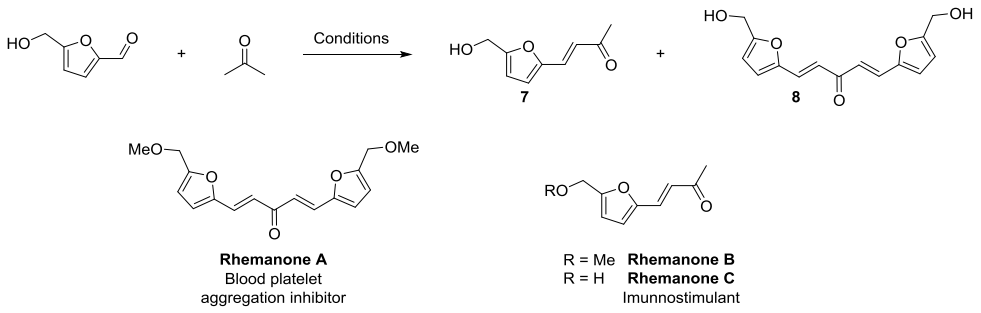
Scheme 4. Morita-Baylis-Hillman reaction of 5-HMF

2.1.2 Formation of C=C bonds

Aldol- and Knoevenagel type condensations are classical transformations of the chemistry of the carbonyl group. Aromatic aldehydes, such as HMF, are very good substrates for such reactions, due to the absence of proton on the carbon adjacent to the carbonyl (no competition possibly arising from self-condensation).

Different research groups have explored the reaction of acetone with 5-HMF under basic conditions. This transformation provides a straightforward access to the natural products rhemanones A, B and C, owning interesting biological activities such as blood platelet aggregation inhibitors or immunostimulant. The challenge relies on the control of the mono- or bis-condensation of the ketone on 5-HMF, as the monoadduct leads to rhemanone B and C, whereas bis-condensation would give an advanced intermediate for the preparation of rhemanone A (Table 2). The group of Tamariz used sodium hydroxide to promote the reaction, and a good control of the selectivity (ratio **7** *vs* **8**) was obtained by tuning the quantity of acetone used.[22] The yield of mono adduct **7** reached 91% when acetone was used in excess, whereas the di-adduct **8** was obtained in a 60 % yield when HMF was used in excess. Palkovits described a quite selective mono-condensation mediated by mesoporous magnesium aluminate as the base.[23] Roman-Leshkov reported the use of hafnium-β zeolite providing compound **7** with >99% selectively and 73% conversion.[24] Another selective mono-condensation, promoted by CO_2 under elevated pressure with a high yield, was reported by Jessop.[25] A similar yield of the mono-adduct **7** could be obtained under heterogeneous catalysis conditions using amine-grafted Faujasite (FAU) zeolite nanosheets (Table 2).[26] Zirconium carbonate was also used to promote the same condensation under mild conditions.[27]

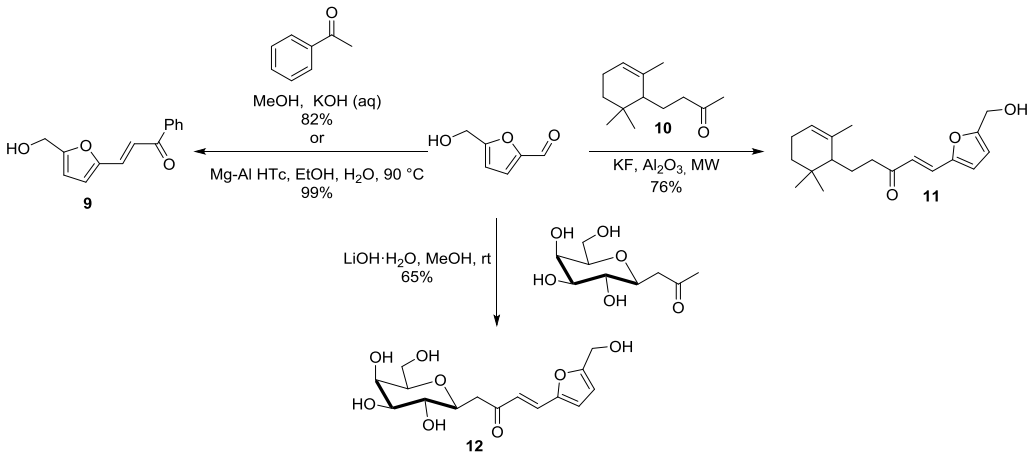
Table 2. Synthesis of the precursors of rhemanones



Entry	Conditions	Product (yield)	Ref
1	Acetone (2 eq.), NaOH (aq), EtOH, rt	**7** (91%)	[22]
2	Acetone (0.5 eq.), NaOH (aq), EtOH, rt	**8** (60%)	[22]

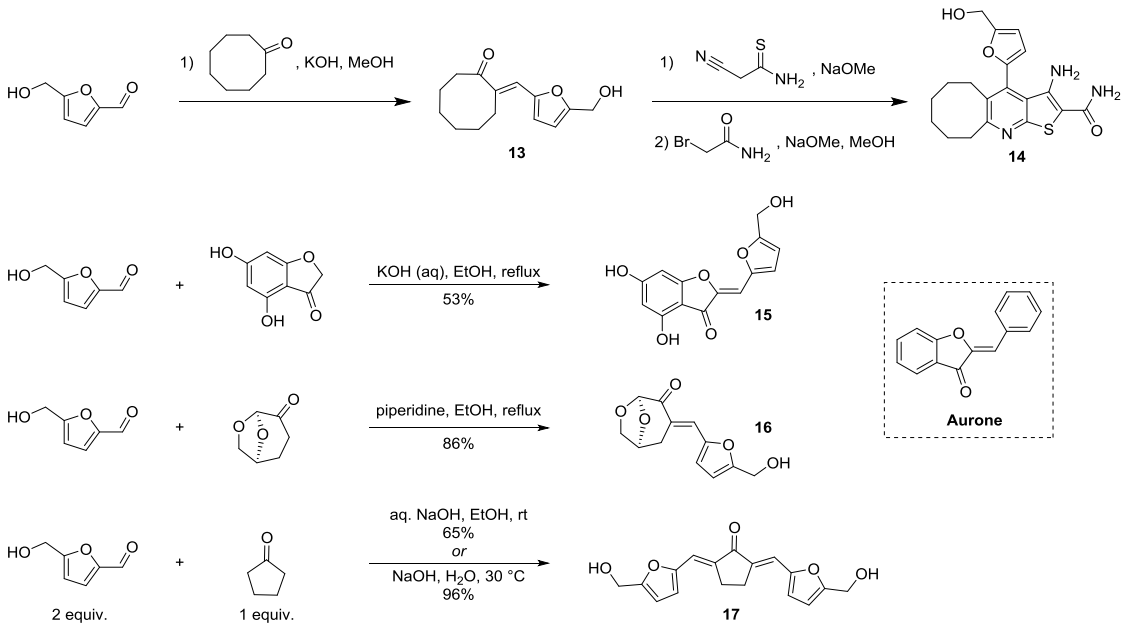
3	Acetone (as solvent), $MgAl_2O_4$, 140 °C	**7** (81%) + **8** (11%)	[23]
4	Acetone (3 eq.), Hf-Beta zeolite, toluene, 90 °C	**7** (73% conv)	[24]
5	Acetone (solvent), H_2O, 2.5 MPa CO_2, 200 °C, 20h	**7** (95%)	[25]
6	Acetone (solvent), amine-grafted FAU nanosheets, 130 °C	**7** (92% conv)	[26]
7	Acetone (20 eq.), zirconium carbonate, H_2O, 54 °C	**7** (92%)	[27]

Skowronski[28] and Corma[29] independently reported the efficient condensation of acetophenone derivatives with HMF. The reaction, promoted by potassium hydroxide in methanol, produced 5-hydroxymethyl-furfurylidene-acetophenone **9**, later named furanochalcone, in 82% yield (Scheme 5). The same transformation was also performed with almost quantitative yield in the presence of a catalytic amount of Mg-Al mixed oxide (HTc). Different 5-hydroxymethyl-furanochalcones have then been prepared following similar strategies, and evaluated for diverse biological activities such as phosphatase inhibitor[30] or synergistic antifungal.[31] The group of Surwayanshi described the preparation of enone **11** by condensation of the dihydro-α-ionone **10** with HMF under microwave irradiation using KF and aluminate as heterogeneous base.[32] The product **11** was then evaluated for its antileshmanial properties. A condensation with 1-*C*-(β-D-galactopyranosyl)-propan-2-one in the presence of lithium hydroxide was performed to prepare galactose derivative **12** in 65% yield, which proved to be an effective antimycobacterial agent (Scheme 5).[33] A *C*-4 epimer of **12** could also be prepared from 1-*C*-β-glucosylacetone in dichloromethane in the presence of pyrrolidine in 87% yield.[34]



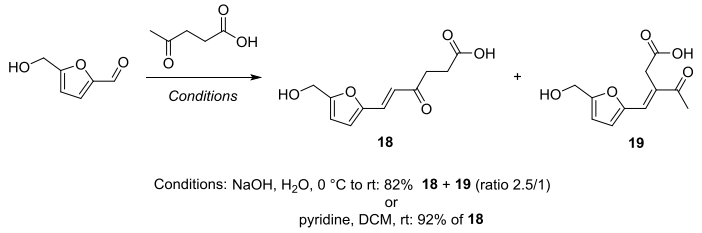
Scheme 5. Condensation with ketones

Some more elaborated ketones have been employed in aldol condensations with 5-HMF to produce molecules with high added-value. One example relies on its condensation with cyclooctanone to generate the intermediate **13**, which can be further converted into the thieno[*2,3-b*]pyridine **14**, found to be active against the elongation factor-2 kinase (eEF2-K) (Scheme 6).[35] Some benzofuran-3-ones were also condensed with 5-HMF to prepare furanic analogues **15** of aurone. The KOH-mediated aldol condensation of di-hydroxybenzofuranone with HMF provided **15** in 53% yield.[36] The microwave activation carried out in a deep eutectic solvent did not bring any improvement in terms of yield.[37] Finally, a base-catalyzed aldol condensation between dihydrolevoglucosenone and HMF was described by Witczak and Bielski.[38] Piperidine gave superior efficiency when the reaction was conducted in refluxing ethanol, providing the chiral building block **16** in 86% yield. The base-mediated double condensation of cyclopentanone on 5-HMF proved to be an efficient route toward molecule **17**. The latter has been studied as a synergistic antifungal compound,[39] but also constituted a valuable intermediate in the preparation of long-chain cycloalkanes from bio-renewable resources.[40]



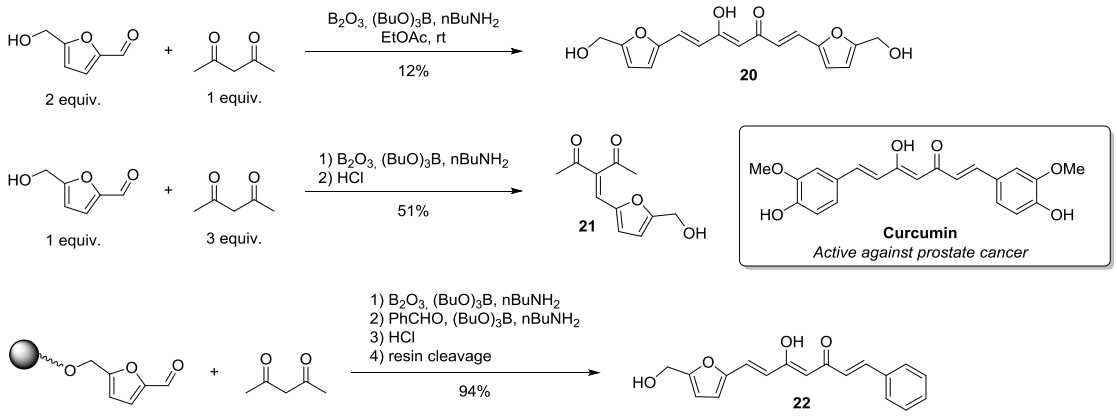
Scheme 6. Condensation on more elaborated ketones as targets in medicinal chemistry

The condensation of unsymmetrically substituted ketones bearing two enolizable positions with 5-HMF raises a problem of regioselectivity. Aqueous sodium hydroxide was employed by Amarasekara and coworkers to condense levulinic acid on 5-HMF.[41] The reaction produced a mixture of kinetic and thermodynamic products (respectively **18** and **19**) in a 2.5:1 ratio and 82% total yield (Scheme 7). This problem could be avoided by performing the reaction under pyridine/DCM conditions.[34] The condensation of 5-HMF with methyl isobutyl ketone (MIBK) in the presence of NaOH, led selectively to the corresponding kinetic enone in 95% GC yield.[42]



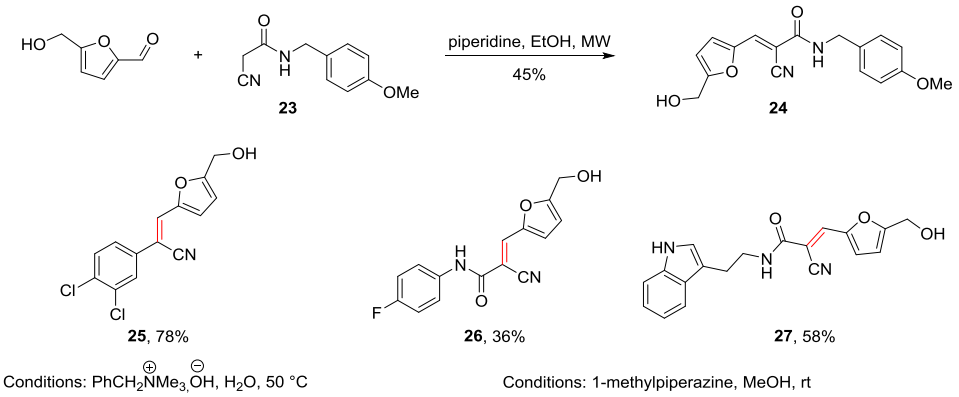
Scheme 7. Regioselective condensation on levulinic acid

The regioselective condensation of acetylacetone with 5-HMF was also studied. Acetylacetone bearing highly acidic protons at C3 position, the selective condensation at C1 and/or C5 without the formation of the Knoevenagel adduct (C3 condensation) represented a synthetic challenge and could lead to curcumin analogs (Scheme 8). A solution emerged from Lee's group[43] through a double C1 and C5 enolization in the presence of boric anhydride, tributylborate, butylamine and an excess of 5-HMF, giving the symmetrical double condensation product **20** in 12% yield. When the same reaction was carried out with an excess of diketone, the Knoevenagel adduct **21**, arising from the functionalization at C3, was obtained in 51% yield (Scheme 8).[44]
The most efficient alternative reported to date for the synthesis of unsymmetrical HMF-derived curcumin analogues such as **22**, consisted in a solid-phase synthesis strategy. Supporting HMF on a 2-chlorotrityl resin led to a significant improvement of the yield.[45] After completion of the reaction, the resin was cleaved by treatment with a mixture of DCM/TFA/MeOH, releasing the final product **22** in excellent yield (Scheme 8).



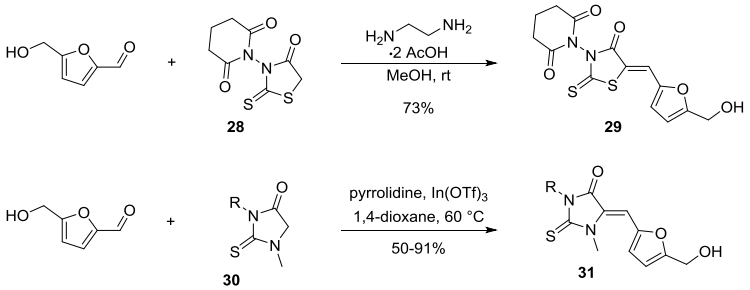
Scheme 8. Strategies for regioselective aldolisation of HMF with acetylacetone

The cyanoamide **23** was reacted with HMF to produce the cyano-acrylamide **24** under microwave irradiation in a modest 45% yield (Scheme 9).[46] McCluskey reported the reaction of dichlorophenylacetonitrile with 5-HMF under phase transfer catalysis which provided the acrylonitrile **25** in 78% yield.[47] In parallel to compound **25**, evaluated for its antitumoral properties, the two other derivatives **26** and **27** (supposed to exhibit significant anti-senile dementia activities) were prepared by condensation with the corresponding activated methylene substrates (Scheme 9).[48]



Scheme 9. Condensation of cyanoamides and nitriles derivatives with 5-HMF

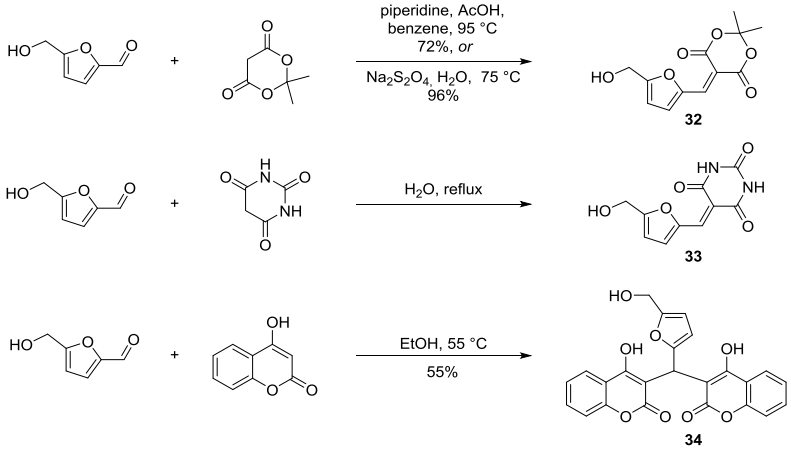
Cyclic amides such as rhodanine **28** [49] and thiohydantoins **30**[50] have been employed for the preparation of 5-hydroxymethylfurfurylidene-substituted heterocycles, designed for pharmacological tests (Scheme 10). The furfurylidene-rhodanine **29** was obtained in the presence of ethylenediammonium diacetate with 73% yield whereas the thiohydantoin **31** was formed in the presence of pyrrolidine and indium triflate as Lewis acid.



Scheme 10. Cyclic amides in the condensation with 5-HMF

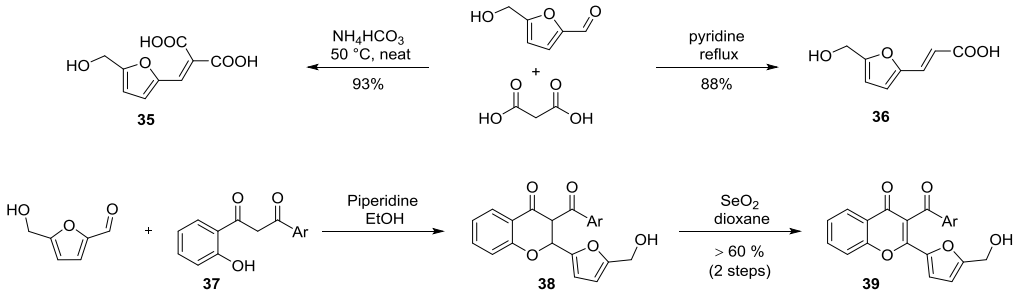
Several activated methylene compounds have been used in Knoevenagel type condensations with HMF yielding push-pull olefins which could be further used as building blocks or directly studied for their biological properties. Highly acidic cyclic 1,3-dicarbonyl derivatives such as Meldrum's acid and barbituric acid proved their efficiency, reacting with HMF smoothly. The condensation with Meldrum's acid using a mixture of piperidine and acetic acid in benzene afforded compound **32** in 72% yield, and its antitumoral and psychotropic activities

were evaluated (Scheme 11).[51] Another experimental procedure reported by Afonso referred to the use of water with 1 wt% $Na_2S_2O_4$ leading to 96% of yield of the same compound **32**.[4] The authors also reported an interesting transformation of **32** to lactone-fused cyclopentenones by treatment with various amines.[52] Nikolov carried out the condensation between HMF and barbituric acid in refluxing water, and assessed the photochemical properties of the product **33**.[53] Finally, 4-hydroxycoumarin reacted in catalyst-free conditions to produce the dimeric compound **34** in 55% yield.[54] The mono-addition led to a Knoevenagel intermediate exhibiting structural analogy with the *ortho*-quinone methide skeleton, facilitating the addition of a second molecule of 4-hydroxycoumarin (Scheme 11).



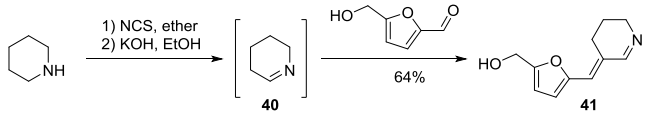
Scheme 11. Condensation of cyclic activated methylene derivatives with 5-HMF

Acyclic activated methylene compounds are also possible nucleophiles for condensation with 5-HMF. For example, the reaction of 5-HMF with malonic acid in the presence of ammonium bicarbonate without solvent at 50 ºC afforded the product **35** in 93% yield.[55] Decarboxylation took place at a higher temperature in pyridine, leading to the acrylic acid **36** up to 88% yield.[28, 34] Finally, Knoevenagel condensation of the dione **37** promoted by piperidine allowed the preparation of the dihydrochromone **38** which could be rapidly converted into the chromone **39**, a photo-activable fluorophore (Scheme 12).[56]



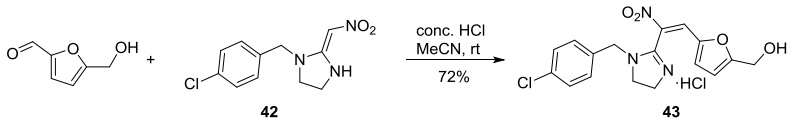
Scheme 12. Condensation of acyclic activated methylene compounds

Compound **41** was identified as a side product of the reaction between D-glucose and L-lysine under acidic conditions. In order to support the mechanism explaining its formation, a larger amount of compound **41** was successfully prepared by reaction of 5-HMF on the cyclic imine **40** (obtained from piperidine, *N*-chlorosuccinimide and potassium hydroxide) in 64% yield (Scheme 13).[57]



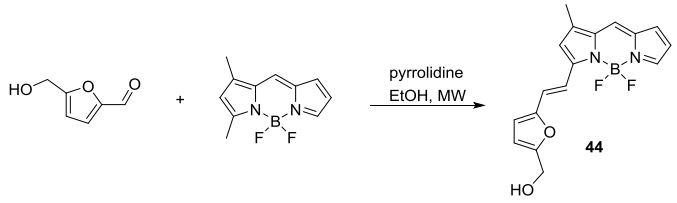
Scheme 13. Condensation of 5-HMF with compound **40**

Condensation of the diaminonitroalkene **42** on 5-HMF provided the new neonicotinoid **43** with insecticidal potency against *Nephotettix bipunctatus*, higher than imidacloprid (Scheme 14).[58]



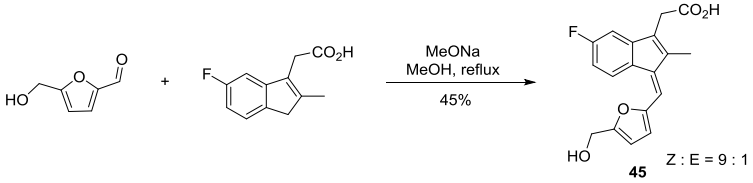
Scheme 14. Condensation of 5-HMF with enediamine **42**

The HMF-modified boron-dipyrromethene (BODIPY) **44** was prepared *via* an aldol-like condensation between HMF and 1,3-dimethyl-BODIPY in the presence of pyrrolidine under microwave irradiation (Scheme 15).[59]



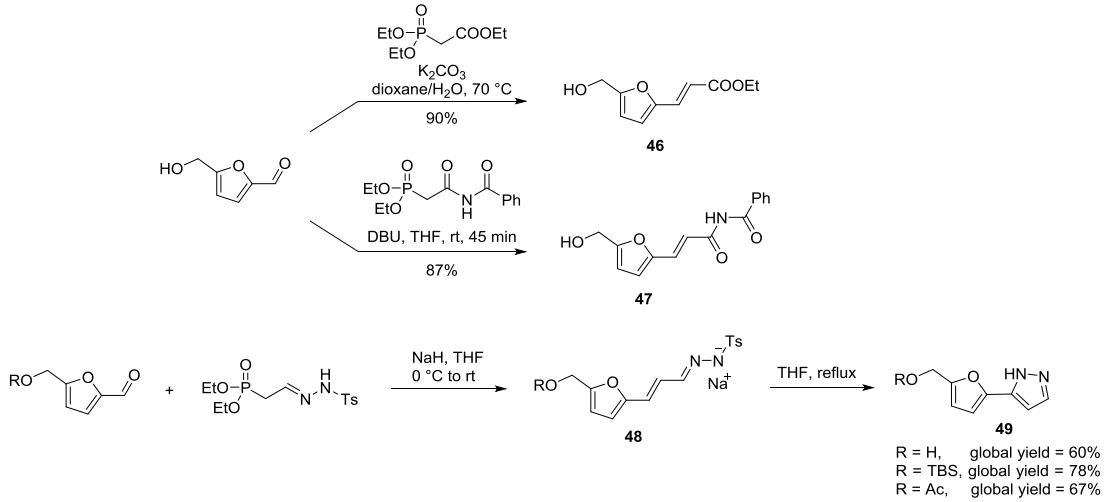
Scheme 15. Synthesis of a BODIPY molecule for bio-imaging application

The indene-derivative **45** was prepared as a mixture of isomers by the condensation of 2-methylindene-3-acetic acid with HMF[60], and its sodium salt displayed anti-proliferative activities (Scheme 16).



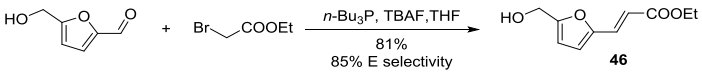
Scheme 16. Condensation with 2-methylindene-3-acetic acid

In 1984, the first Horner-Wadsworth-Emmons reaction of HMF was reported by Delmas. Reaction with triethylphosphonoacetate using potassium carbonate in a mixture of 1,4-dioxane and water afforded α,β-unsaturated ester **46** as *E* isomer exclusively in 90% yield (Scheme 17).[61] When the reaction was performed in alcoholic medium such as *n*-octanol, further transesterification occurred.[62] A DBU-mediated Horner-Wadsworth-Emmons reaction on HMF was performed to synthesize α,β-unsaturated imide **47**, which was obtained as a single diastereoisomer in 87 % yield, and might further serve as a precursor of β-amino acids.[63] The Horner-Wadsworth-Emmons reaction of HMF was also reported as the key step in a one-pot preparation of substituted pyrazoles.[64] HMF or *O*-protected derivatives reacted with diethoxyphosphorylacetaldehyde tosylhydrazone in the presence of NaH in THF, yielding α,β-unsaturated tosylhydrazones sodium salts **48**, which in refluxing THF provided the pyrazoles **49** in 60-78% yield for 2 steps (Scheme 17).



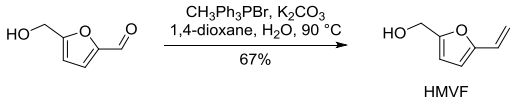
Scheme 17. Horner-Wadsworth-Emmons reaction on 5-HMF

The α,β-unsaturated ester **46** could also be prepared by one-pot Wittig reaction. The *in situ* formed Wittig reagent reacted with 5-HMF in the presence of tetra-*n*-butylammonium fluoride (TBAF) providing **46** with 81% yield and 85% selectivity in favor of *E* isomer (Scheme 18).[65]



Scheme 18. One-pot Wittig reaction on 5-HMF

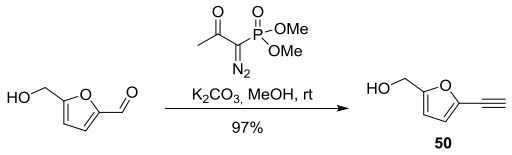
The monomer 5-hydroxymethyl-2-vinylfuran (HMVF) was synthesized using methyltriphenylphosphonium bromide and potassium carbonate in 67% yield, as an adaptation of a procedure used on furfural (Scheme 19).[66] The resulting HMVF could be efficiently polymerized by AIBN-initiated radical polymerization. Recently, Ji demonstrated that HMVF itself exhibits strong adhesion to metals *via in-situ* polymerization and crosslinking after either heating or acid treatment, concluding that HMVF could serve as a bio-based adhesive.[67]



Scheme 19. Direct alkenylation of 5-HMF

2.1.3 Formation of C≡C bonds

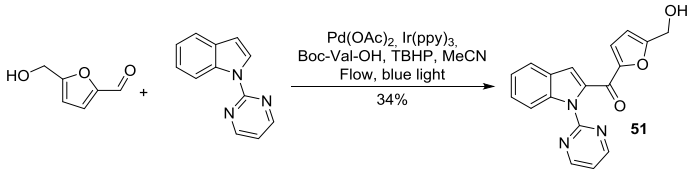
Direct alkynylation of 5-HMF was performed in 97% yield using Ohira–Bestmann reagent in MeOH in the presence of K_2CO_3 (Scheme 20). 2-Hydroxymethyl-5-ethynylfuran **50** was used as a platform to conduct various chemical transformations targeting furanic pharmaceuticals as well as conjugated polymers.[68]



Scheme 20. Direct alkynylation of 5-HMF

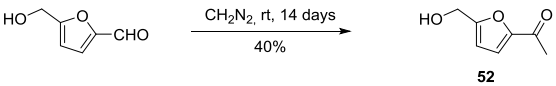
2.1.4 Oxidative transformations

Van der Eycken and Noël reported an acylation protocol at *C*2 of *N*-pyrimidylindoles using a range of aldehydes as acylating reagents *via* dual photoredox/transition-metal catalysis in flow conditions (Scheme 21).[69] In this work, HMF also showed certain reactivity leading to compound **51**, but with a low isolated yield of 34% in comparison with furfural (85%). This important difference of yield between similar substrates suggests detrimental effect of the hydroxymethyl group, moderately compatible with oxidative SET pathways.



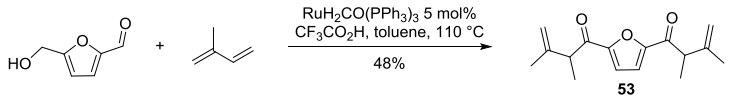
Scheme 21. Acylation of indole using HMF in a photoredox strategy

Following a Büchner-Curtius-Schlotterbeck reaction, HMF was reacted with diazomethane yielding 1-(5-(hydroxymethyl)furan-2-yl)ethan-1-one (**52**) in 40% yield after 14 days (Scheme 22).[70]



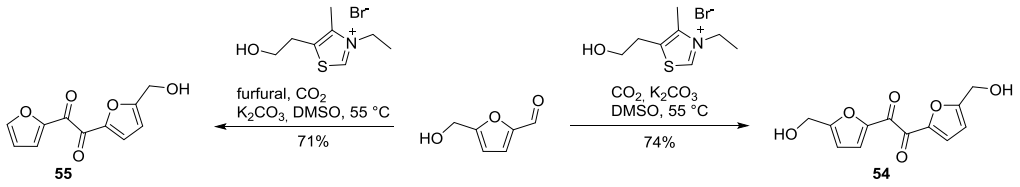
Scheme 22. Reaction between 5-HMF and diazomethane

A ruthenium dihydride complex was employed as a catalyst for the coupling of 5-HMF and isoprene on both C2 and C5 positions leading to the bis-ketofurane **53** in 48% yield (Scheme 23).[71]



Scheme 23. Coupling of 5-HMF and isoprene

Das reported a novel route to prepare α-diketone by performing the NHC-catalyzed HMF self-condensation in DMSO under CO_2 atmosphere (Scheme 24).[72] DFT calculations lightened the role of CO_2 in the mechanism, by reacting with the hydroxyl of so formed furoin, producing a carboxylate which is a good leaving group. DMSO was prone to therefore act as an oxidation reagent allowing the access to diketone **54**. The non-symmetrical α-diketone **55** could also be prepared in good yield employing a 1:1.5 ratio of furfural and HMF, although the formation of the homo α-diketone could not be suppressed completely.



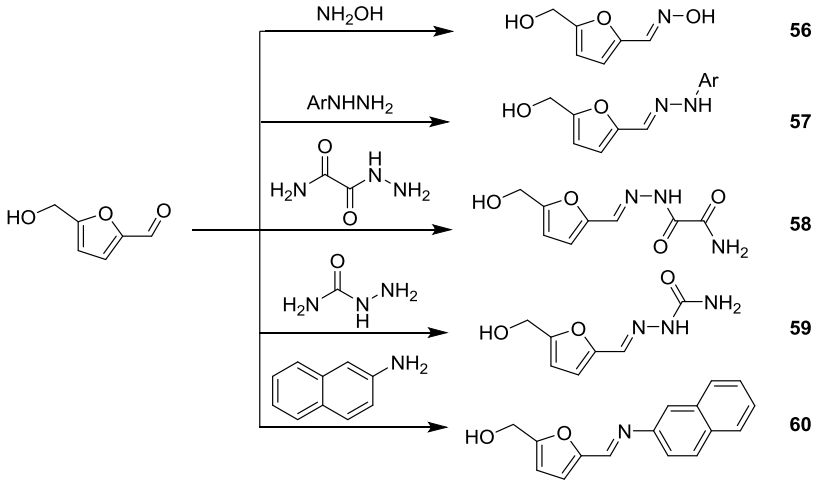
Scheme 24. NHC and CO_2-mediated homo and cross-coupling of HMF

2.2 Carbon-nitrogen bond formation reactions

The condensation of nitrogen nucleophiles on the aldehyde of HMF is a straightforward way to produce a variety of new molecules with interesting properties, but can also be a step of more complex chemical sequences toward original nitrogen-containing scaffolds, useful for agrochemical and pharmaceutical industries.

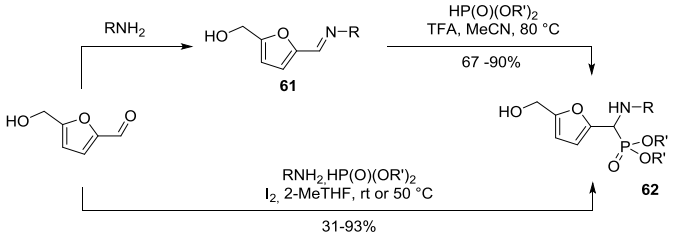
2.2.1 Synthesis of imines, hydrazones, oximes, nitrones and their applications

In the early stage study on HMF from the end of the 19th century to the beginning of the 20th century, researchers already showed that HMF could react with a range of nitrogen nucleophiles, such as hydroxylamine, arylhydrazine, semioxamazide, semicarbazide and amine to form respectively oxime **56**, hydrazone **57**, semioxamazone **58**, semicarbazone **59** and imine **60**[73] (Scheme 25).[74] These reactions with nitrogen nucleophiles were carried out mainly for purification and identification purposes because the products are often crystalline and easy to handle.



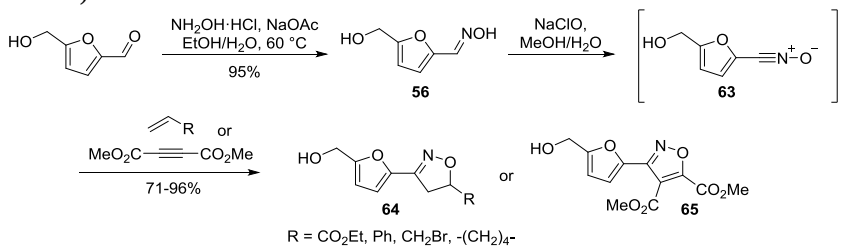
Scheme 25. Reactions between HMF and diverse nitrogen-nucleophiles in early studies

The imines **61** obtained from HMF were subjected to TFA-catalyzed Pudovik reaction to afford the α-aminophosphonates **62** (Scheme 26).[75] In 2018, our group reinvestigated the reaction conditions in a direct 3-CR strategy between 5-HMF, amine and dialkylphosphite. This one-pot approach named Kabachnik-Fields reaction was efficient in the presence of mild Lewis acid catalyst I_2.[76]



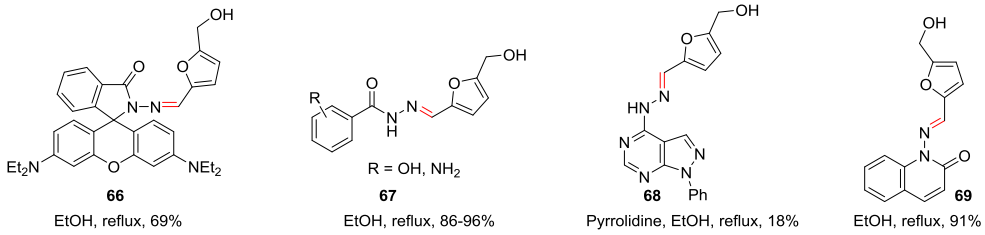
Scheme 26. Synthesis of α-aminophosphonates *via* Pudovik or Kabachnik-Fields reactions

Amarasekara reported an interesting application of the HMF-derived oxime **56**.[77] Oxidation of **56** in aqueous bleach solution provided the nitrile oxide **63**, which readily underwent 1,3-dipolar cycloaddition with alkenes or alkynes to give the corresponding dihydro-isoxazoles **64** or isoxazoles **65** depending on the nature of the dipolarophiles (Scheme 27).



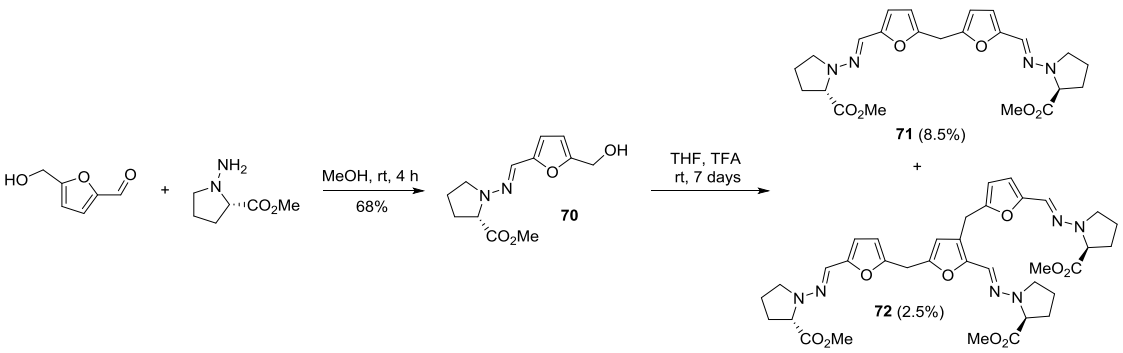
Scheme 27. Application of HMF-derived oxime in 1,3-dipolar cycloaddition

The condensation of HMF with rhodamine B hydrazide delivered hydrazone **66**, which could serve as a chemosensor for the detection of pH and Cu^{2+}.[78] A couple of HMF-derived *N*-acyl-hydrazones **67** were prepared as nifuroxazide analogues for antimicrobial activity screening.[79] Unfortunately, the HMF-based hydrazones **67** displayed no interesting biological properties. Hydrazone **68** was also prepared to study its activity as a kinase inhibitor,[80] whereas compound **69** (from 1-aminoquinolin-2(1*H*)-one) was studied as a ligand for making metal complexes (Scheme 28).[81]



Scheme 28. Examples of valuable HMF-based acylhydrazones and hydrazones

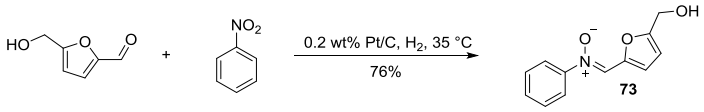
Capon isolated naturally occurring prolinimines from a fish gastrointestinal tract-derived fungus, *Trichoderma sp*. CMB-F563 (Scheme 29).[82] To confirm their structures, the authors performed a biomimetic synthesis of the prolinimine **70** by reacting HMF with *N*-amino-L-Pro methyl ester. Further treatment of prolinimine **70** in acidic conditions led to oligomeric prolinimines **71** and **72**.



Scheme 29. Synthesis of natural prolinimines from 5-HMF

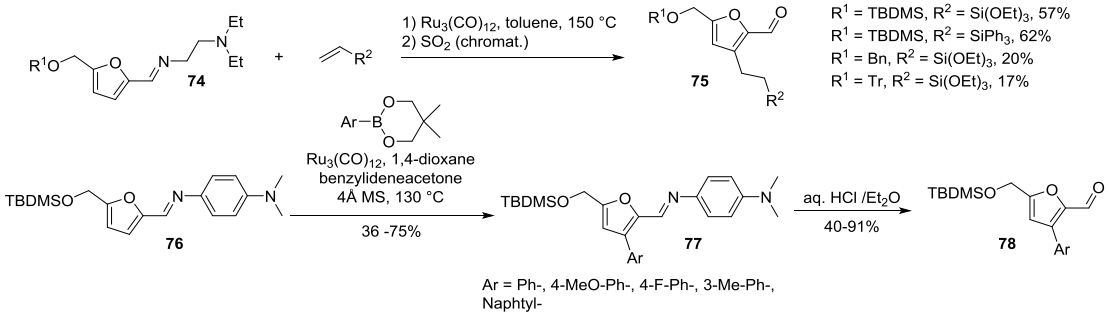
The preparation of nitrone **73** was investigated by heterogeneous reductive coupling of nitrobenzene and HMF

under H_2 atmosphere in the presence of platinum nanoparticles (Scheme 30).[83] The conversion was complete and the selectivity was evaluated at 89% (76% yield) in favor of the nitrone (side products expected: partial reduction into imine, total reduction into secondary amine or reduction of 5-HMF into the corresponding symmetrical diol).



Scheme 30. Preparation of nitrone

The Murai reaction *via* imine directing group assisted C-H activation on the furan ring of HMF derivatives was first reported by Poli, Oble and coworkers (Scheme 31).[84] A diamine reacted with the aldehyde group of *O*-protected HMF derivatives to form products **74** in which the amino-imine moiety served as a *N,N'*-bidentate directing group. The reaction was performed using a typical ruthenium catalyst and vinylsilanes as olefin partners in toluene at high temperature. The directing group was removed by hydrolysis during the silica gel column chromatography purification to release the *C*3-functionalized furfurals **75**. More recently, the same group reported the Ru-catalyzed imine-directed *C*3-arylation of compound **76** with aryl boronate esters.[85] In this case, a *p*-dimethylaminophenylimine proved to be the best directing group. In contrast to their previous study, the arylated imine **77** could be isolated by silica gel chromatography, the arylated aldehydes **78** being further released after hydrolysis with aqueous HCl (Scheme 31).

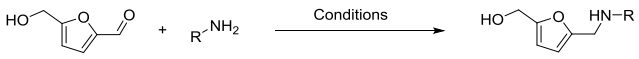


Scheme 31. Imine as directing group for C-H activation

2.2.2 Preparation of amines

Many examples of reductive amination of HMF to target 5-aminomethyl-2-furfuryl alcohols have been reported (Table 3). The utilization of $NaBH_4$ as a reducing agent was proved to be efficient,[86] but many studies describe also the use of H_2 together with a wide range of heterogeneous catalysts. Other reducing agents such as water or silanes have also been reported. Throughout these studies, aromatic and aliphatic amines, as well as ammonia, were introduced on the HMF scaffold.

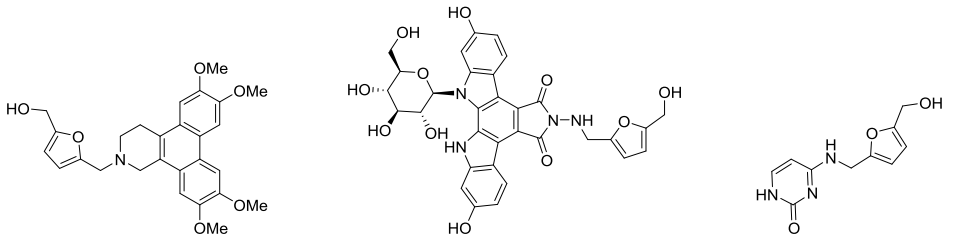
Table 3. Reductive amination with simple amines



Entry	Conditions	RNH_2	Yield	Ref.
1	$NaBH_4$, H_2O or EtOH	aromatic/aliphatic amines	77-99%	[86]
2	H_2, Raney Ni	NH_3 (liq.)	72%	[87]
3	H_2 (1.2 MPa), $Ru(DMP)_2Cl_2$, EtOH, 60 °C	aromatic/aliphatic amines	66-95%	[88]
4	H_2 (2 MPa), Rh/Al_2O_3, 80 °C	NH_3 (aq.)	86%	[89]
5	H_2 (4 MPa), Ru/Nb_2O_5, MeOH, 90 °C	NH_3 (in MeOH solution)	96%	[90]
6	H_2 (2 MPa), RuNPs, MeOH, 90 °C	NH_3 (in MeOH solution)	95%	[91]
7	H_2 (4 MPa), Co nanoparticles, ^{t}BuOH, 120 °C	NH_3 (gas)	89%	[92]
8	H_2O/CO (2 MPa)/MeOH, Au/TiO_2-R, 60°C	aromatic/aliphatic amines	60-99%	[93]

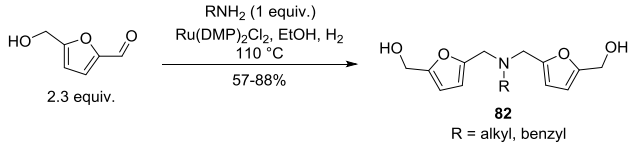
9	$PhMe_2SiH$, Au@APTES@SBA, IPA, 60 °C	aniline	65%	[94]

The reductive amination was applied to a phenanthropiperidine derivative using $NaBH(OAc)_3$ as reducing agent, to deliver the *N*-substituted phenanthropiperidine derivative **79** in 72% yield (Scheme 32). This tylophorine analogue was evaluated with respect to its biological activity and found to inhibit the proliferation of MCF-7 cells but only at micromolar concentration.[95] The indolopyrrolocarbazole derivative **80** [96] and cytosine derivative **81** [97] were also synthesized by reductive amination, and their antitumor effect and DNA methylation inhibition activity were respectively studied (Scheme 32).



Scheme 32. Reductive amination with complex amines and derivatives

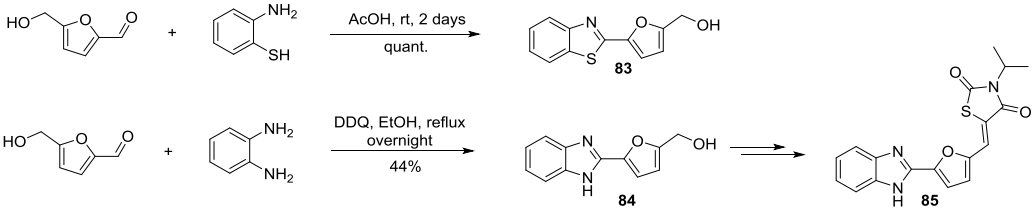
By switching the ratio of HMF and amine, Zhang et al. were able to convert HMF to bis(hydroxylmethylfurfuryl)amines **82** using $Ru(DMP)_2Cl_2$ as catalyst (Scheme 33).[98] The *in situ* generated secondary amine further reacted with excess of HMF to form an iminium-ion intermediate, followed by hydrogenation to produce bis(hydroxylmethylfurfuryl)amines **82**.



Scheme 33. Double reductive amination

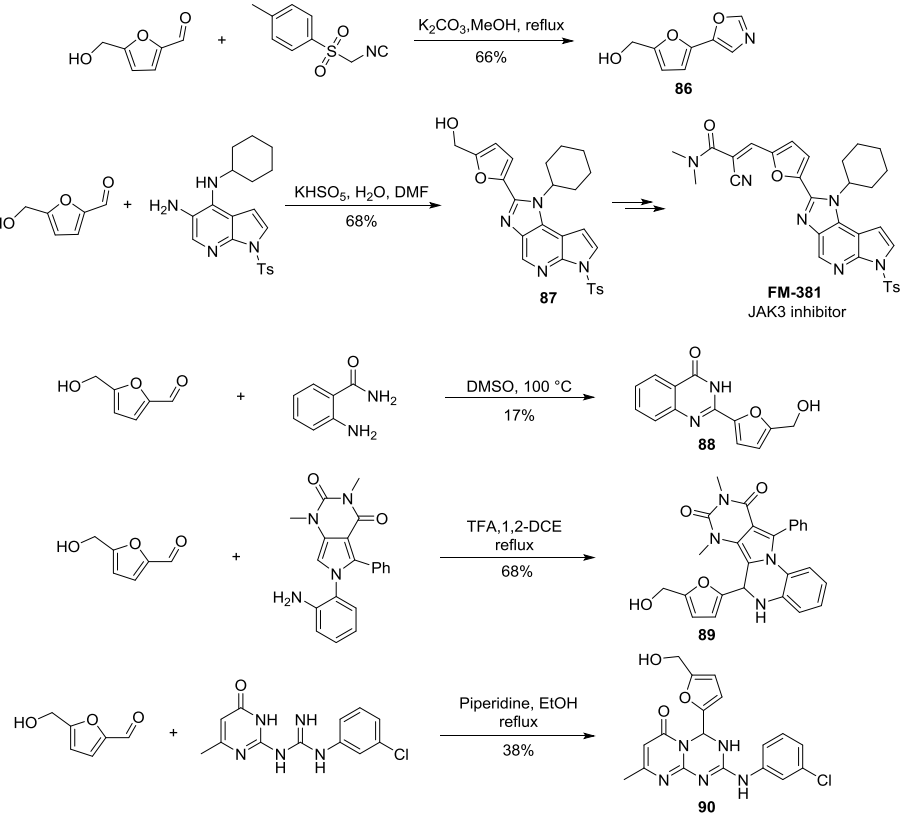
2.2.3 Synthesis of nitrogen-containing heterocycles

The condensation of 5-HMF with 2-aminothiophenol took place smoothly in AcOH giving rise to the benzothiazole **83** quantitatively after spontaneous oxidation (Scheme 34).[99] Similarly, the benzo[*d*]imidazole derivative **84**, prepared by reaction of HMF with *o*-phenyldiamine in the presence of DDQ in refluxing EtOH, served as an intermediate for the preparation of molecule **85**, a potential Myc modulator.[100]



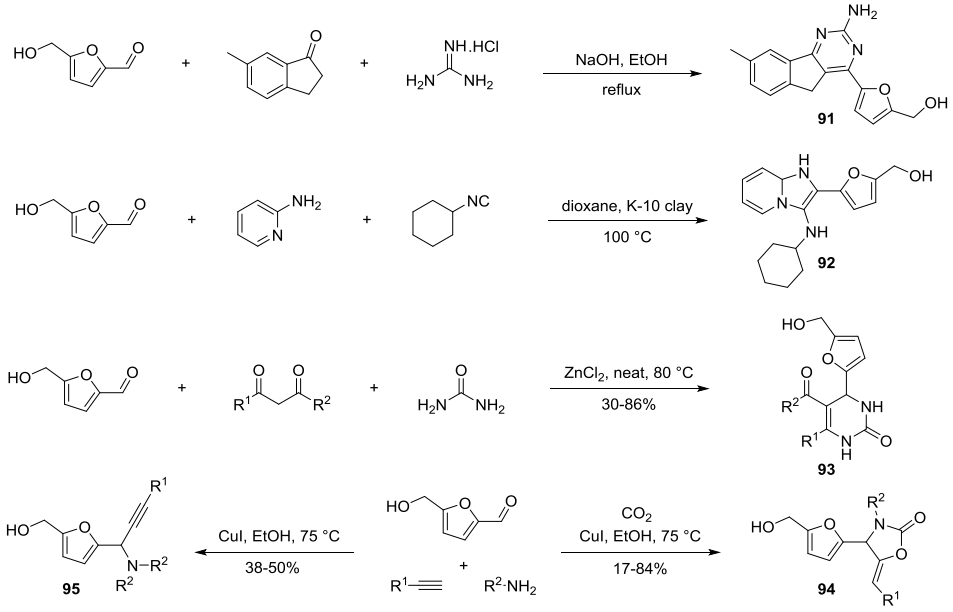
Scheme 34. Synthesis of benzothiazole and benzimidazole derivatives

HMF was often introduced as an aldehyde component in combinatorial chemistry to synthesize libraries of complex heterocyclic derivatives designed for bioactivity screening (Scheme 35). Treatment of HMF with *p*-toluenesulfonylmethyl isocyanide and potassium carbonate in refluxing methanol produced the 5-(5-hydroxymethyl-2-furyl)oxazole **86** in 66% yield.[101] In FM-381, an outstanding JAK3 inhibitor, synthesized by Laufer and coworkers,[102-103] the furan moiety plays a crucial role with respect to the inhibitory activity, as replacement of the furan link by a phenyl one generally induced lower activities. The 5-HMF was condensed on 4,5-diamino-7-azaindole to provide the tricyclic skeleton **87** as a precursor of FM-381. Sova prepared a range of quinazolinone derivatives such as **88** to study their antimicrobial activities, among which the HMF-derived product has no significant effect.[104] A fused tetracyclic heterocycle **89** was prepared in 68% yield by the TFA-catalyzed condensation of HMF and a 2-(1*H*-pyrrol-1-yl)aniline derivative.[105] The condensation of HMF with pyrimidinylguanidine furnished the desired pyrimido[1,2-*a*][1,3,5]triazin-6-one **90** in 38% yield.[106]



Scheme 35. Synthesis of nitrogen-containing heterocycles

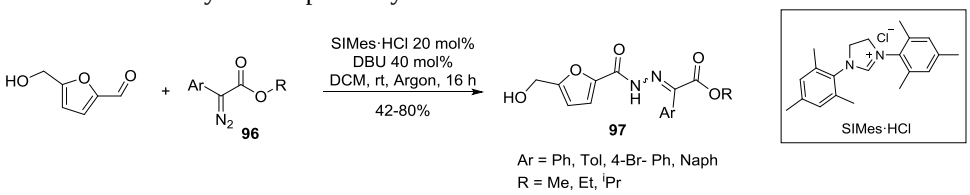
An interesting extension of the scope to access more complex molecules was achieved by using multicomponent reactions (Scheme 36). The 3-component condensation of HMF, indanone and guanidine produced the compound **91**, which was found to be a potent A_{2A} adenosine receptor antagonist.[107] A montmorillonite K-10 clay-catalyzed condensation of HMF, 2-aminopyridine and isocyanide was performed to generate the 1,8a-dihydroimidazo[1,2-*a*]pyridine derivative **92**.[108] More recently, our group disclosed the Biginelli reaction of 5-HMF using zinc chloride as Lewis acid catalyst, allowing access to furan-based 3,4-dihydropyrimidin-2-ones **93**.[109] The urea scope could be extended to thiourea and heterocyclic urea derivatives. Another interesting multicomponent reaction is the coupling of HMF, terminal aromatic alkynes, primary aliphatic amines and carbon dioxide using copper iodide as catalyst, to deliver oxazolidinones **94**.[110] In the case of anilines and secondary aliphatic amines, the A^3 coupling (aldehyde, amine and alkyne) took place under same conditions providing compounds **95**.



Scheme 36. MCR strategies involving 5-HMF

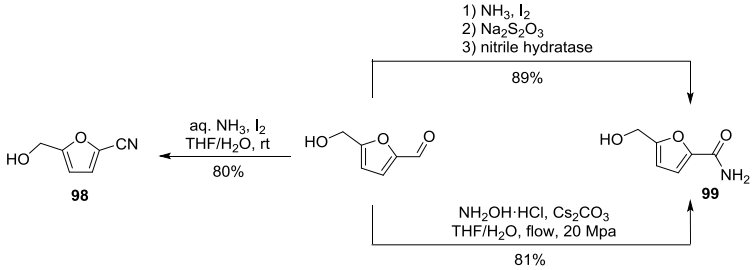
2.2.4 Oxidative transformations

The reaction of diazo derivatives **96** on 5-HMF catalyzed by *N*-heterocyclic carbene (NHC) allowed the preparation of acylhydrazones **97** displaying some antitumoral activity (Scheme 37).[111] An *in situ*-generated NHC catalyst (prepared by reacting imidazolidinium SiMes·HCl with DBU) was used to reverse the reactivity of the aldehyde group of HMF. The authors observed neither Cannizzaro reaction nor NHC-catalyzed benzoin condensation. In some cases, the expected acylhydrazones were obtained as mixtures of *E/Z* geometric isomers. The extension of the scope to hydroxymethyl protected substrates pointed out significant differences in terms of reactivity. For example, benzoyl HMF gave only 3% yield of acylhydrazone, while HMF benzyl and TBDMS ethers afforded 89% and 99% yields respectively.



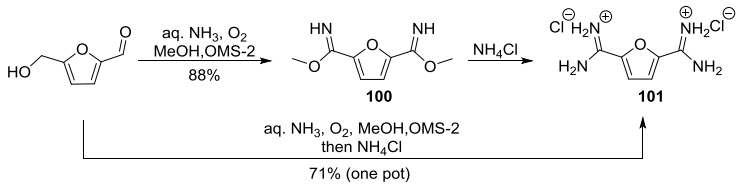
Scheme 37. Reaction between 5-HMF and diazo derivatives

HMF has been converted to the nitrile **98** by treatment with an ammonia solution in the presence of molecular iodine in a mixture of water and THF (Scheme 38).[112] A similar oxidative cyanation was implemented in a one-pot procedure for converting HMF into amide **99**,[113] where the *in situ*-generated nitrile was hydrolyzed to the corresponding carboxamide under the action of a nitrile hydratase from *R. rhodochrous* IFO 15564. The same transformation could be performed under modified experimental conditions by flow process with hydroxylamine hydrochloride as nitrogen source.[114] The reaction was completed in 5 minutes taking advantage of the flow chemistry technique (Scheme 38).



Scheme 38. Conversion 5-HMF to nitrile **98** and amide **99**

Catalytic oxidation of 5-HMF in the presence of aqueous ammonia and manganese oxide octahedral molecular sieves (OMS-2) as catalyst afforded the bis-imidate **100** in good yield (Scheme 39). Subsequent treatment with ammonium chloride provided the corresponding bis-amidine **101**.[115]

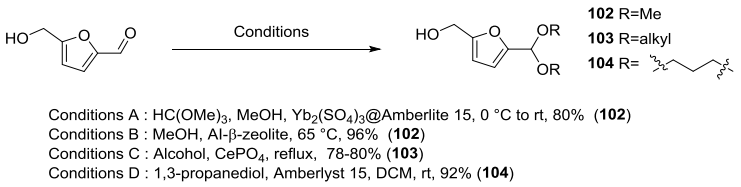


Scheme 39. Transformation of 5-HMF to dicarboximidate and diamidine salt

2.3 Carbon-oxygen and carbon-sulfur bond formation reactions

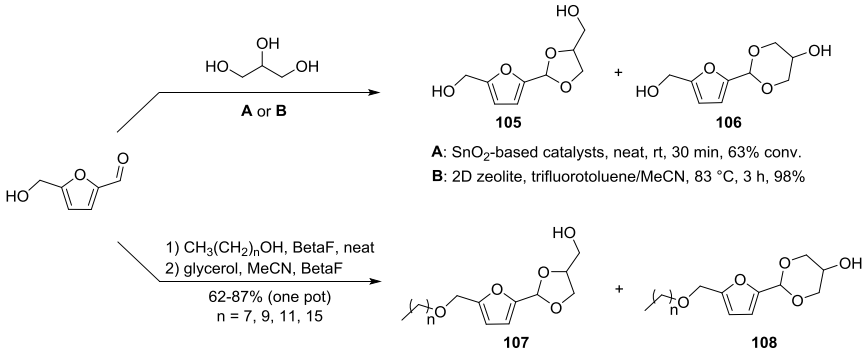
The nucleophilic attack of alcohols on aldehyde groups forms acetals, which are often applied as strategies for carbonyl compounds protection due to the reversibility of the acetal formation. Treatment of HMF with trimethyl orthoformate in the presence of ytterbium sulfate supported on Amberlite 15 gave access to the acetal **102** in 80% yield (Scheme 40).[116] The same protected HMF was obtained in high yield by Al-beta-Zeolite-catalyzed acetalization in methanol.[117] Using cerium phosphate as a catalyst in alcohols, both cyclic and acyclic acetals have been obtained in good yields.[118] Amberlyst 15 was also found to be an efficient catalyst for the preparation

of cyclic acetals.[119]



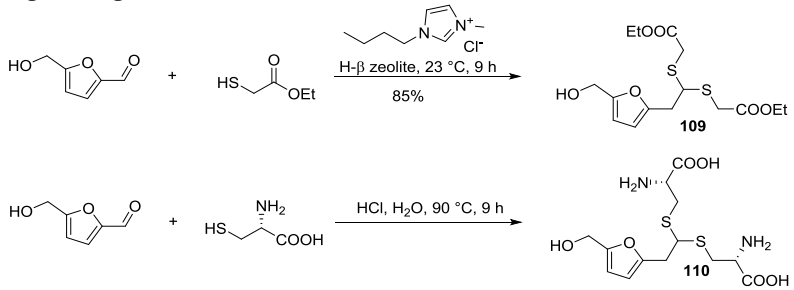
Scheme 40. Acetalization of HMF with simple alcohols

The acetalization of HMF with glycerol was performed by means of solid acid catalysis, yielding a mixture of 1,3-dioxolane **105** and 1,3-dioxane **106** (Scheme 41).[120-121] The acetalization with glycerol was extended to several *in situ* formed 5-(alkyloxymethyl)furfurals for the preparation of potential surfactant molecules **107** and **108** in a one-pot process.[122] The resulting compounds with HLB values in the range of 4.9 to 6.6 and good thermal and water stability could be useful for industrial applications as W/O emulsifiers.



Scheme 41. The acetalization of HMF and its derivative with glycerol

Likewise, thioacetalization of HMF under various catalytic conditions has been also reported. The reaction with ethyl-2-mercaptoacetate in the presence of acidic H-β zeolite and 1-butyl-3-methylimidazolium chloride provided the corresponding dithioacetal **109** in 85% yield (Scheme 42).[123] Ou prepared dithioacetal **110** by the reaction of HMF and cysteine in order to evaluate its cytotoxicity because this dithioacetal could be formed during food processing and digestion.[124]



Scheme 42. Thioacetalization of 5-HMF

3 Reactions on the hydroxyl group

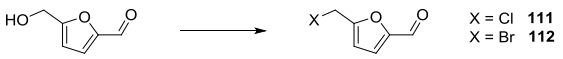
This section covers the strategies taking advantage of the reactivity of this benzylic alcohol to produce valuable chemicals. Apart from reactions where the hydroxymethyl group of HMF has been exploited for grafting it onto solid supports or polymers, several other transformations involving the CH_2OH group of HMF were reported, such as conversion to esters, ethers, halides and amines, as well as its reactivity as an alkylating reagent in Friedel-Crafts alkylations.

3.1 Conversion to halides

HMF can be easily converted to 5-chloromethylfurfural **111** or 5-bromomethylfurfural **112** *via* halogen substitution of the hydroxyl group. A range of classical halogenating conditions could be successfully applied to HMF (Table 4). The resulting halogenated HMF derivatives proved to be useful intermediates for the synthesis

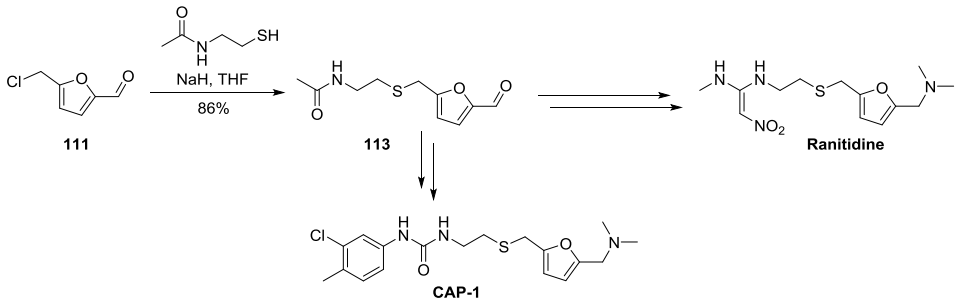
of several valuable furan-based complex compounds. 5-Chloromethylfurfural **111** being easily and directly obtained from sugars is now also claimed as a platform chemical itself.[125]

Table 4. Halogenation experimental conditions



Entry	Product	Conditions	Yield	Ref.
1	**111**	HCl (gas), Et_2O, 9 h	87%	[126]
2		HCl (aq), DCM or DCE, rt, 24 h	86-92%	[1, 127-128]
3		$SOCl_2$, pyridine, DCE, 5 h	71%	[126]
4		Me_3SiCl, $CDCl_3$, 6 h	92%	[126]
5		$POCl_3$, DMF, 5 h	77%	[129]
6	**112**	HBr (gas), Et_2O, 5 h	64%	[126, 130]
7		HBr (aq), DCE, 65 °C, 1 h	94%	[127]
8		$SOBr_2$, pyridine, DCE, 5 h	75%	[126]
9		PBr_3, $CaCO_3$, DCE, 5 h	62%	[126]
10		Me_3SiBr, $CHCl_3$ or $CHCl_2CH_2Cl$, 3 h	>98%	[126, 131]
11		NBS, PPh_3, DCM, -5 °C, 0.5 h	87%	[132]

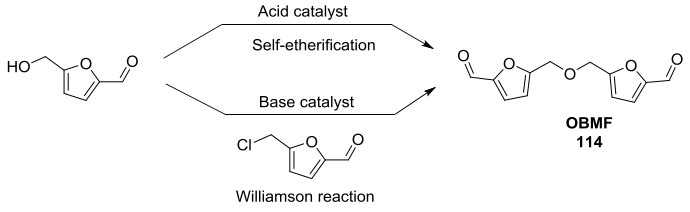
Taking advantage of chlorination of HMF as a key step, Ananikov reported an efficient synthetic route to ranitidine, a medication which decreases stomach acid production (Scheme 43).[1] The synthetic route consisted of the nucleophilic substitution of 5-chloromethylfurfural **111** by *N*-acetylcysteamine. Subsequent transformations of the thioether **113** afforded smoothly ranitidine in 65% overall yield from HMF. Changing the reagent to an arylisocyanate in the last step provided CAP-1, a novel compound with inhibition of HIV-1 capsid protein assembly activity.[128]



Scheme 43. Synthesis of ranitidine and CAP-1 from 5-HMF

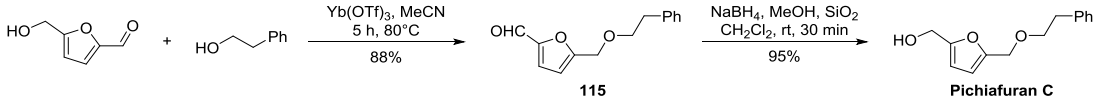
3.2 Conversion to ethers and acetals

HMF can undergo self-etherification to yield 5,5'-[oxybis(methylene)]bis-2-furfural (OBMF) **114** under acidic medium (Scheme 44). It is one of the (undesired) processes occurring during degradation of HMF upon storage.[1] The dehydration of HMF in the presence of *p*-TSA and phosphorus pentoxide in toluene with a continuous water removal using a Dean-Stark trap provides OBMF in 76% yield.[133] OBMF can also be obtained in 55% yield by thermal dehydration in DMSO without any acidic catalyst.[134] Additionally, several heterogeneous solid acids were reported to catalyze this reaction (e.g., Amberlyst-15, Amberlite IR 120, Preyssler heteropolyacids, graphene oxide).[1, 135-140] Finally, OBMF could also be obtained by Williamson reaction of HMF and 5-chloromethylfurfural.[141]



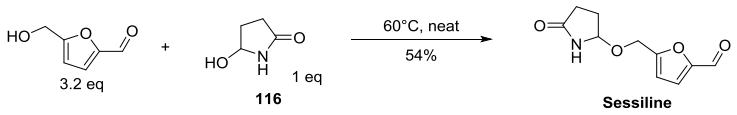
Scheme 44. Conversion HMF to OBMF

Simple alkyl ethers (e.g. 5-ethoxymethylfurfural) can be prepared by catalytic etherification of HMF and alcohols at high temperature.[142-143] A milder alternative is the Williamson reaction between HMF and an alkyl halide. It was reported that treatment of HMF with sodium hydride/iodomethane could give the methyl ether in 94% yield.[22] HMF reacted with benzyl bromide in the presence of Ag_2O in DMF to afford 5-benzyloxymethylfurfural in 72% yield.[135] Pichiafuran C, a monofuran metabolite isolated from *Pichia membranifaciens* yeast, was synthesized *via* $Yb(OTf)_3$–catalyzed reaction of HMF with 2-phenylethanol and subsequent reduction of **115** with $NaBH_4$ (Scheme 45).[144]



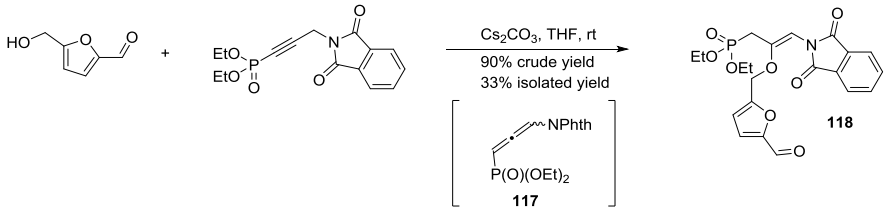
Scheme 45. Synthesis of Pichiafuran C

Sessiline, an alkaloid isolated from the fruits of *Acanthopanax sessiliflorus* was prepared in 54% yield in neat conditions by reaction of 5-HMF with amidocarbinol **116** (obtained in 3 steps and 28% yield from succinimide).[145] The proposed mechanism is the nucleophilic addition of HMF onto the iminium intermediate, which is in equilibrium with the amidocarbinol (Scheme 46).



Scheme 46. Synthesis of Sessiline

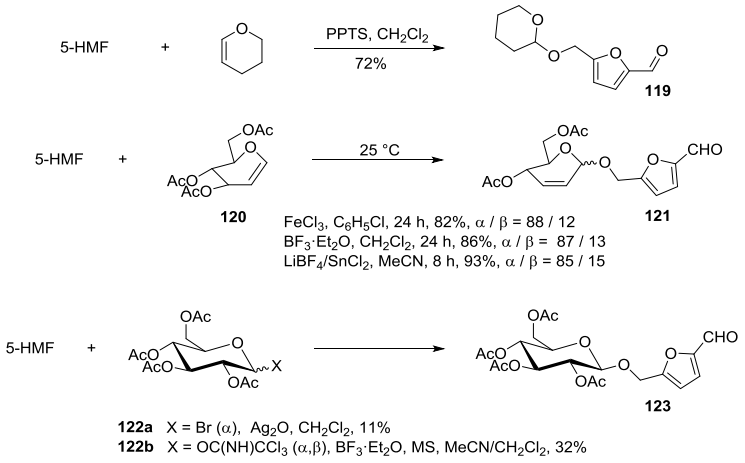
Stevens and coworkers performed the β-alkoxylation of the *in situ* formed 3-imidoallenylphosphonate **117** with a range of alcohols (Scheme 47).[146] Despite a crude yield estimated to 90%, the product **118** was isolated only in 33% yield, probably due to partial degradation during reverse phase flash chromatography purification.



Scheme 47. Alkoxylation of 3-imidoallenylphosphonate with 5-HMF

Descotes prepared the tetrahydropyranyl ether **119** in 72% yield by reaction between HMF and dihydropyran catalyzed by pyridinium *p*-toluenesulfonate (Scheme 48).[147] The Ferrier rearrangement of HMF and

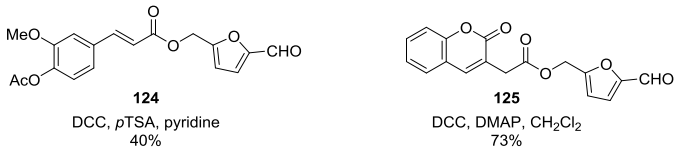
peracetylated glycal **120** under Lewis acid catalysis was reported by the same group in 2001 (Scheme 48).[148] The best yield was obtained when the combination $LiBF_4/SnCl_2$ was employed as Lewis acid catalysts. More recently, Zhang described the transformation of various glycals including **120** with HMF in the presence of $FeCl_3.6H_2O/C$ as a recyclable catalyst in DCE, leading to a range of 2,3-unsaturated glycosides in 67-92% yields.[149] Other carbohydrate derivatives of HMF have also been studied. Cottier investigated several possible pathways to prepare β-glucosylmethylfurfural **123** starting from HMF and glycosyl donors such as **122**.[116] The Ag_2O-catalyzed coupling of HMF and glycosyl bromide **122a** gave only 11% yield of the *β*-glucosylmethylfurfural. The yield was improved to 32% using the imidate **122b** and boron trifluoride diethyl etherate (Scheme 48).



Scheme 48. Acetal formation

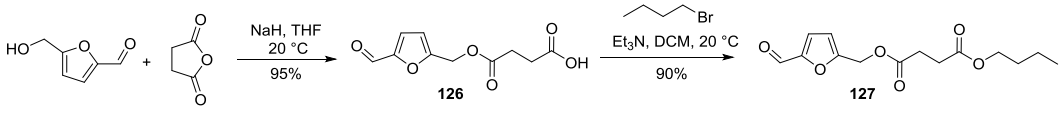
3.3 Esterifications

Classical esterification conditions were applied for the functionalization of the hydroxyl group of 5-HMF. The reaction with acetic anhydride in the presence of a base such as pyridine or sodium acetate, furnished 5-acetoxymethylfurfural in up to 93% yield.[16, 135] Benzoate esters can be prepared by reaction with benzoyl halides under similar conditions.[150-151]
The esterification of 4-*O*-acetylferulic acid with HMF was performed in pyridine using DCC as coupling reagent in the presence of *p*-toluenesulfonic acid, providing the corresponding ester **124** in 40% yield (Scheme 49).[152] The ester **125** was also prepared *via* DCC-promoted coupling reaction between HMF and the coumarin-derived acid, and its inhibitory activity against protein tyrosine phosphatase 1B was studied.[153]



Scheme 49. DCC-promoted esterification between HMF and carboxylic acids

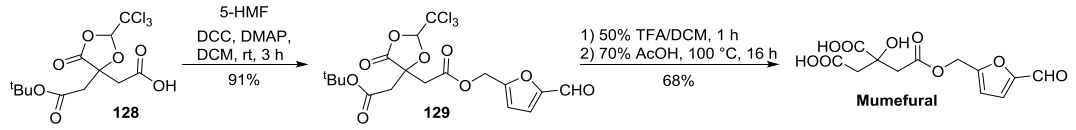
Tamariz's group prepared the natural product **127**, isolated from the Noni fruit, by two successive esterifications: first, the esterification of HMF hydroxyl group with succinic anhydride leading to the intermediate ester-acid **126**, then the alkylation of this latter with *n*-butyl bromide (Scheme 50) leading to the diester **127**. The stepwise and one-pot process gave same overall yields (85%).[154]



Scheme 50. Synthesis of natural succinate derivative

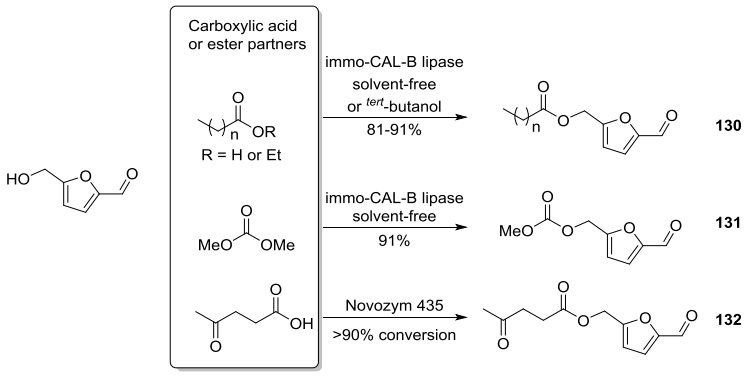
Mumefural, a citrate ester of 5-HMF known to improve human blood fluidity, can be prepared from malic acid

and HMF.[155] The intermediate **128** (prepared from malic acid) reacted with HMF in the presence of DCC and a catalytic amount of DMAP in dichloromethane to deliver the ester **129** in 91% yield (Scheme 51). Subsequent deprotection gave access to mumefural in 68% yield.



Scheme 51. Synthesis of mumefural from HMF

Biocatalytic esterification of HMF with different acyl donors such as carboxylic acids and methyl or ethyl esters has been reported (Scheme 52).[156] Good to excellent yields of esters **130** were obtained using the lipase CAL-B as catalyst in solvent-free conditions. In the case of short-chain acids, a mixture of carboxylic acid and *tert*-butanol (1:1 v/v) was used instead of solvent-free conditions to avoid the deactivation of the lipase due to the high acidity of the medium. Interestingly the same enzyme proved also to be efficient to prepare methyl carbonate **131** from dimethyl carbonate as well as HMF-esters directly from soybean oil.
The enzymatic esterification between HMF and levulinic acid to levulinate **132** was reported by Li et al.[157] Novozym 435 was selected as the best catalyst and the reaction could proceed in alcoholic solvents such as *tert*-butanol, or 2-methyl-2-butanol as well as in ethereal solvents (CPME, or 2-MeTHF), with more than 90% conversion.

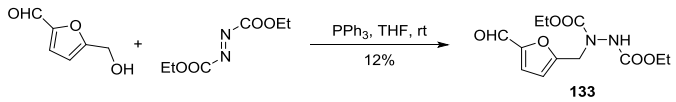


Scheme 52. Biocatalytic esterifications

3.4 Amination reactions

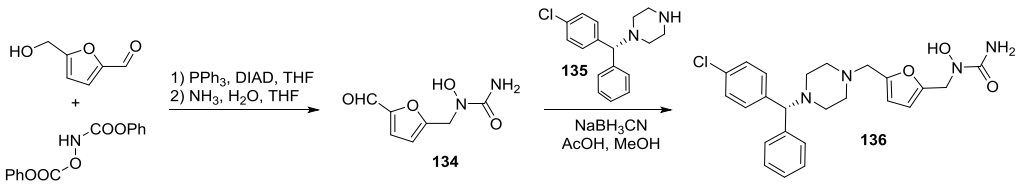
Strictly speaking, there are no examples of real amination on the OH group of HMF to make amino-deoxy-HMF. However, a few studies about the preparation of amides, hydrazines and ureas have been reported.

The group of Wierenga reported the direct preparation of hydrazine 133 under Mitsunobu conditions from 5-HMF.[158] In the absence of any other nucleophile, the reduced DEAD reagent acts as a nucleophile in SN2 reaction to produce compound **133** in 12% yield (Scheme 53). Comparatively, furfuryl alcohol or the acetal-protected HMF provided much higher yields (60% and 86% respectively) under the same conditions.



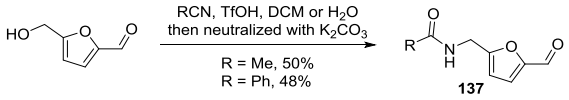
Scheme 53. Reaction between HMF and diethyl azodicarboxylate

Lewis et al. prepared the *N*-hydroxyurea derivative **134** by reacting HMF with *N,O*-(bisphenoxycarbonyl)hydroxylamine under Mitsunobu conditions, followed by treatment with ammonia. Subsequent reductive amination with piperazine **135** released the final product **136** (yields not reported),which exhibited antihistaminergic activity (Scheme 54).[159]



Scheme 54. Reaction between HMF and *N,O*-(bisphenoxycarbonyl) hydroxylamine

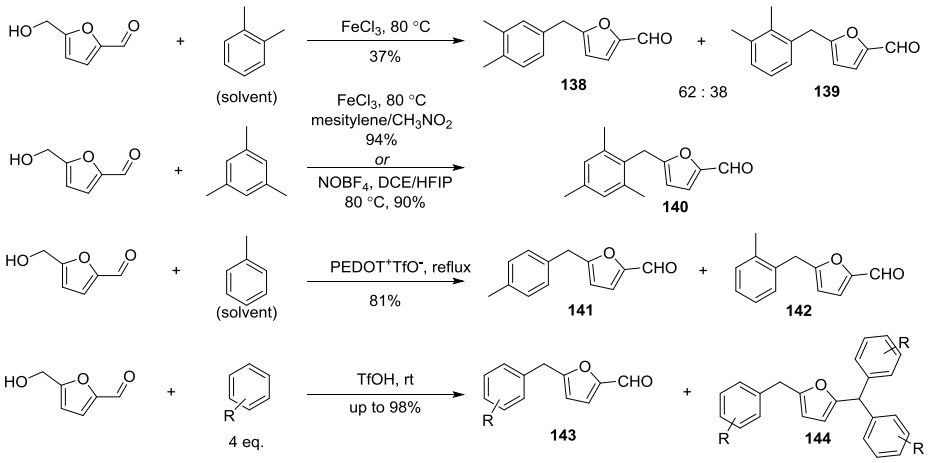
The Ritter reaction was also applied to HMF, which gave access to the corresponding amides **137** in around 50% yield by treatment with trifluoromethanesulfonic acid in acetonitrile or benzonitrile at room temperature (Scheme 55).[135]



Scheme 55. Reaction between HMF and nitriles

3.5 Construction of a C-C(Ar) bonds

The Friedel–Crafts alkylation of arenes using HMF as the alkylating agent has been reported by different research groups. Beller et al. implemented the alkylation of *o*-xylene using $FeCl_3$ (10 mol%) as a catalyst providing a mixture of regioisomers in 37% yield (ratio **138**/**139** of 62:38) (Scheme 56).[160] The reaction with mesitylene, either promoted by $FeCl_3$ or nitrosonium tetrafluoroborate, provided the product **140** in excellent yield.[161-162] Heating HMF in refluxing toluene in the presence of poly(3,4-ethylenedioxythiophene) salt gave rise to a mixture of two isomers **141** and **142** in a global 81% yield.[163] Employing Glu–Fe_3O_4–SO_3H as a magnetic carbonaceous solid acid catalyst led to a regioisomeric mixture of **141** and **142** containing some traces of the *meta* isomer.[164] Recently, Vasilyev and coworkers reported the arylation of HMF with arenes in trifluoromethanesulfonic acid medium at room temperature.[165] 5-Arylmethylfurfurals **143** were prepared in 17–91% yields, along with by-products 2-arylmethyl-5-(diarylmethyl)furans **144** (5-37% yield) when highly nucleophilic arenes were used. Increasing the reaction time significantly affected the yield of the by-product. The same reactions using acidic zeolites CBV-720 as catalysts at 130 °C resulted in the selective formation of 5-arylmethylfurfurals (11–79% yield).



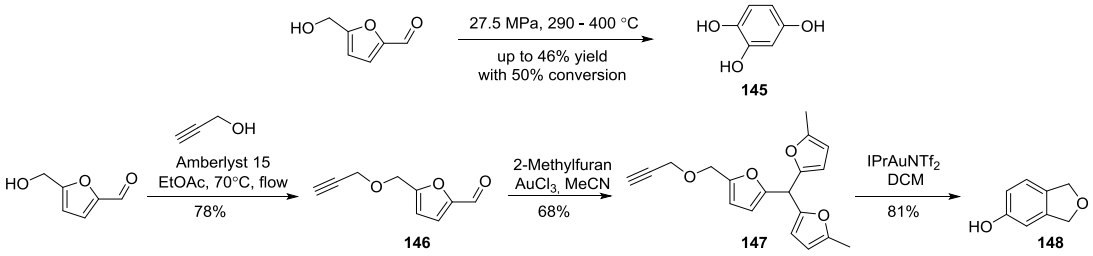
Scheme 56. Friedel–Crafts alkylation of arenes

4 Reactions on the furan ring

4.1 Ring opening/rearrangement

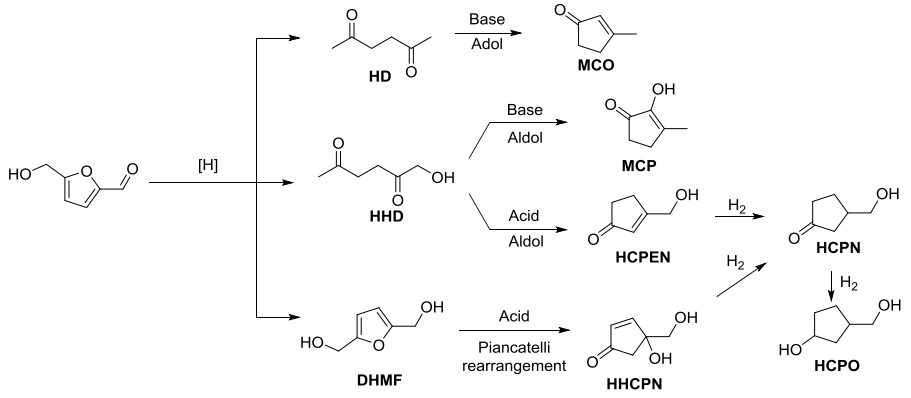
It is well known that HMF decomposes under acidic conditions at elevated temperature leading to the ring-opening product levulinic acid.[2,166] However, other derivatives arise from rearrangements of the furanic systems of HMF. For example, subjecting HMF to hydrothermolysis at high temperature and pressure led to 1,2,4-benzenetriol **145** as the major product in yields up to 46% with 50% HMF conversion (Scheme 57).[167] The other example is the conversion of HMF to phenols which was reported by Hashmi et al.[168] In this reaction,

HMF first undergoes a *O*-propargylation and the resulting aldehyde **146** is converted into trifurylmethane **147** under gold(III) catalysis. Finally, gold (I) catalysis promoted the conversion of **147** into the fused phenol **148** through ring rearrangement.



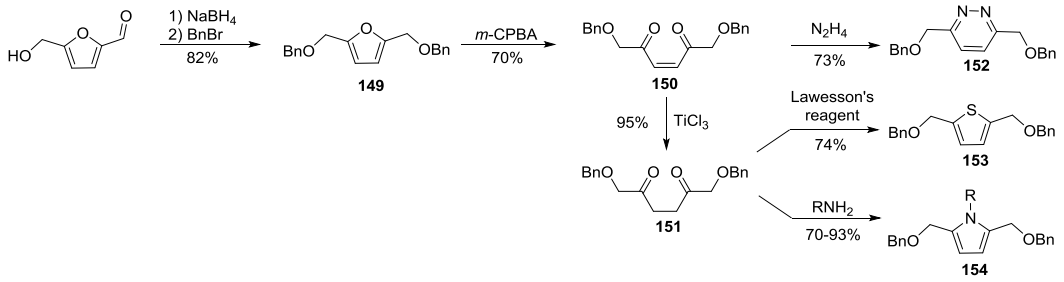
Scheme 57. Transformation of HMF and its derivatives to phenols

The hydrogenative/hydrolytic ring-opening of HMF in water provided 2,5-hexanedione (HD)[169-170] or 1-hydroxy- 2,5-hexanedione (HHD)[171-172] depending on the catalytic conditions employed (Scheme 58). The latter was reported to be used as 1,4-diketone partner in the Paal-Knorr pyrrole synthesis.[173] HD and HHD can be converted into cyclopentanic derivatives, respectively 3-methyl-2-cyclopent-2-en-1-one (MCO)[174] and 2-hydroxy-3-methylcyclopent-2-enone (MCP)[175-176] *via* base-catalyzed intramolecular aldol reactions. Following an acid-catalyzed aldol reaction and subsequent hydrogenation sequence, HHD can be transformed into 3-hydroxymethyl cyclopentanone (HCPN)[177-178]. An alternative route toward cyclopentanic derivatives from HMF relies on a first catalytic reduction of the aldehyde generating 2,5-dihydroxymethylfuran (DHMF), followed by a Piancatelli rearrangement to 4-hydroxy-4-(hydroxymethyl)cyclopent-2-en-1-one (HHCPN) and further reduction of the produced cyclopentenone under the reaction conditions (Scheme 58).[179]



Scheme 58. Ring-opening/rearrangement of HMF derivatives

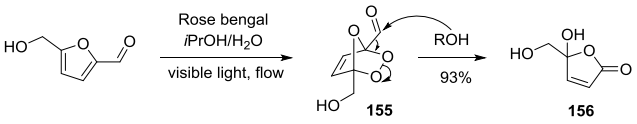
Oxidative conditions have also been employed to achieve ring opening transformations of intermediates arising from 5-HMF. Lichtenthaler and coworkers reported the preparation of various heterocycles such as the pyridazine **152**, the thiophene **153** or the pyrrole **154** from HMF (Scheme 59),[180] relying on a first reduction of the aldehyde and benzylation of the diol intermediate to produce **149**. This symmetrical disubstituted furan can undergo oxidative ring opening upon treatment with *m*-CPBA to yield diketone **150**. Chemoselective hydrogenation of **150** would provide diketone **151**. These 1,4-diketones were rapidly converted in heterocyclic scaffolds **152-154** *via* diverse transformations.



Scheme 59. Heterocycles obtained in three steps from HMF involving a furan ring-opening reactions

4.2 Singlet oxygen oxidation

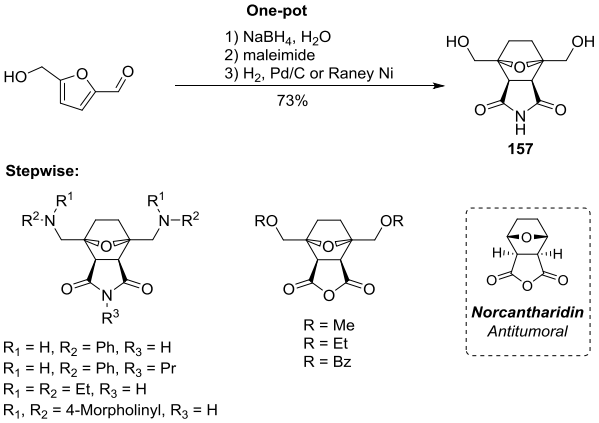
HMF can react with singlet oxygen *via* [4 + 2] cycloaddition to give rise to 5-hydroxy-5-(hydroxymethyl)-furan-2(*5H*)-one (**156**).[135] The cycloadduct **155** rearranged *via* a solvent-assisted decarbonylation reaction to produce efficiently the butenolide **156**. The reaction was recently reinvestigated by Kappe under continuous flow conditions (Scheme 60).[181] The best yield obtained was 93% using 1 mM rose bengal as photosensitizer in a mixture of *i*-PrOH/H_2O as solvent with 0.5 mL/min flow rate.



Scheme 60. Reaction of HMF with singlet oxygen

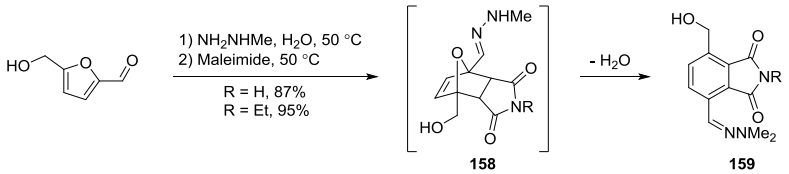
4.3 Diels-Alder reactions

Electron-rich furans have been widely employed as dienes in Diels-Alder reactions with electron-deficient dienophiles. In contrast to other furanic compounds, the presence of the strongly electron withdrawing aldehyde on the furan ring of HMF tends to deactivate the aromatic ring toward Diels-Alder reactions. In order to use HMF in this cycloaddition process, it usually requires chemical modification such as reduction toward 2,5-dihydroxymethylfuran (DHMF) or 2,5-dimethylfuran (DMF).
Ananikov and co-workers reported the synthesis of a series of oxabicyclic compounds starting from HMF and maleimide *via* one-pot reduction/cycloaddition/hydrogenation sequence or in a stepwise process taking advantage of a Diels-Alder reaction as the key step (Scheme 61).[182] Reduction of HMF to 2,5-dihydroxymethylfuran followed by *endo*-selective Diels-Alder cycloaddition with maleimide and hydrogenation in a single pot provided the product **157** in 73% yield (that could also be prepared in sequential-step procedure). The authors also applied the Diels-Alder reaction on HMF-derived bis(aminomethyl)furans, and bis(alkoxymethyl)furans and maleic anhydride could be employed as dienophile to prepare analogues of the anticancer drug norcantharidin.[183]



Scheme 61. Diels-Alder reaction of DHMF, bis(aminomethyl)furans and bis(alkoxymethyl)furans

Sheppard's group reported a strategy to efficiently react HMF with dienophiles, without changing the oxidation state of the aldehyde (Scheme 62).[184] HMF was first reacted with *N*-methylhydrazine to produce the corresponding hydrazone, before reacting with maleimides providing the cycloadducts **158**. The latter underwent deoxyaromatisation to produce the phthalimides **159**. The reaction was carried out in water and the products were isolated in high yields by simple filtration.



Scheme 62. Diels-Alder reaction of HMF-derived hydrazone

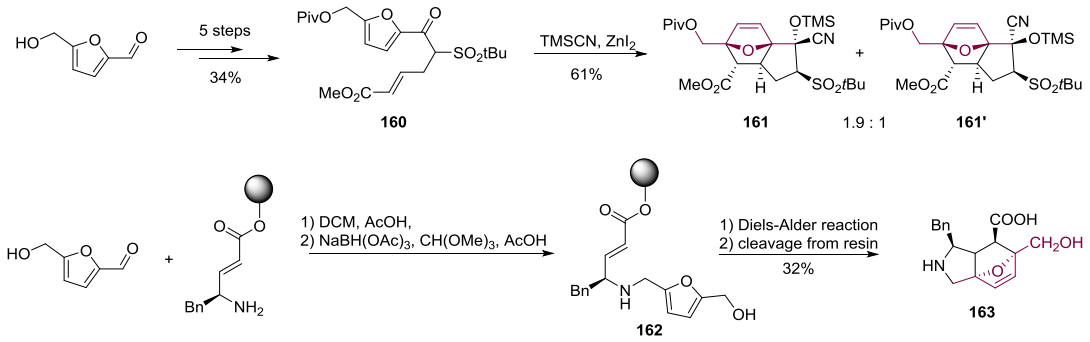
In addition, a range of HMF-derived furans such as 2,5-dimethylfuran (DMF) and dimethyl furan-2,5-dicarboxylate have been utilized as dienes in reactions with various dienophiles (e.g., ethylene, acrolein and benzyne) to accomplish the Diels-Alder reaction. Subsequent deoxyaromatisation of the Diels-Alder adducts led to *p*-xylene or other substituted aromatic compounds.[185-193]

5 Multi-step and multi-functionalization sequences

As it has been shown throughout this review article, several methodological studies on the chemical modifications of HMF have been conducted, showing the high versatility of this C-6 synthon. In a synthetic perspective, 5-HMF has also been used in more complex multistep sequences, targeting complex and/or natural scaffolds.

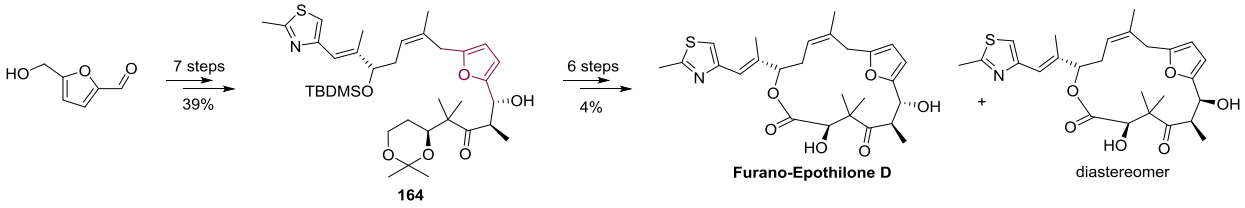
In a study on intramolecular Diels-Alder reactions (IMDA) of furan derivatives, Sternbach used the 5-HMF as a platform for the preparation of the highly substituted keto-sulfone **160** (Scheme 63).[194] This substrate is poorly reactive in IMDA cycloaddition, however the conversion of the ketone to a cyanohydrin group using $TMSCN/ZnI_2$ reactivates the furan ring, which then can undergo an IMDA reaction in good yield producing tricyclic derivative **161** and epimer **161'** though with moderate diastereoselectivity.

A supported intramolecular Diels-Alder reaction was also performed on the furan ring of HMF after its coupling with a resin-bound amine (Scheme 63).[195] The polycyclic compound **163** could be obtained from the intermediate compound **162** after IMDA reaction followed by cleavage from the resin.



Scheme 63. Intramolecular Diels-Alder reaction on furan ring

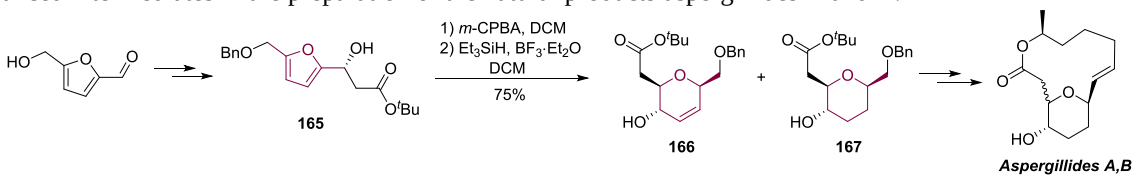
Schinzer et al. completed the stereoselective synthesis of furano-epothilone D, analog of natural epothilone which is a powerful antitumoral molecule, using HMF as a building block (Scheme 64).[196] Bromination of the hydroxymethyl group was the first step of functionalization. A sequence of a Negishi-type coupling and a diastereoselective aldol reaction with a chiral ketone produced the secondary alcohol **164**. This advanced intermediate was then converted to the furanic analogs of epothilone D. Both furano-epothilone D and its diastereoisomer displayed only moderate effect on tubulin assembly.



Scheme 64. Synthesis of furano-epothilone D from HMF

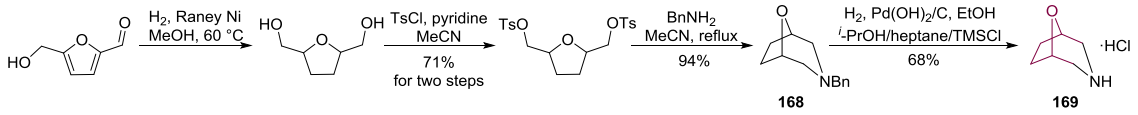
Loh *et al.* reported a synthetic route to natural products aspergillides A and B which exhibit potent cytotoxic activities towards mouse lymphocytic leukemia cell (Scheme 65).[197] In this route, all the carbon atoms in target molecules come from biomass-derived platform chemicals such as levulinic acid and HMF. The key steps in this synthesis were a Noyori's asymmetric transfer hydrogenation to produce enantiopure alcohol **165** which was then subjected to an Achmatowicz rearrangement and subsequent reduction leading to pyranes **166** and **167**,

advanced intermediates in the preparation of the natural products aspergillides A and B.



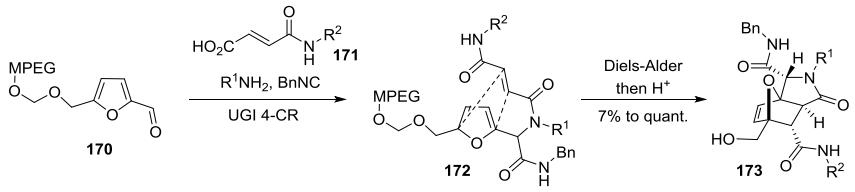
Scheme 65. Synthetic route to aspergillides A and B

A four-step process to prepare 8-oxa-3-aza-bicyclo[3.2.1]octanehydrochloride **169** starting from 5-HMF was described by Connolly et al.[198] Reduction of 5-HMF to the corresponding saturated diol followed by double tosylation and double S_N2 with benzylamine generated the bicyclic intermediate **168**. The latter was hydrogenolyzed using Pearlman's catalyst in good yield to provide the final tricyclic adduct **169** (Scheme 66).



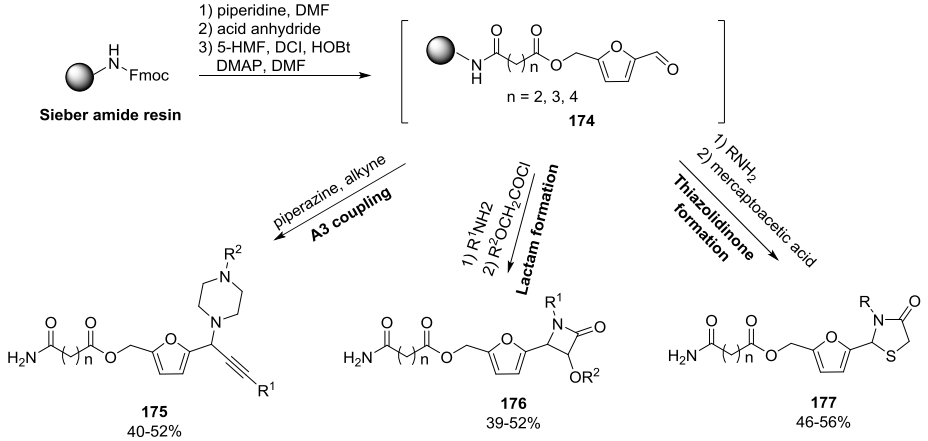
Scheme 66. Synthesis of 8-oxa-3-aza-bicyclo[3.2.1]octane hydrochloride **169**

MPEG-grafted 5-HMF **170** has been used as a substrate to prepare a series of tricyclic molecules **173** (Scheme 67).[199] The authors employed a 4-component Ugi reaction of supported HMF **170**, benzyl isocyanide and various primary amines and fumaric acid mono-amides (**171**) to generate intermediates **172**, that can undergo a tandem intramolecular Diels-Alder reaction of the furan ring followed by acidic workup to release final products **173**.



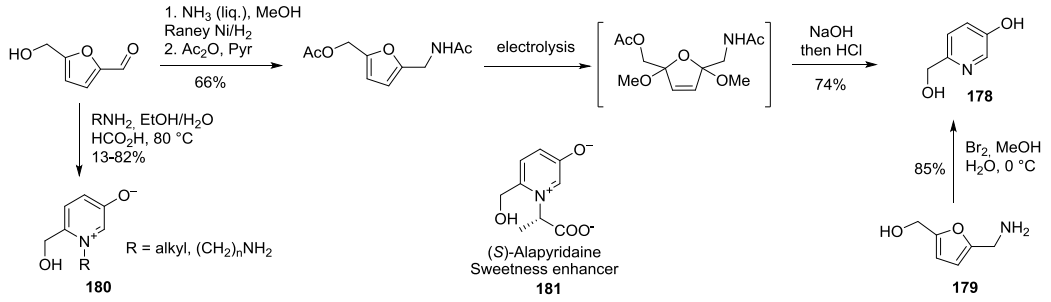
Scheme 67. Ugi/Diels-Alder tandem reaction

As illustrated above in Ugi/Diels-Alder reactions, the hydroxymethyl group present in 5-HMF offers a convenient handle for connection onto a solid support. The solid-supported HMF with a free carbonyl group could serve as a useful scaffold in combinatorial synthesis of furan-based libraries. Kundu and coworkers loaded HMF onto Sieber amide resin *via* the formation of amide and ester bonds using aliphatic dicarboxylic acid anhydride (Scheme 68).[200] The resin-supported HMFs **174** could be engaged in multicomponent A^3 couplings to provide, after separation from the solid support, propargylamines **175**. Other multi-step transformations giving access to diverse nitrogen-containing heterocycles such as **176** and **177** were also successfully implemented using this supported synthesis strategy.



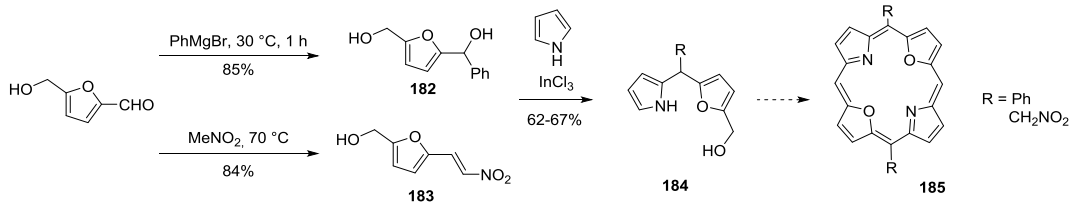
Scheme 68. Solid-phase combinatorial synthesis of HMF-based scaffolds

In 1956, Elming reported the synthesis of 6-hydroxymethyl-3-pyridinol **178** starting with reductive amination of HMF, followed by acetylation and electrolysis (Scheme 69).[87] The 3-pyridinol **178** could also be prepared by exposing 5-hydroxymethylfurfurylamine **179** to bromine in water/methanol at 0 °C.[201] Enantiopure synthesis of pyridinium salt (*S*)-alapyridaine **181** (a sweetness enhancer) was achieved under Br_2/MeOH/H_2O conditions from the amine formed by reductive amination of HMF with L-alanine.[202] Direct treatment of HMF with alkylamines in refluxing EtOH/H_2O under basic conditions (pH adjusted ~9.4 with NaOH) has been a frequently-used method to prepared pyridinium inner salts **180** in the past.[203-205] Several pyridinium betaines derived from glycine, β-alanine and γ-aminobutyric acid proved to be potential bitter-suppressing candidates. More recently, an alternative method employing formic acid as a catalyst in EtOH/H_2O to synthesize pyridinium inner salts **180** from HMF was reported by Afonso.[206]



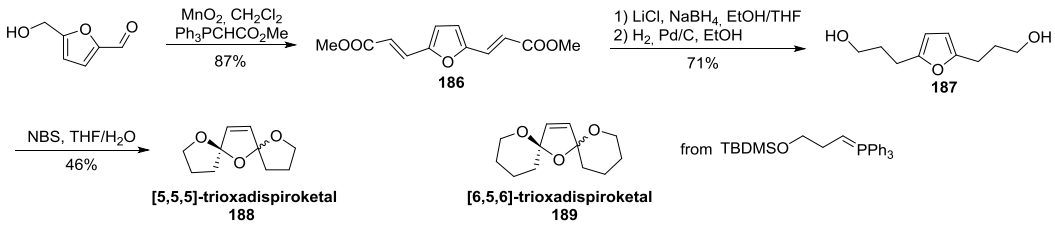
Scheme 69. Conversion of 5-HMF to pyridinol and pyridinium salt

The preparation of key intermediates of synthetic routes towards 21,23-dioxaporphyrins **185** from HMF was reported as an alternative to known but complex synthetic procedures, addressing drawbacks such as low yields and purification issues (Scheme 70).[207] The addition of a phenyl-Grignard reagent on HMF, or the Henry reaction with nitromethane gave access to the furylcarbinol **182** and nitroalkene **183** respectively in good yields. Those intermediates were then reacted with pyrrole under indium chloride catalysis to generate diversely substituted bis-heteroarylmethanes **184**, highly valuable building-blocks for the preparation of 21,23-dioxaporphyrins **185**.



Scheme 70. Preparation of key intermediates to 21,23-dioxaporphyrin from 5-HMF

An example illustrating the usefulness of the olefination of HMF is the synthesis of trioxadispiroketal reported by Stockman.[208] In this strategy, HMF was subjected to tandem oxidation/Wittig reaction providing the diester **186** as a 6.6:1 mixture of (*E*,*E*)- and (*E*,*Z*)-isomers (Scheme 71). Reduction of both esters followed by hydrogenation of the two carbon-carbon double bonds on side chains afforded the corresponding diol **187**. Further treatment with *N*-bromosuccinimide furnished the [5,5,5]-trioxadispiroketal **188**. [6,5,6]-Trioxadispiroketal **189** was also prepared *via* a similar strategy using a homologated phosphonium ylide.



Scheme 71. Application of the olefination of HMF to the synthesis of trioxadispiroketals

6 Conclusion

As it has been shown throughout this review article, 5-HMF has been the object of numerous studies on its use in fine chemical synthesis. Its relatively modest stability has been shown to be overcome by choosing adequately mild reaction conditions, notably with respect to acid-catalyzed reactions. Thanks to the presence of different functional groups on this platform molecule, it proved to be an excellent starting substrate for the preparation of analogs of drugs, photo-responsive molecules or complex heterocyclic scaffolds. The use of this C-6 synthon in novel synthetic routes is appealing, as it allows the incorporation of renewable carbon-sources into the final targets. The commercial availability of HMF being now fully established, it is expected to exhibit, in a foreseeable future, a growing number of such applications toward complex chemicals.

7 Acknowledgements

Financial support from CNRS, UCBL, INSA Lyon and CPE Lyon is gratefully acknowledged, as well as the ANR for a post-doctoral fellowship to C. V. (FurCab project, ANR-15-CE07-0016) and the China Scholarship Council for PhD grants to W. F.

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