Upgrading Biogenic Furans: Blended C10-C12 Platform Chemicals via Lyase-Catalyzed Carboligations and Formation of Novel C12 – Choline Chloride-Based Deep-Eutectic-Solvents

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ARTICLE TYPE

Upgrading Biogenic Furans: Blended C_{10}-C_{12} Platform Chemicals via Lyase-Catalyzed Carboligations and Formation of Novel C_{12} – Choline Chloride-Based Deep-Eutectic-Solvents.

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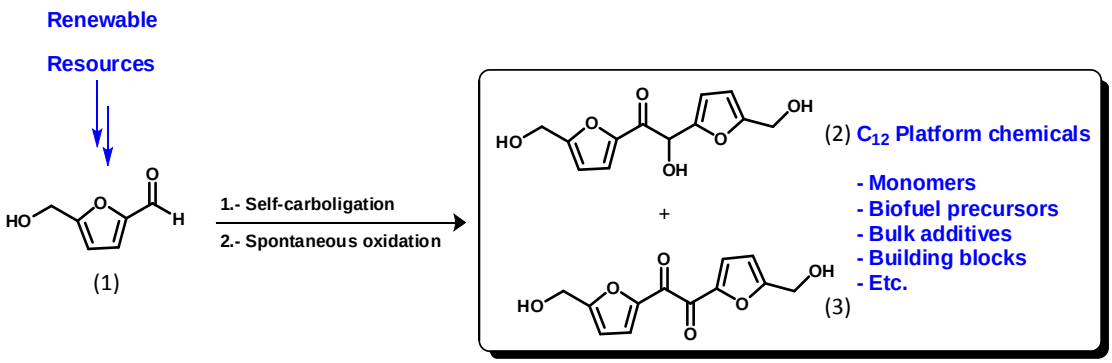
Benzaldehyde Lyase (BAL) results in an efficient biocatalyst for the *umpolung* carboligation of furfural, HMF, and mixtures of them, leading to blended C_{10}-C_{12} platform chemicals. Subsequently, the mixing and gentle heating (< 100 ºC) of the formed hydroxy-ketone with choline chloride leads to the formation of a novel biomass-derived deep-eutectic-solvent.

A key challenge in the production of cellulose-based chemical intermediates, fuels and novel solvents is the cost-effective transformation of highly functionalized carbohydrate moieties into value-added chemicals. One highly promising route is the production of furan derivatives, such as furfural or 5-hydroxymethylfurfural (HMF), from the acid-catalyzed dehydration of hexoses and pentoses. In particular, HMF is extremely versatile and has the potential to become a key precursor to produce a range of chemicals and fuels in a sustainable biorefinery.[1] For example, HMF can be converted into a range of C_4 organic acids suitable for the production of biopolymers by selective oxidation reactions, whereas stable gasoline blending agents (such as dimethyl furan) or solvents (THF) can be produced from decarbonylation and hydrogenation. Moreover, key pharmaceutical precursors can also be produced by amidation or esterification reactions, e.g. the etherification of HMF to yield larger intermediates suitable for retroviral drugs or polymer precursors. However, to further broaden the applications, e.g. to access suitable surfactants or precursors to jet and diesel fuels, the carbon number must be increased to the C_{10}-C_{18} range. This can be achieved chemically through HMF self-condensation – yielding a C_{12} derivative – or from aldol condensation with additional acetone to access higher carbon range precursors.[2-4] Moreover, starting with fractions containing different proportions of furfural and HMF, blended mixtures (C_{10} to C_{12}) may be achieved. All these compounds can then be either partially hydrogenated to retain functionality for additives or fully hydrogenated to yield hydrocarbon fuels. In this area, a promising but not yet sufficiently explored option for HMF valorization would be its self-condensation in *umpolung* fashion to afford C_{12} platform chemicals, both the formed hydroxy-ketone and the subsequently oxidized diketone.

By looking at the high functionalization of those molecules, from a chemical perspective a broad range of options can be anticipated (Scheme 1). HMF is highly reactive, being prone to self-oligomerizations, by-product formation and undesired reactions under severe process conditions. Thus, the set-up of HMF-based derivatizations operating under mild and efficient conditions at the same time would become of utmost importance. To this end, for the self-condensation of HMF, organocatalysis – based on NHC carbenes –, has been proposed by several research groups, as a mild technology avoiding product degradation.[5]



Scheme 1 Self-carboligation of HMF in *umpolung* fashion, produced molecules and some applications thereof.

In this communication, biocatalysis was successfully assessed for the self-carboligation of HMF for the first time. The use of enzymes (both free or immobilised) and whole-cells has gained considerable interest over the past decades, with an ample range of industrial processes already implemented.[6] Compared to other catalytic technologies, apart from the well-known high selectivities and mild reaction conditions inherent to enzymes, another important asset is that biocatalysts can be produced at large scale *via* fermentation of recombinant microorganisms.

Thus, once (bio)catalyst design is performed (e.g. *via* directed evolution), the requested quantities of the enzyme can be straightforwardly produced under environmental conditions. Last but not least, once the most appropriate biocatalyst has been designed, the use of (immobilized) biocatalysts – either free enzymes or whole-cells – may decrease process costs considerably,[7] an aspect that will become obviously crucial in the production of low-added value (bio)commodities, e.g. the aforementioned HMF-based ones.

For the condensation of HMF the use of lyases,[8] specifically thiamine-diphosphate dependent lyases (ThDP-lyases), was considered. ThDP-Lyases represent a useful group of enzymes delivering α-hydroxy-ketones by the carboligation of two aldehydes. In this group, Benzaldehyde Lyase (BAL) from *Pseudomonas fluorescens* is a remarkable case, from which many enantio- and diastereo-selective applications including aromatic and aliphatic aldehydes as substrates have been reported over the last few years.[8,9] Furthermore, there are some outstanding examples of lyases in general, and BAL in particular, catalyzing highly efficient processes with excellent productivities by means of whole-cell overexpressing systems.[10] Thus, once the proof-of-concept is shown, a subsequent optimization would allow the set-up of a robust biocatalytic process for HMF condensation.

While BAL-catalyzed furoin production (condensation of furfural to afford C_{10} derivatives) was described years ago,[8,9] to our knowledge the use of lyases for (the more challenging) HMF condensation has not been assessed to date. In our concept, BAL would operate under mild aqueous conditions – using a cosolvent for substrate solubility – at room temperature leading to the formation of the hydroxy-ketone 2. It may be expected that some spontaneous oxidation of 2 to afford the diketone 3 will be

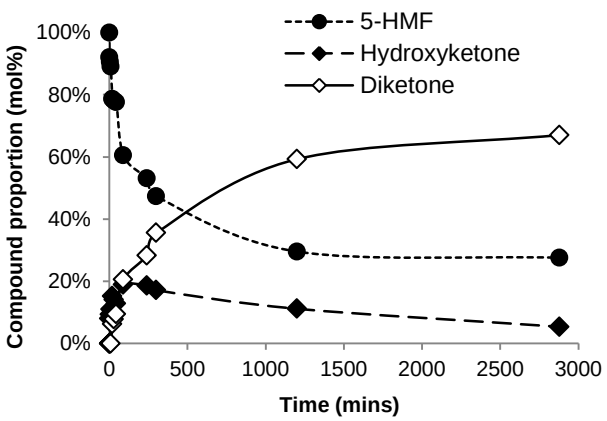


Fig. 1 BAL-catalyzed condensation of HMF. Conditions: 20 mM HMF, 1 mg mL^{-1} BAL, 40 mM ThDP, potassium phosphate buffer (pH 8) with 20 vol% DMSO co-solvent at room temperature

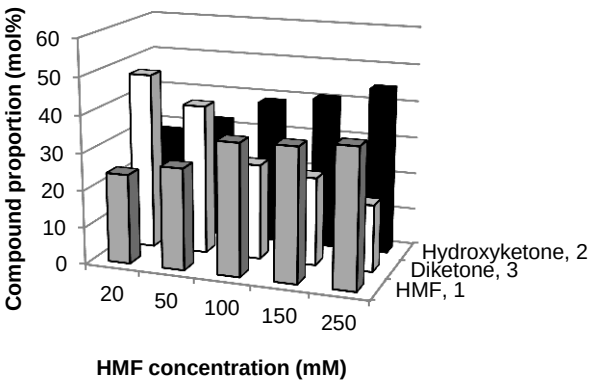


Fig. 2 Ratio of substrate (HMF), hydroxy-ketone and diketone at 18 h and at different HMF concentrations. Conditions: variable 20-250 mM HMF, 1 mg mL^{-1} BAL, 40 mM ThDP, potassium phosphate buffer (pH 8) with 20 vol% DMSO co-solvent at room temperature, 18 h.

observed. Kinetic results of the BAL-catalyzed process using HMF (20 mM) for proof-of-principle experiments are depicted in Figure 1. Gratifyingly, BAL is able to accept HMF as substrate to afford the hydroxy-ketone 1. Moreover, under these proof-of-concept and non-optimized conditions an initial rate of ~ 7 g L^{-1} h^{-1} of hydroxy-ketone 2 was observed. The reaction proceeded until a conversion of around 70 % was reached. This is a slightly reduced yield in comparison to the NHC carbene catalysts that have been reported to produce yields in excess of 90% on heating over an hour.[5] Presumably BAL – herein used as free enzyme (less stable than within a whole cell or when immobilized) – becomes deactivated at that time. Furthermore, the oxidized diketone 3 is also observed after some time, formed at the cost of 2. This spontaneous oxidation is not observed in the carbene catalysed processes.[5] From a process development viewpoint, the establishment of immobilized BAL-containing whole-cells should enable the stable production of 2 under continuous processing, thus performing rapidly the downstream processing and avoiding further oxidation to the diketone. Nevertheless, it must be noted that both products, 2 and 3, may encounter potential applications in many fields.

Once BAL-catalyzed proof-of-concept was successfully shown, further experiments with regard to HMF concentration (20-250 mM) and oxidation patterns were conducted. Reactions were run for 18 h, and then analyzed (Figure 2). Interestingly, BAL is able to perform the carboligation even at higher HMF loadings of up to 250 mM, leading to a remarkable accumulation of ~ 35 g L^{-1} of hydroxy-ketone 2, though the conversion of HMF was reduced slightly from 75% to 63%. The presence of the oxidized diketone 3 is detected at the higher loadings of HMF yet at significantly lower proportions than in the previous experiment. For example, the diketone made up only 18% of the product mixture at an HMF loading of 250mM compared with near 60% at 30mM HMF loading. Presumably, the spontaneous (non-enzymatic) oxidation rate remains constant in all reaction conditions, whereas the enzymatic process undergoes faster at higher concentrations (before the free enzyme gets deactivated), thus accumulating 2 in the reaction system.

Encouraged by these results, subsequent alternative aqueous mixtures of furfural and HMF were assessed (as would be

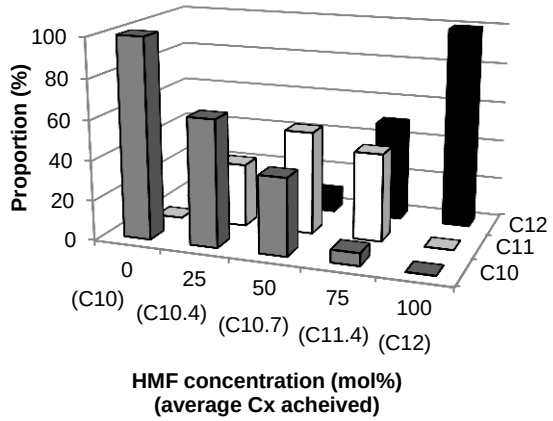


Fig. 3 BAL-catalyzed carboligation of aqueous mixtures of furfural and HMF in different proportions, leading to blended C_{10}-C_{12} compounds. Conditions: 20mM total substrate consisting of varying proportions of HMF and furfural, 1 mg mL^{-1} BAL, 40 mM ThDP, potassium phosphate buffer (pH 8) with 20vol% DMSO co-solvent at room temperature over 18h.

produced from actual biorefineries whereby pretreatment has been conducted). Depending on the initial proportion of both furans, different blended mixtures C_{10}-C_{12} may be expected. This may open a novel way of valorizing such mixtures, especially when mixtures with a C_x average range are needed. Results are depicted in Figure 3. Gratifyingly, BAL is able to also form mixtures of furfural-HMF, thus leading to C_{11} derivatives. Depending on the initial concentration of the furans, mixtures with C_x averages from C_{10} to C_{12} were achieved.

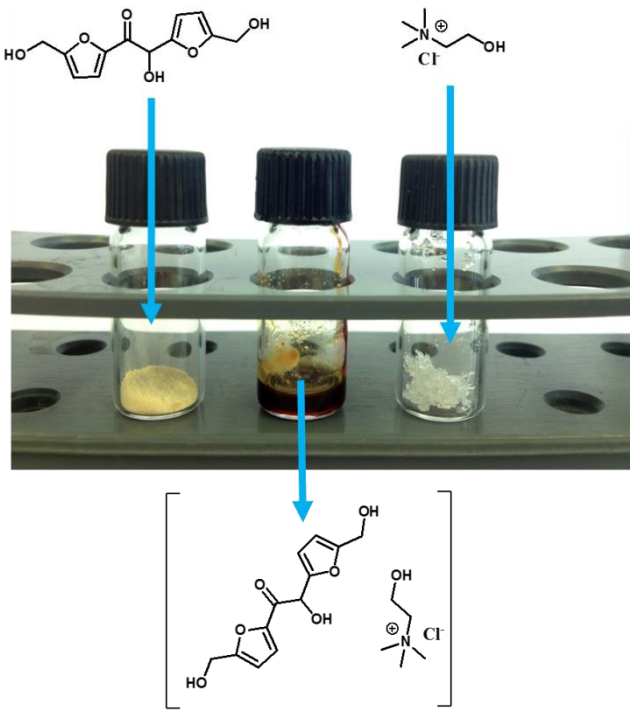


Fig. 4 Formation of a DES composed of hydroxy-ketone 2 (1 mol) and choline chloride (1 mol), to afford a liquid viscous solution at room temperature.

This was achieved with the BAL retaining higher activity than on conversion of the HMF alone. Given the broad substrate range acceptance of BAL – also using aliphatic aldehydes such as acetaldehyde or butyraldehyde, among others, with the concept herein provided, numerous possibilities for bio-based product upgrading can be envisaged.

Apart from HMF upgrading to C_{12} derivatives, within biorefineries another important trend is the identification of novel biomass-derived neoteric solvents that may be further used for varied applications. For instance, several deep-eutectic-solvents (DES) formed by the combination of a hydrogen-bond donor (HBDs, e.g. alcohols, carboxylic acids) and quaternary ammonium salts, such as choline chloride, have been recently reported.[11] Herein, the obtained HMF-based hydroxy-ketone 2 resulted to be a yellowish solid powder. However, bearing three –OH groups in its structure, it might become a promising HBD to form DES. If successful, this approach might lead to the provision of a series of novel neoteric solvents based on HMF-C_{12} derivatives. Thus, the formation of a deep-eutectic-solvent (DES) between 2 as HBD and choline chloride (1:1 mol: mol) was assessed. Successful results are depicted in Figure 4, where it is seen that the combination and gentle mixing (< 100 ºC) of two solids leads to the formation of a stable viscous liquid at room temperature.

Conclusions

In summary, this communication reports successfully for the first time the use of lyases as biocatalysts for the *umpolung* carboligation to upgrade HMF to C_{12} platform chemicals. Under non-optimized conditions initial rates of ~ 7 g hydroxy-ketone 2 L^{-1} h^{-1} have been observed, with accumulation of the product up to 35 g L^{-1}. Moreover, aqueous mixtures of furfural and HMF can be valorized, leading to blended C_{10}-C_{12} composition, promising for further hydrogenation to deliver tailored blends. For these synthetic approaches, the further choice of a better cosolvent – rather than challenging DMSO –, together with biocatalyst design and process set-up (e.g. use of immobilized BAL or immobilised whole-cells overexpressing BAL) may certainly deliver robust reaction conditions for the valorization of biogenic furans, furfural and HMF. The intrinsic reactivity makes the biocatalytic approach highly appealing for further research and development. Furthermore, the formation of novel DES may lead to novel exciting applications of them as biomaterials and / or solvents.

Notes and references

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† Benzaldehyde lyase from *Pseudomonas fluorescens* was cloned and overexpressed in *E. coli* cells, and produced by fermentation.[9] After fermentation, BAL was lyophilized and stored at -20°C until use. BAL characterization was performed using benzaldehyde as substrate, and benzoin formation as reaction test, as reported elsewhere.[9]*Standard reaction with BAL for HMF carboligation*.- To a mixture of 40 mL potassium phosphate buffer (pH 8) with DMSO (20 vol%) was added ThDP (2 mg, 4.03 x 10^{-3} mmol) and BAL (40 mg). HMF (100.89 mg, 0.8 mmol) was then added to the reaction and the vessel stoppered. The reaction was allowed to stir for 18 h at room temperature. The reaction was quenched by addition of 80 mL EtOAc and the product extracted into the same. EtOAc was removed under reduced pressure and the product dried under high vacuum. Characterisation was effected through NMR spectroscopy. *Standard reaction with BAL with aqueous mixtures of furfural and HMF*.- To mixtures of 20 mL potassium phosphate buffer (pH 8) with DMSO (20 vol%) was added ThDP (1mg, 2.02 x 10^{-3} mmol) and BAL (20 mg). HMF and furfural were then added in varying molar proportions (75/25, 50/50, 25/75) to make up 0.4 mmol total substrate and the reaction vessels stoppered. The reactions were allowed to stir for 18 h at room temperature. The reactions were quenched by addition of 40 mL EtOAc and the products extracted into the same. EtOAc was removed under reduced pressure and the products dried under high vacuum. Characterisation was effected through NMR spectroscopy and mass spectrometry. *DES formation*.- 100 mg (0.41 mmol) HMF hydroxyl-ketone 2 and 59.0 mg choline chloride (0.41 mmol) (both solids) were stirred in a GC vial in a molar ratio of 1:1 at 60-70 °C for ~ 1 hour. When cooled down, the viscous liquid remained.

We would like to thank Dr. Catherine Lyall (Bath, UK) for her outstanding assistance in the NMR analysis, and gratefully ackonwledge financial support from DFG training group 1166 "BioNoCo" ("Biocatalysis in Non-conventional Media"). The authors would also like to extend their thanks to the EPSRC for partially funding this work through the Doctoral Training Centre in Sustainable Chemical Technologies (EP/G03768X/1) and to Roger and Sue Whorrod for their kind endowment to the University resulting in the Whorrod Fellowship in Sustainable Chemical Technologies held by Dr. C. Chuck.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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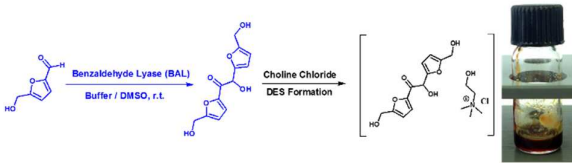
GRAPHICAL ABSTRACT



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Upgrading Biogenic Furans: Blended C_{10}-C_{12} Platform Chemicals via Lyase-Catalyzed Carboligations and Formation of Novel C_{12} – Choline Chloride-Based Deep-Eutectic-Solvents.**

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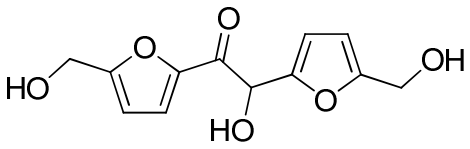
Analysis of products.

NMR-Spectroscopy. NMR spectra for HMF coupled products were recorded on a 300 MHz (^{1} H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz) Bruker device from BioSpin GmbH at 20 °C. ^{1}H NMR spectra for HMF-furfural cross coupled products were recorded on a 500 MHz Bruker Ultrashield Plus device. Chemical shifts are relative to the used solvents (acetone-d_6: ^{1}H: δ = 2.09 ppm, ^{13}C: δ = 30.6 ppm (CD$_3$)), indicated in ppm.

Mass Spectrometry. EI Mass spectra for coupled furfural products were measured with a "Finnigan SSQ 7000" device. Spectra for HMF-furfural coupled products were recorded using a “Bruker MicrOTOF” ESI-TOF device.

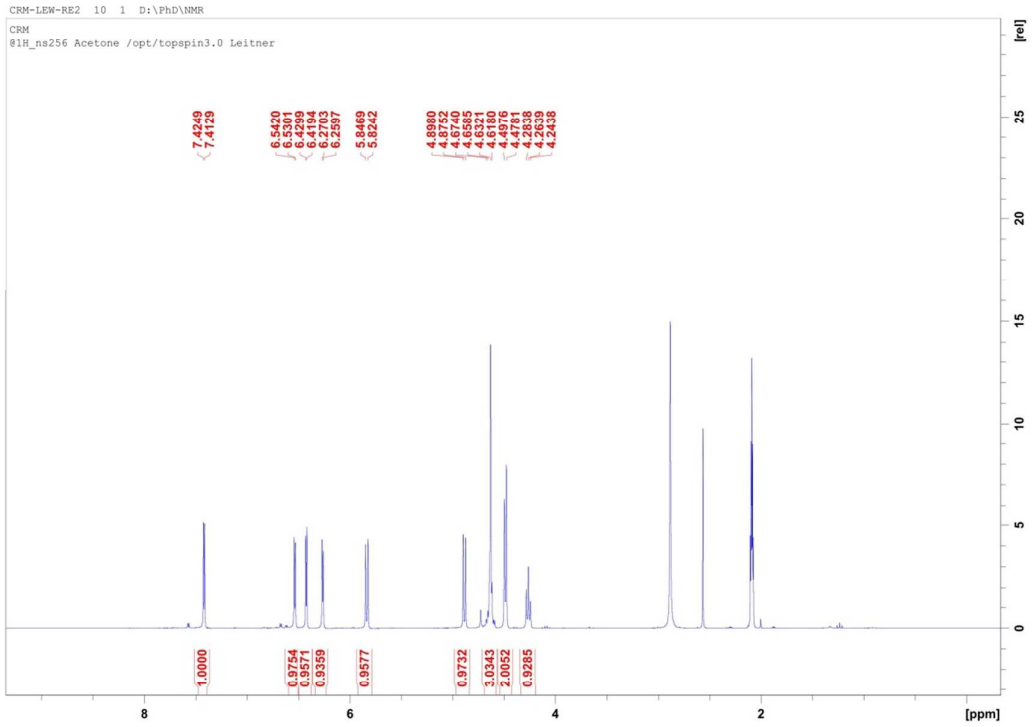
IR Spectroscopy. IR spectra were measured with a "Perkin-Elmer 100FT-IR" spectrometer and detected with an "UATR Diamond/KRS-5" device. The measurement was per-formed as differance spectra versus $CHCl_3$. The unit of the absorption signals is cm^{-1}. Signal intesities are characterized by following abbreviations: vs = very strong (0 - 20 %), s = strong (21 - 40 %), m = medium (41 - 60 %), w = weak (61 - 80 %), vw = very weak (81 - 90 %).

2-hydroxy-1,2-bis(5-(hydroxymethyl)furan-2-yl)ethanone



^{1}H NMR(acetone-d_6): δ 7.42 (d, J = 3.6 Hz, 1 H), 6.54 (d, J = 3.5 Hz, 1 H), 6.42 (d, J = 3.1 Hz, 1 H), 6.27 (d, J = 3.2 Hz, 1 H), 5.84 (d, J = 6.8 Hz, 1 H), 4.67 – 4.62 (m, 3 H), 4.49 (d, J = 5.9 Hz, 1 H), 4.26 (t, J = 6.0 Hz, 1 H) ppm.

^{13}C NMR (acetone-d_6): δ 185.9, 163.1, 157.7, 153.6, 150.7, 122.8, 111.0, 110.8, 109.5, 71.3, 58.3, 58.0 ppm;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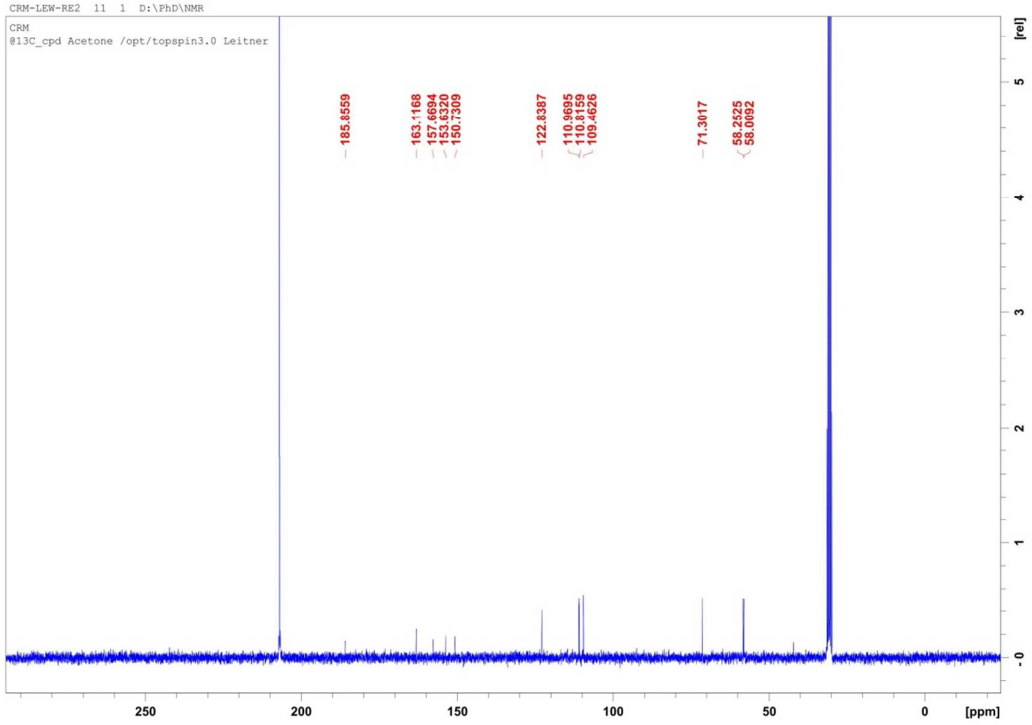
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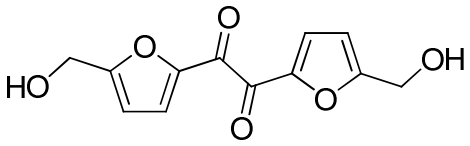
[ppm]

1,2-bis(5-(hydroxymethyl)furan-2-yl)ethane-1,2-dione



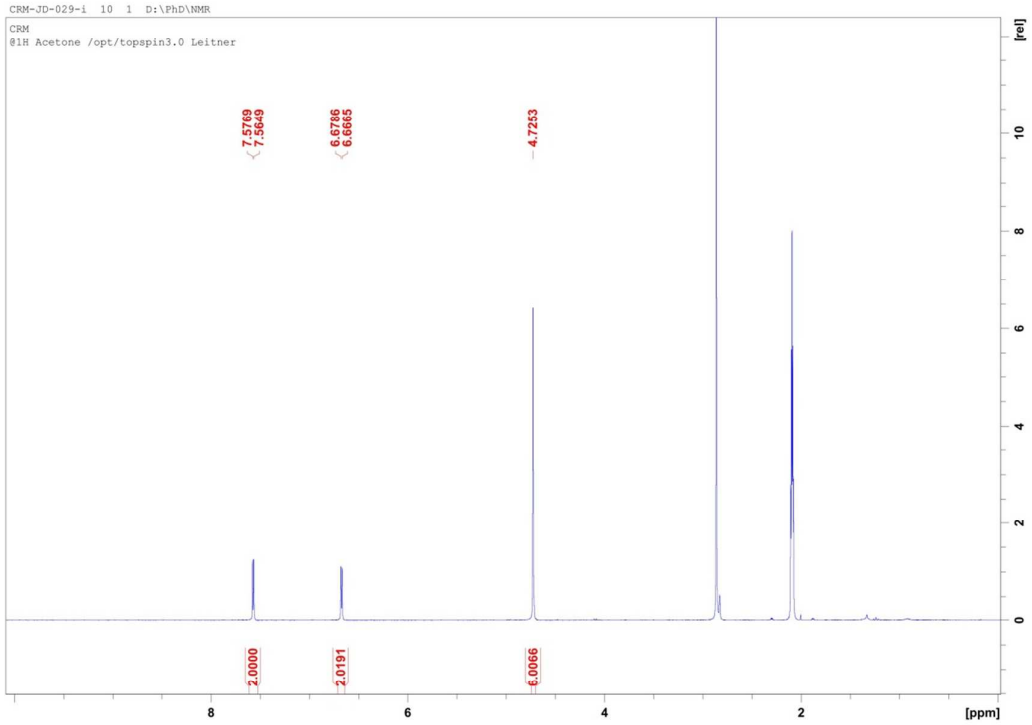
^{1}H NMR(acetone-d_6): δ 7.57 (d, J = 3.6 Hz, 2 H), 6.67 (d, J = 3.6 Hz, 2 H), 4.73 (m, 6 H) ppm;

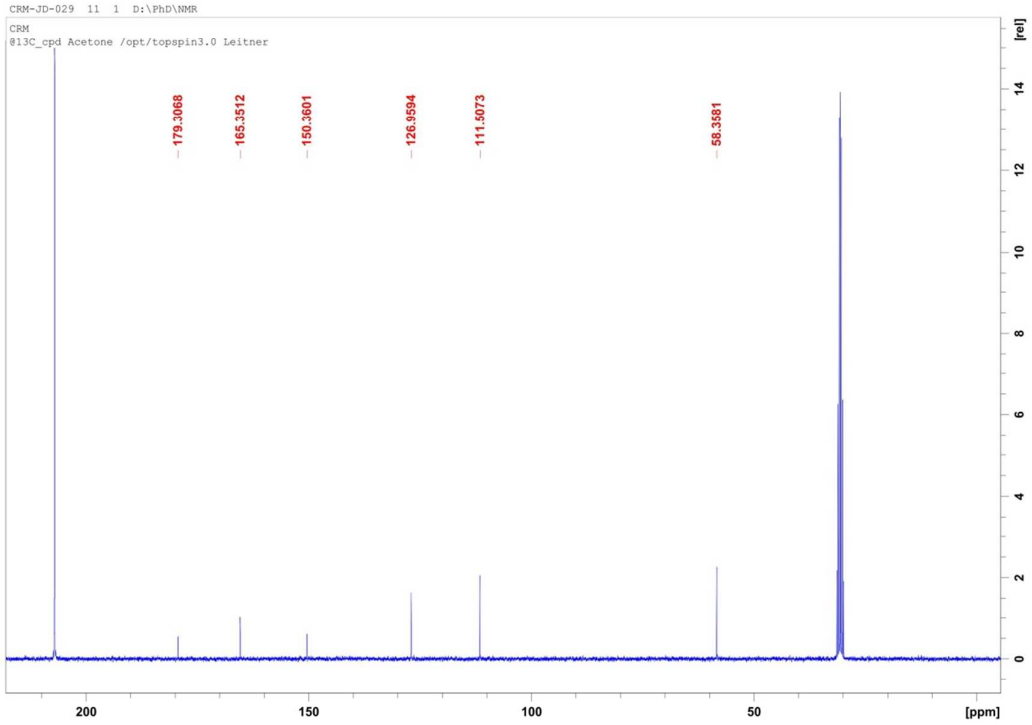
^{13}C NMR (acetone-d_6): δ 179.3, 165.4, 150.4, 127.0, 111.5, 58.4 ppm;

IR (KBr): ν = 3249 (s), 3120 (m), 2942 (vw), 2104 (vw), 1739 (m), 1633 (vs), 1497 (vs), 1437 (m), 1387 (m), 1339 (w), 1273 (m), 1231 (w), 1190 (s), 1019 (vs), 949 (vs), 822 (vs), 781 (vs), 685 (w) cm^{-1};

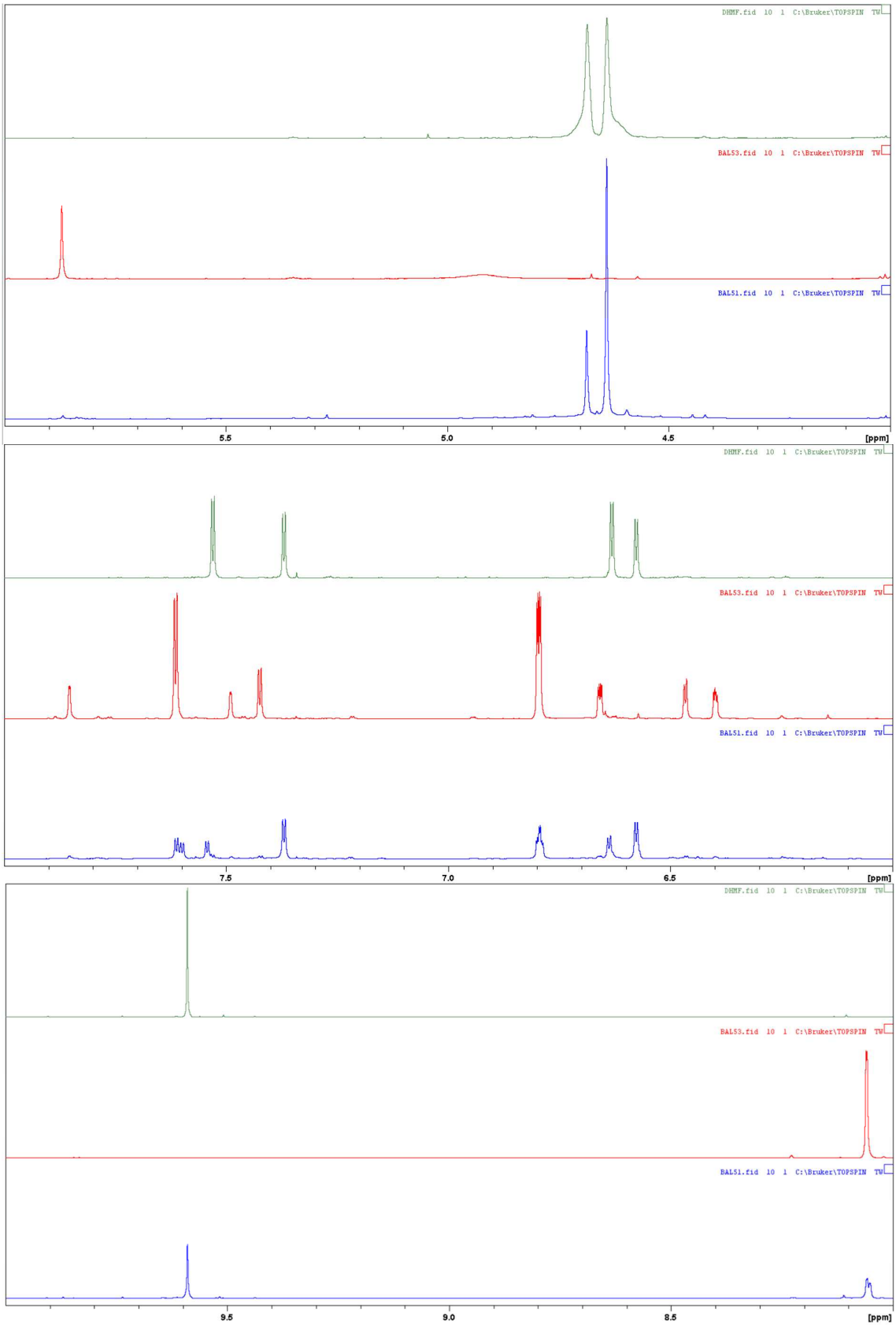
MS (EI, 100 eV): m/z (%) = 250 ([M]+, 15), 233 (43), 125 ($[C_6H_5O_3]^+$, 100), 69 (19), 52 (18), 51 (23), 50 (20).

HRMS (ESI): $[M]+Na^+$ calculated for $[C_{12}H_{10}O_6Na]^+$: 273.03696, found: 273.03699.


CRM-JD-029-i 10 1 D:\PhD\NMR
CRM
@1H Acetone /opt/topspin3.0 Leitner
7.5769
7.5649
6.6786
6.6665
4.7253
2.0000
2.0191
6.0066
[rel]
[ppm]

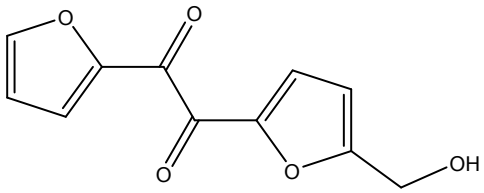

CRM-JD-029 11 1 D:\PhD\NMR
CRM
@13C_cpd Acetone /opt/topspin3.0 Leitner
179.3068
165.3512
150.3601
126.9594
111.5073
58.3581
[rel]
[ppm]

^{1}H NMR spectra for coupling reactions with HMF/Furfural substrate ratios of 100/0 (green), 0/100 (red) and 50/50 (blue)


DHMF.fid 10 1 C:\Bruker\TOPSPIN TW
BAL53.fid 10 1 C:\Bruker\TOPSPIN TW
BAL51.fid 10 1 C:\Bruker\TOPSPIN TW
5.5
5.0
4.5
[ppm]
DHMF.fid 10 1 C:\Bruker\TOPSPIN TW
BAL53.fid 10 1 C:\Bruker\TOPSPIN TW
BAL51.fid 10 1 C:\Bruker\TOPSPIN TW
7.5
7.0
6.5
[ppm]
DHMF.fid 10 1 C:\Bruker\TOPSPIN TW
BAL53.fid 10 1 C:\Bruker\TOPSPIN TW
BAL51.fid 10 1 C:\Bruker\TOPSPIN TW
9.5
9.0
8.5
[ppm]

Conversions were calculated by identification of product peaks through comparison to substrate spectra and spectra of isolated coupled HMF products. Subsequent integration of relevant peaks yielded relative quantities of each product.

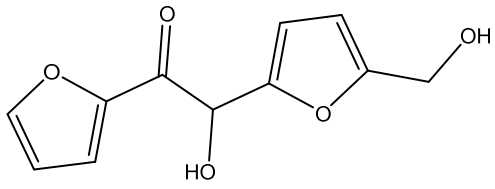
1-(furan-2-yl)-2-(5-(hydroxymethyl)furan-2-yl)ethane-1,2-dione



^{1}H NMR (500 MHz, acetone-*d6*): 4.68 ((br)s, 2H) 6.64 (dt, *J*= 3.7, 0.7 Hz, 1H) 6.79 (dd, *J*= 3.6, 1.7 Hz, 1H) 7.55 (dt, *J*= 3.6, 0.4 Hz, 1H) 7.60 (dd, 3.7, 0.7 Hz, 1H) 8.05 (dd, *J*= 1.7, 0.8 Hz, 1H)

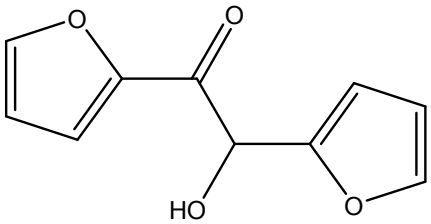
HRMS (ESI): $[M]+Na^{+}$ calculated for $[C_{11}H_8O_5Na]^{+}$: 243.0298, found: 243.0255.

1-(furan-2-yl)-2-hydroxy-2-(5-(hydroxymethyl)furan-2-yl)ethanone



HRMS (ESI): $[M]+Na^{+}$ calculated for $[C_{11}H_{10}O_5Na]^{+}$: 245.0398, found: 245.0407.

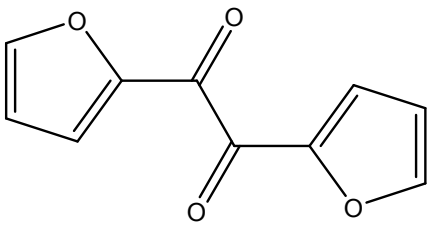
1,2-di(furan-2-yl)-2-hydroxyethanone



^{1}H NMR (500 MHz, acetone-d_6): 5.87 (s, 1H) 6.40 (ddd, *J*= 3.3, 1.8, 0.3 Hz, 1H) 6.47 (ddd, *J*= 3.3, 0.8, 0.4 Hz, 1H) 6.66 (dd, *J*=3.6, 1.7 Hz, 1H) 7.43 (dd, *J*= 3.6, 0.7 Hz, 1H) 7.49 (dd, *J*= 1.8, 0.8 Hz, 1H) 7.85 (dd, *J*= 1.7, 0.7 Hz, 1H)

HRMS (ESI): $[M]+Na^+$ calculated for $[C_{10}H_8O_4Na]^+$: 215.0298, found: 215.0278.

1,2-di(furan-2-yl)ethane-1,2-dione



^{1}H NMR (500 MHz, acetone-d_6): 6.80 (dd, *J*= 3.7, 1.7 Hz, 2H) 7.62 (dd, *J*= 3.7, 0.7 Hz, 2H) 8.06 (dd, *J*= 1.7, 0.7 Hz, 2H)

HRMS (ESI): $[M]+Na^+$ calculated for $[C_{10}H_6O_4Na]^+$: 213.0198, found:213.0161.