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Biobased solvents for the Baylis-Hillman reaction of HMF[†]

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Electronic Supporting Information

1.1 General Methods.

All reactions were performed without the protection with an inert atmosphere. Solvents were either ACS reagent grade or HPLC grade. Isomaltulose was a gift from Cargill. HMF was purchased from Carbosynth and furfural from Sigma-Aldrich. Solvents were used without any further purification. The reactions were monitored by TLC, on Silica Gel 60 F254 (Merck), and detection was carried out with UV light (254 nm) and/or charring with a 5% phosphomolybdic acid solution in ethanol containing 10% H_2SO_4, or a 1% potassium permanganate solution in water. Silica gel (Kieselgel 60, 70-230 mesh ASTM, Merck) was employed for column chromatography. All reagents were purchased at the highest commercial quality and used without further purification, unless otherwise noted. The ^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 100 MHz) spectra were recorded with Brucker ALS300, DRX300 and DRX400 spectrometers. Chemical shifts are given in ppm. Coupling constants are expressed in Hertz and splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra were obtained using an electro spray technique in positive mode, with a Thermo-Finnigan MAT 95 XL spectrometer.

Conditions for BH reactions of HMF:

In a typical reaction, HMF (126 mg, 1.0 mmol) was mixed with DABCO (112 mg, 1.0 mmol) and ethyl acrylate (200 mg, 2.0 mmol) in 2 mL of EtOH/H_2O (1/1, v/v), under air. The reaction was monitored by TLC and, upon completion, the reaction mixture was diluted with tert-butyl methyl ether (20 mL) and HCl (1 M, 2 mL) and then neutralized with a saturated $NaHCO_3$ solution. The aqueous layer was separated and further extracted with tert-butyl methyl ether (2 x 20 mL). After drying the combined organic layers over $NaSO_4$, followed by filtration and evaporation under reduced pressure (10-100 mm Hg, rotary evaporator), the crude mixture was purified by column chromatography, eluting with CH_2Cl_2/Et_2O (1:1), to give the product (169 mg, 75%) as a colourless liquid. When higher boiling point solvents were used, such as THFA, the evaporation step prior to chromatography was continued by distillation under vacuum (0.1-1 mm Hg).

Ethyl 2-[hydroxy-(5-hydroxymethyl-furan-2-yl)methyl] acrylate (3). Colorless liquid, ^{1}H NMR (300 MHz, MeOD) 1.24 (t, 3H, J_a = 6.9 Hz, J_b = 14.1 Hz, $OCH_2C\underline{H_3}$), 4.10~4.25 (m, 2H, $OC\underline{H_2}CH_3$), 4.48 (s, 2H, H-6), 5.59 (s, 1H, H-7), 6.06 (d, 1H, *J* = 1.2 Hz, H-9a), 6.14 (d, 1H, *J* = 3.0 Hz, H-3), 6.24 (d, 1H, *J* = 2.7 Hz, H-4), 6.37 (d, 1H, *J* = 0.9 Hz, H-9b); ^{13}C NMR (75 MHz, MeOD) 14.4 ($OCH_2\underline{C}H_3$), 57.4 (C-6), 61.9 ($O\underline{C}H_2CH_3$), 66.4 (C-7), 108.8 (C-3), 109.1 (C-4), 125.7 (C-9), 142.6 (C-8), 155.8 (C-5), 156.1 (C-2), 167.2 ($\underline{C}O_2Et$). MS m/z (ESI) calculated for $C_{11}H_{14}NaO_5$, $[M + Na]^+$ 249.0733; found 249.0734.

Furfural as the starting aldehyde:

The same procedure as above was followed except that, in the final purification, Et_2O was used as the eluent.

Ethyl 2-[hydroxy-(furan-2-yl)methyl] acrylate (5).

Reference: D. Basavaiah, M. Krishnamacharyulu, A. J. Rao. *Synth. Commun.* **2000**, *30*, 2061-2069.

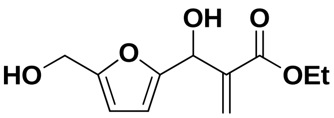
Pale yellow liquid, ^{1}H NMR (300 MHz, MeOD): 1.22 (t, 3H, J_a = 7.2 Hz, J_b = 14.4 Hz, $OCH_2C\underline{H}_3$), 4.10~4.25 (m, 2H, $OC\underline{H}_2CH_3$), 5.60 (s, 1H, H-7), 6.03 (s, 1H, H-9a), 6.14 (dd, 1H, J_a = 1.8 Hz, J_b = 3.0 Hz, H-3), 6.19 (d, 1H, *J* = 3.0 Hz, H-4), 6.36 (s, 1H, H-9b); 7.44 (d, 1H, *J* = 0.9 Hz, H-5); ^{13}C NMR (75 MHz, MeOD): 14.4 ($OCH_2\underline{C}H_3$), 61.9 ($O\underline{C}H_2CH_3$), 66.4 (C-7), 108.1 (C-3), 111.3 (C-4), 125.6 (C-9), 142.3 (C-8), 143.4 (C-5), 156.4 (C-2), 167.2 ($\underline{C}O_2Et$).MS m/z (ESI) calculated for $C_{11}H_{14}NaO_5$, $[M + Na]^+$ 219.0628; found 219.0638.

GMF as the starting aldehyde:

Reference : J. -N. Tan, M. Ahmar, Y. Queneau, *RSC*. Adv., **2013**, *3*, 17649-17653.

GMF was prepared as previously reported by Lichtenthaler et al.: D. Martin, F. W. Lichtenthaler, *Tetrahedron: Asymmetry.* **2006**, *17*, 756-762. A solution of 10.0 g (30.0 mmol) isomaltulose in anhydrous DMSO (70 mL) was heated to 120 °C, 1.2 g of Dowex 50 WX4 (H^+ form) and freshly desiccated molecular sieve (4A°, 6.0 g) were added, and stirring was continued for 3 h at 120 °C, at which point TLC indicated the absence of educts in favor of GMF and some HMF. Filtration, removal of the solvent in a vacuum provided syrup, which was then purified by elution from a silica gel column with acetone, yielded the desired product: 5.5 g (63%) of GMF as a yellow liquid.

GMF (145 mg, 0.5 mmol) was then mixed with DABCO (56 mg, 0.5 mmol) and ethyl acrylate (100 mg, 1.0 mmol) in 1 mL of EtOH/H_2O (1/1, v/v), under air. The reaction was monitored by TLC and, upon completion; HCl (1 M, 1 mL) was added and then neutralized with a saturated $NaHCO_3$ solution. After removing the solvent under vacuum, the crude mixture was purified by column chromatography, eluting with AcOEt/CH_3OH (95:5), to give the product (97 mg, 50%) as a colorless liquid. When higher boiling point solvents were used, there was no need for complementary distillation under high vacuum as the R_f of the solvent and the adduct **7a** are very different. Adduct **7a** was identified by comparison with an authentic sample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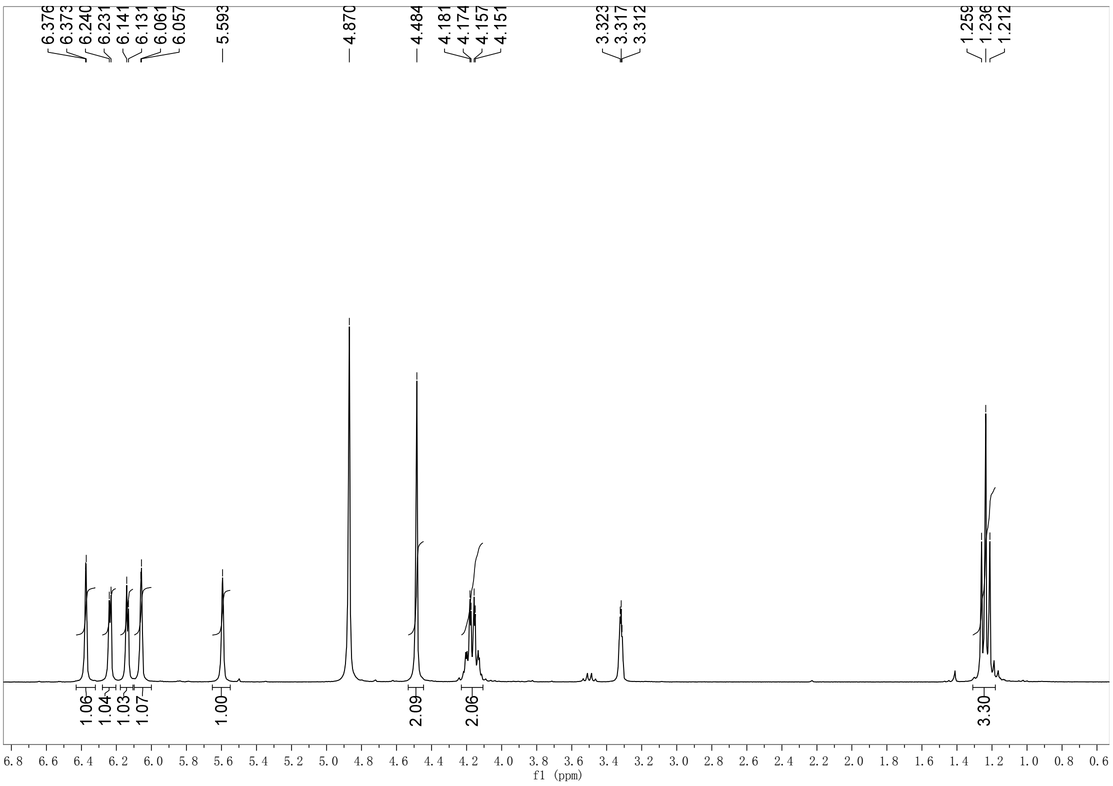
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1.04
1.03
1.07
1.00
2.09
2.06
3.30
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
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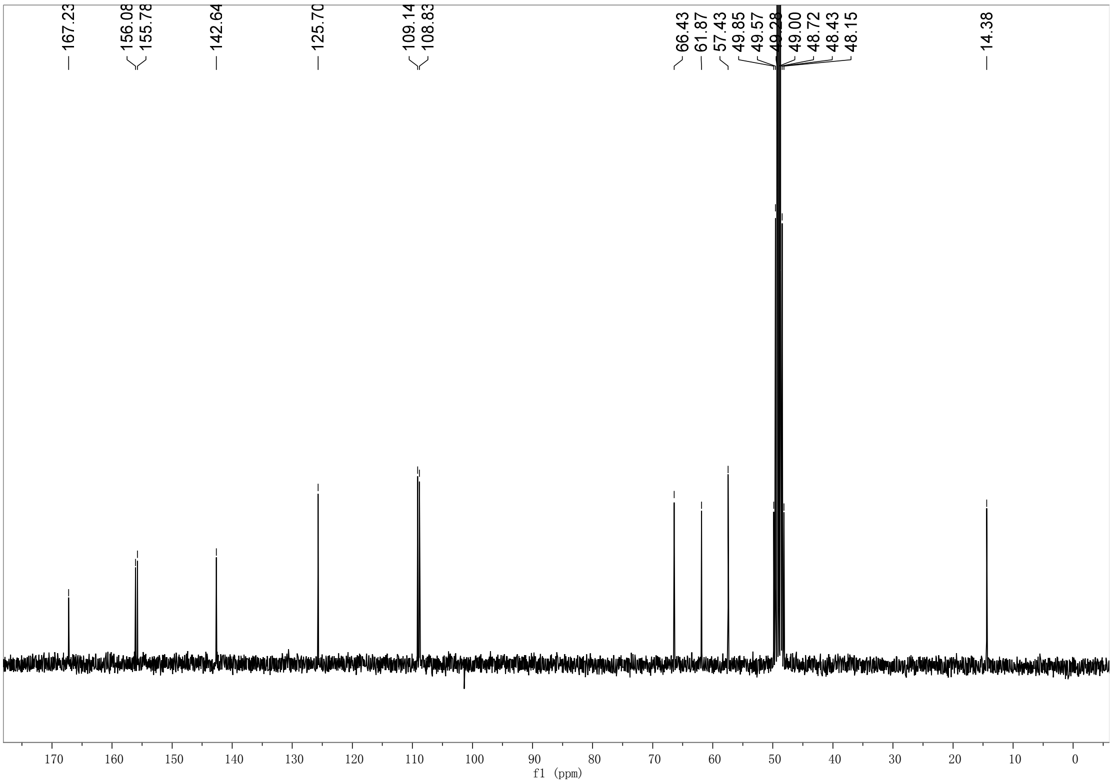
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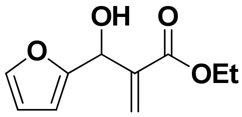
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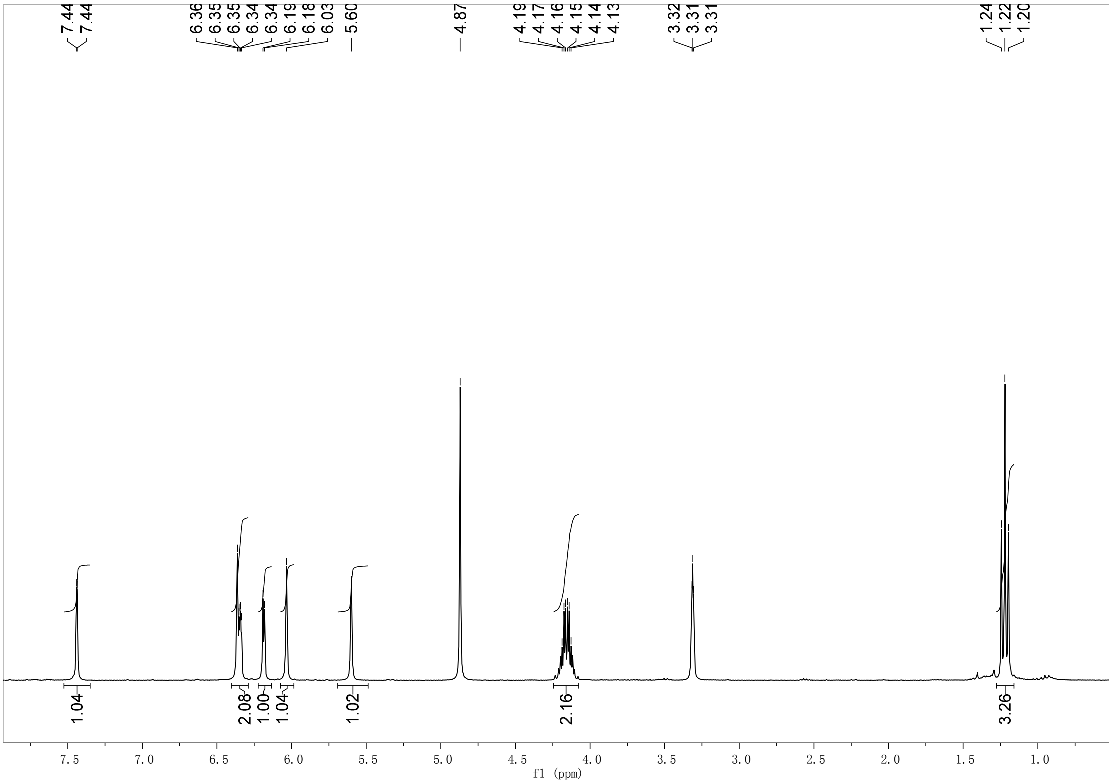
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3.31
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2.08
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1.02
2.16
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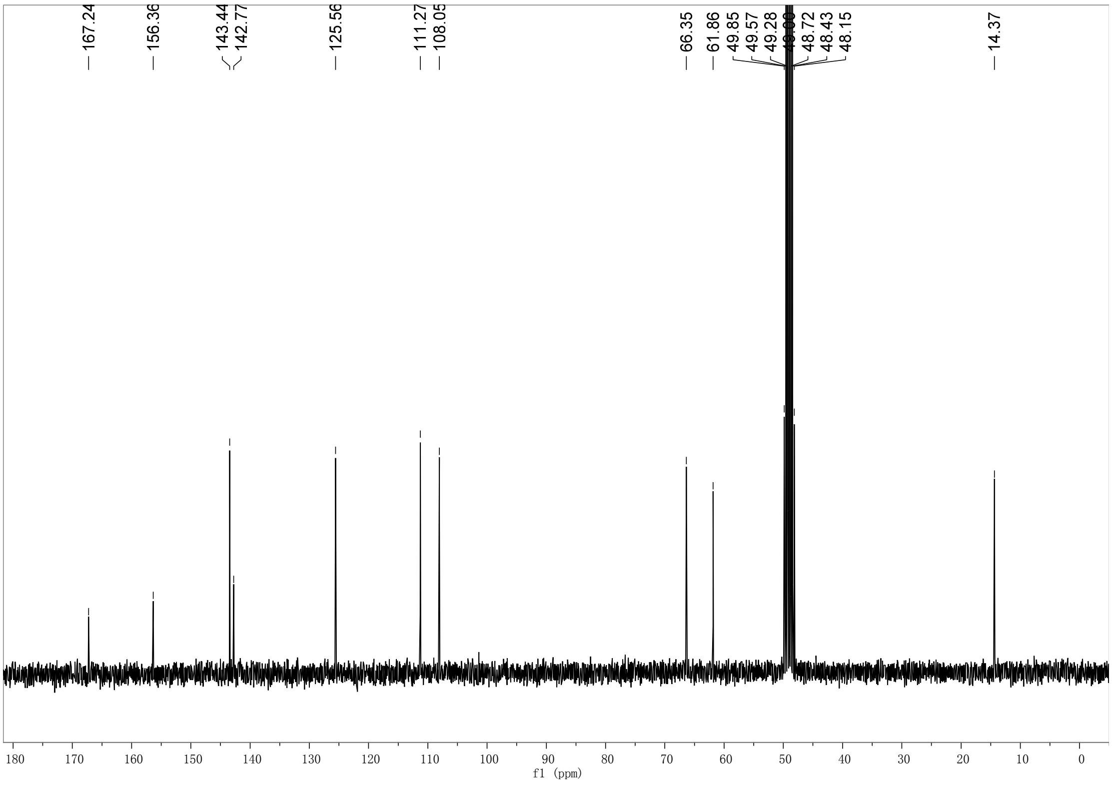
f1 (ppm)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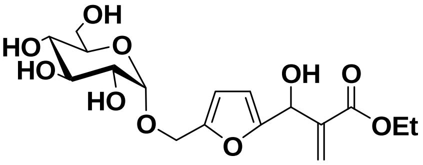
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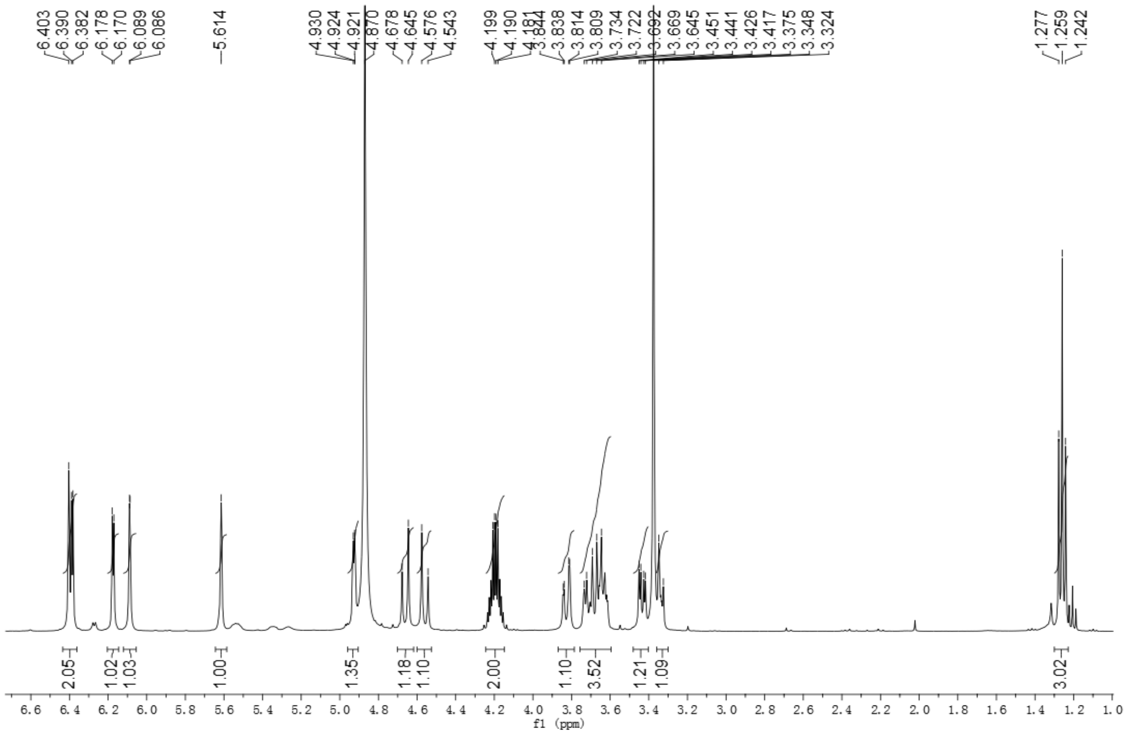
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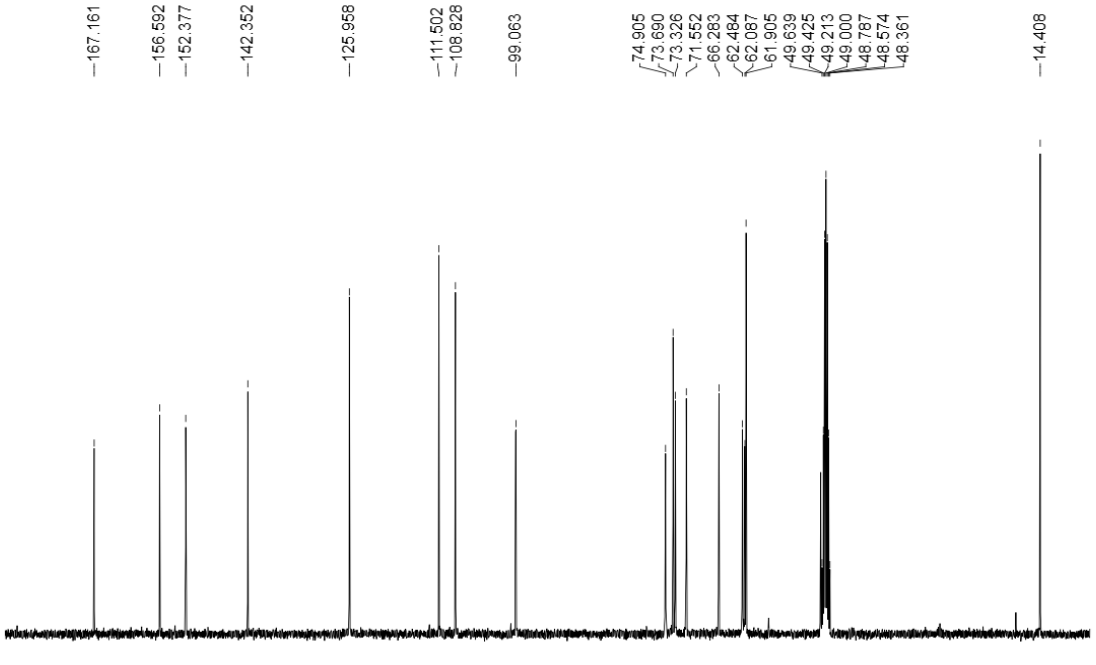
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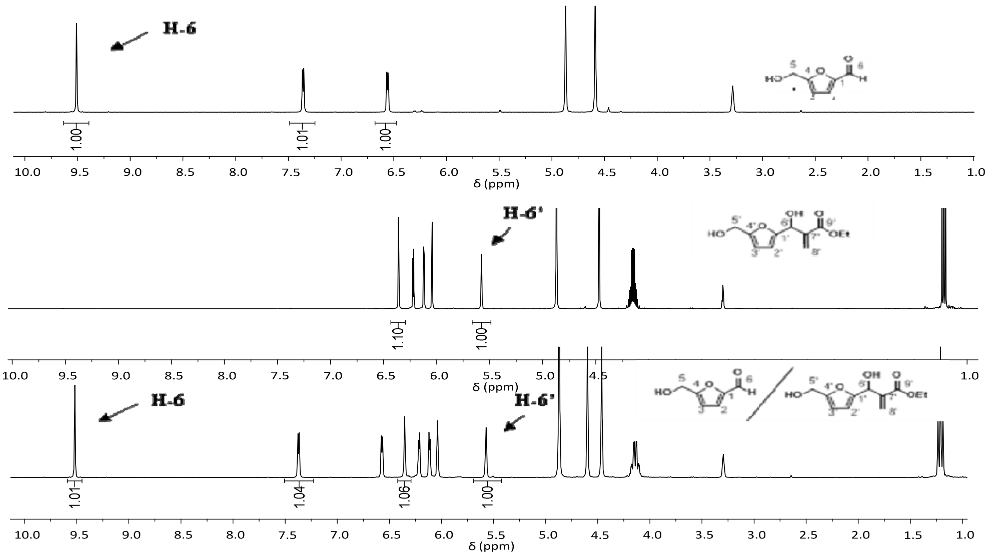
14.408
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

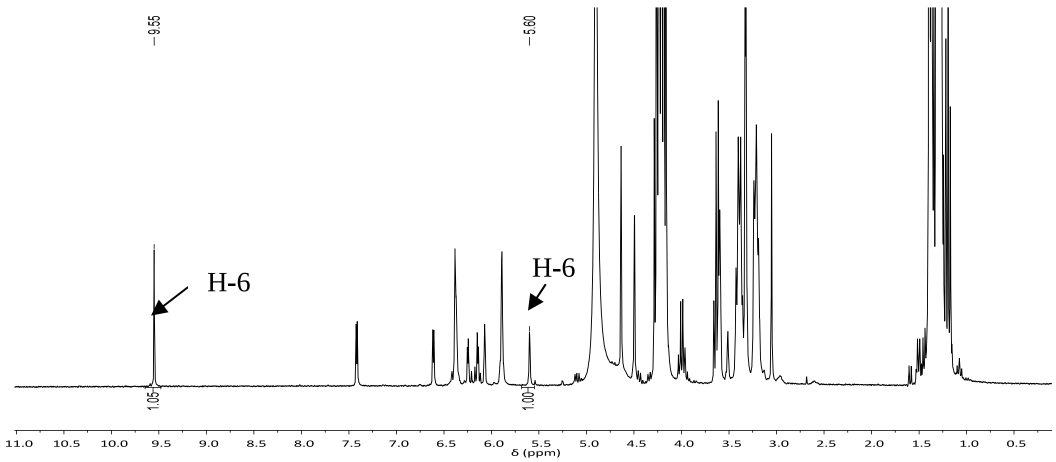
Solvent screening by NMR measuring the efficiency of the HMF to BH adduct transformation.

All reactions were conducted using a 1:2 molar ratio of HMF and ethyl acrylate, with one equimolar amount of DABCO. The efficiency of the reaction was estimated by measuring the **[3] / [1] + [3]** ratio by ^{1}H NMR, after 24 h at room temperature. The validity of the method was checked carefully by preparing authentic mixtures of **1** and **3**. Variations in these analytical ratios were consistent with the variations of isolated yields measured for a selected number of examples.

The conversions were estimated by measuring the integrations of specific peaks, in the ^{1}H NMR spectra, of an aliquot of the crude mixture of the BH reaction diluted in MeOD. Integrations were specifically measured on the aldehyde group at δ 9.51 ppm for HMF, while the MBH adducts were measured on the peak of the newly formed CHOH at δ 5.58 ppm. The figure below shows the ^{1}H NMR spectra of the mixture of some molar ratios of HMF and the MBH adducts which enabled us to verify the accuracy and validity of this method.



^{1}H NMR spectra of HMF, MBH adducts, and HMF/ MBH adducts (1/1) in MeOD



^{1}H NMR spectrum of an aliquot of the crude the MBH reaction of HMF in ethyl lactate/water in MeOD

Results of the preliminary solvent screening

$$\text{BH efficiency} \quad \frac{\text{peak area (MBH adducts)}}{\text{peak area (MBH adducts + HMF)}} \quad 100\%$$

Entry	Solvent	Solvent volume (mL/mL)	[3] / [1] + [3] (%)
1	EtOH	2	53
2	H_2O	2	82
3	isopropanol	2	38
4	ethyl lactate	2	30
5	diethyl succinate	2	0
6	MeTHF	2	0
7	THFA	2	60
8	2-hydroxymethyl furan	2	62
9	γ-valerolactone	2	14
10	isopropylideneglycerol	2	47
11	isopropanol/H_2O	1/1	90
12	EtOH/H_2O	1/1	91
13	ethyl lactate/H_2O	1/1	35
14	diethyl succinate/H_2O	1/1	50
15	MeTHF/H_2O	1/1	50
16	THFA/H_2O	1/1	90
17	2-hydroxymethyl furan/H_2O	1/1	71
18	γ-valerolactone/H_2O	1/1	37
19	isopropylideneglycerol/H_2O	1/1	89