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$CuAlO_x$ catalyst for the batch-flow tandem synthesis of amino acid-derived furfurylamines

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Contents

1. Chemicals

L-Alanine (99%), glycine (99%), DL-serine (99%), DL-valine (>99%), DL-phenylalanine (99%), DL-aspartic acid (>99%), DL-methionine (>99%), and furfural (99%) from Acros Organics (Belgium), as well as 5-hydroxymethylfurfural (99%) from Sigma-Aldrich (USA), were used without additional purification. Methanol (99.8%) from J.T. Baker (USA) was employed as a solvent.

2. Catalyst preparation

Cu-Al layered double hydroxide was prepared by co-precipitation method at pH 9.0 and temperature of 70 °C using the mixture of copper(II) nitrate and aluminum nitrate as starting material and solution containing NaOH and Na_2CO_3 ($[CO_3^{2-}]/[Al^{3+}]$ = 0.86, $[OH^-]$ = $1.6([Al^{3+}]+[Cu^{2+}])$ as precipitant agent. The aging of the obtained suspension was performed at 70 °C for 4 h. The precipitate was then filtered, washed with hot water, dried at 110 °C for 14 h, and calcined at 650 °C for 4 h.

3. General procedure for two-step reductive amination of furfural derivatives with amino acid salts

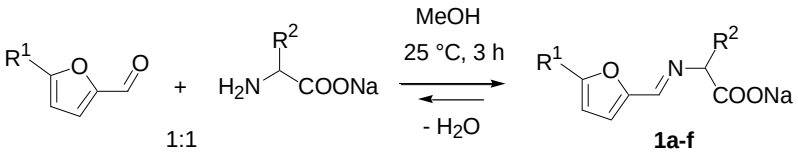
In a standard experiment, amino acid (1.25 mmol) and solid NaOH (1.25 mmol; 2.5 mmol in the case of aspartic acid) were dissolved with stirring in methanol (25 ml) at 35 °C. The resulting solution was mixed with an equimolar amount of HMF or furfural and kept at room

temperature for 3 h. To determine the imine yield, the solvent was removed from 0.5 ml aliquot in a flow of air, and the residue was analyzed by ^{1}H NMR in CD_3OD.

The obtained reaction mixture was hydrogenated in flow reactor. Catalytic experiments were performed in H-Cube Pro setup (Thalesnano, Hungary) equipped with stainless-steel CatCart®30 reactor (catalyst bed length of 24 mm, inner diameter of 4 mm). Before the catalytic run, the catalyst (0.17 g of 250–500 μm particles) was reduced with hydrogen in MeOH at 120 °C for 1 h (total pressure of 10 bar, flow rates of MeOH and H_2 were 0.5 and 30 ml min^{-1}, respectively). Afterwards, the reaction mixture was pumped through the reactor instead of pure solvent, and this point in time was chosen as the starting point of the experiment. The reaction was carried out at 100–110 °C, total pressure of 10 bar, liquid feed rate of 0.5 ml min^{-1} and hydrogen flow rate of 30 ml min^{-1} (inlet H_2/substrate molar ratio was 54). The performance of the catalyst was evaluated by analysis of the samples taken in the interval of 30–33 minutes from the beginning of the experiment. After the reaction, the catalyst was washed with methanol flow (0.5 ml min^{-1}) for 30 min and it can be introduced into the next reaction cycle. The composition of the reaction products was determined using ^{1}H NMR spectroscopy in D_2O.

4. Imine formation

Table S1 Condensation of HMF or furfural with amino acid sodium salts. [a]



Entry	R^1	R^2	Imine	Yield (%)
1	CH_2OH	Me	**1a**	91
2	H	Me	**1b**	91
3	CH_2OH	H	**1c**	93
4	CH_2OH	CH_2Ph	**1d**	90
5	CH_2OH	CH_2OH	**1e**	93
6	CH_2OH	CH_2COONa	**1f**	88

[a] Reaction conditions: aldehyde (0.05 M), sodium salt of amino acid (0.05 M), methanol, batch reactor, 25 °C, 3 h. The reaction products were analyzed by ^{1}H NMR in CD_3OD.

5. Elemental composition of the catalyst samples and final reaction mixture

The Cu, Al and Na content was measured by atomic absorption spectroscopy (AAS) on an Optima 4300 DV instrument (Perkin Elmer, USA).

After the reaction was finished, the reaction flow was switched to the flow of pure methanol (0.5 ml min^{-1}), and washing of the catalyst was proceeding during 30 min. The catalyst was then carefully removed from the cartridge and dried under vacuum at 40 °C for 3 h.
The resulting sample was analyzed by AAS. The elemental composition of the catalyst samples is shown in Table S2.

Table S2 Elemental composition of the catalyst samples.

Sample	Cu, %	Al, %	Na, %
As-prepared	47.2	19.9	0.004
After one cycle	47.2	19.6	0.14
After two cycles	47.3	19.3	0.37

To determine Na, Al and Cu content in the final reaction mixture, methanol was removed from 15 ml of the liquid product and the same amount of distilled water was added. According to AAS, the liquid product obtained by reductive amination of HMF with alanine sodium salt on as-prepared $CuAlO_x$ catalyst contains 0.04 M Na, 0.0002 M Al and a negligible amount of Cu ($<10^{-5}$ M).

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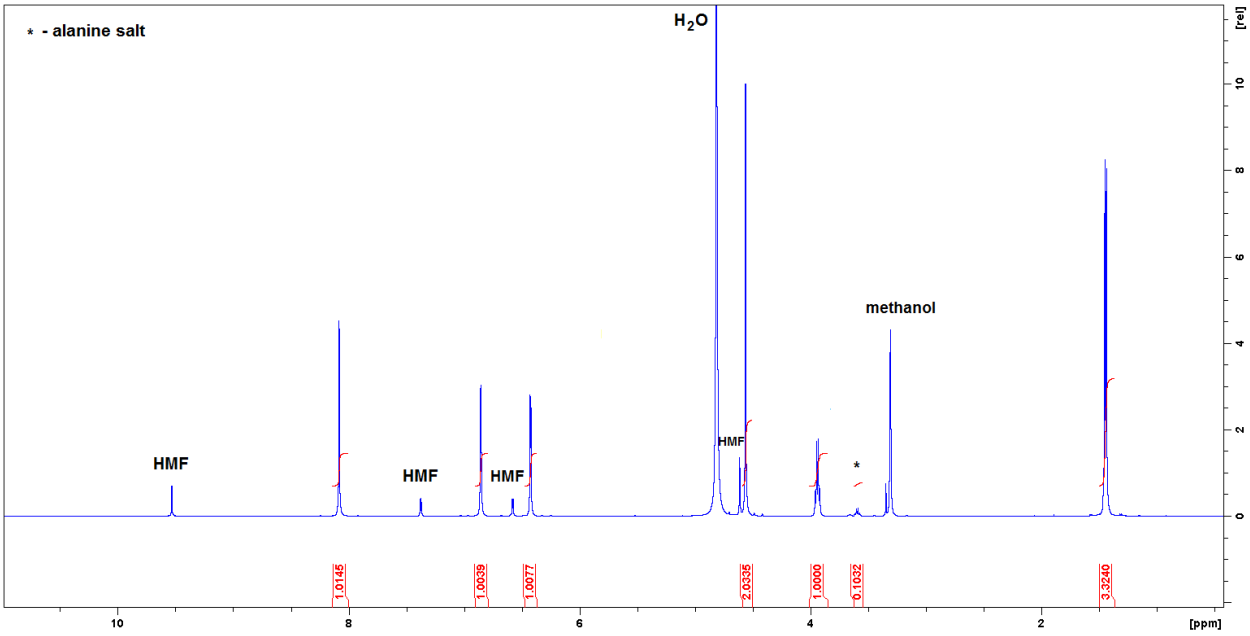
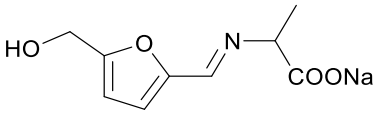
6. NMR data

^{1}H NMR spectra were recorded at 500.03 MHz on a Bruker Avance III 500 spectrometer using D_2O (99.9 atom % D, Chemical Line, Russia) and CD_3OD (99.5 atom % D, Chemical Line, Russia) as a solvent. The signals from residual protons (δ_H of 4.68 ppm) of D_2O and (δ_H of 3.30 ppm, a quintet) of methanol-d4 were used as the internal standard for the chemical shifts. ^{1}H assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and doublet of doublets (dd).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 1):



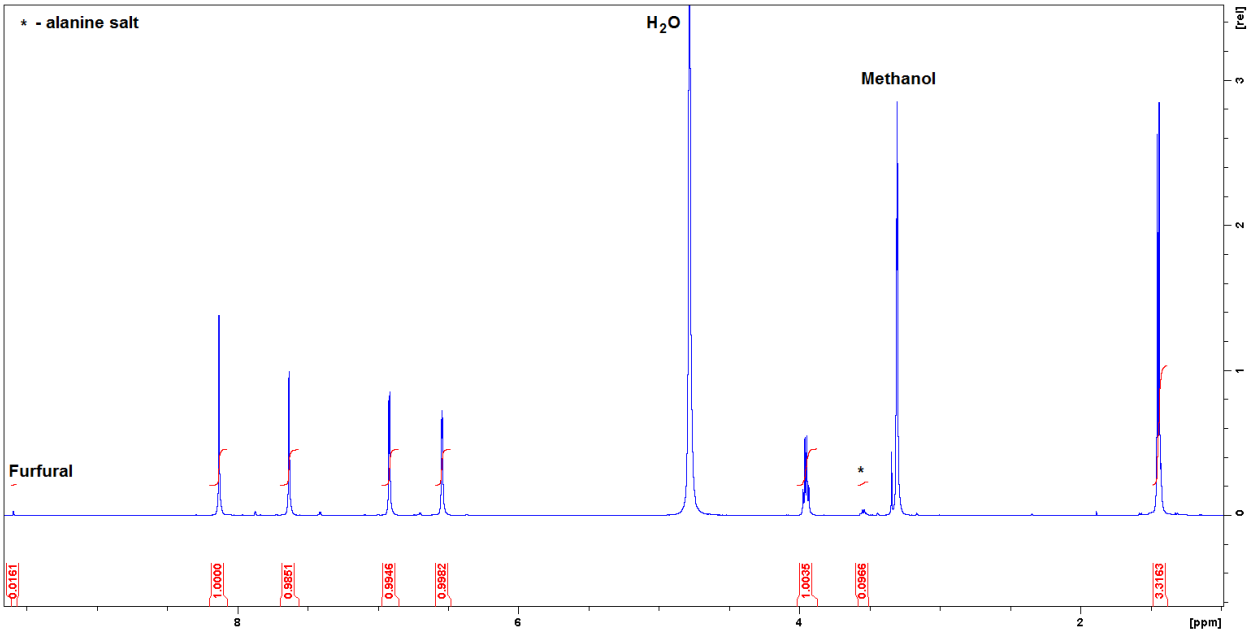
The spectrum contains peaks of compounds: **1a** (main product), HMF and alanine salt.



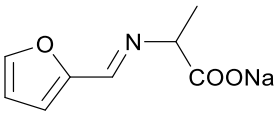
Sodium 2-(((5-(hydroxymethyl)furan-2-yl)methylidene)amino)propanoate (1a)

^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.44 (d, *J*=6.9 Hz, 3H), 3.94 (q, *J*=6.9 Hz, 1H), 4.56 (s, 2H), 6.42 (d, *J*=3.3 Hz, 1H), 6.85 (d, *J*=3.3 Hz, 1H), 8.08 (s, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 2):



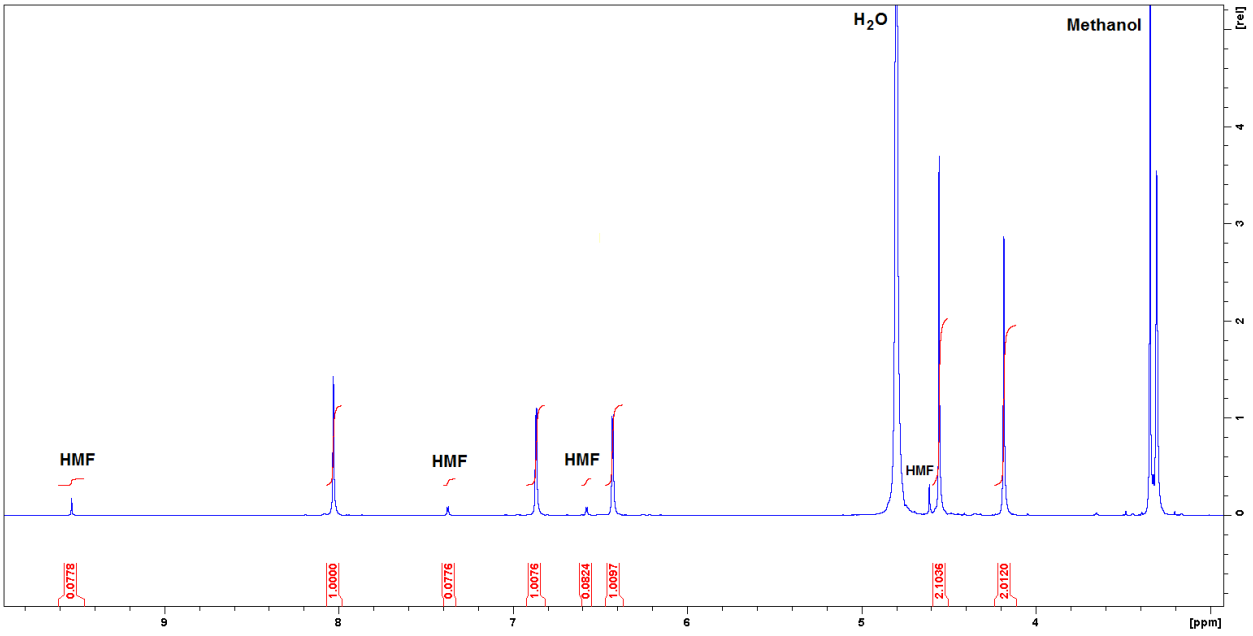
The spectrum contains peaks of compounds: **1b** (main product), furfural and alanine salt. In this spectrum, the signals from the furfural protons are too low, which is probably due to the evaporation of furfural during the removal of methanol from the reaction mixture.



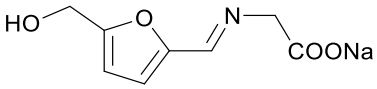
Sodium 2-((furan-2-ylmethylidene)amino)propanoate (1b)

^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.45 (d, *J*=6.9 Hz, 3H), 3.95 (q, *J*=6.9 Hz, 1H), 6.54 (q, J_1=1.7 Hz, J_2=1.7 Hz, 1H), 6.92 (d, *J*=3.3 Hz, 1H), 7.63 (d, *J*=1.1 Hz, 1H), 8.13 (s, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 3):



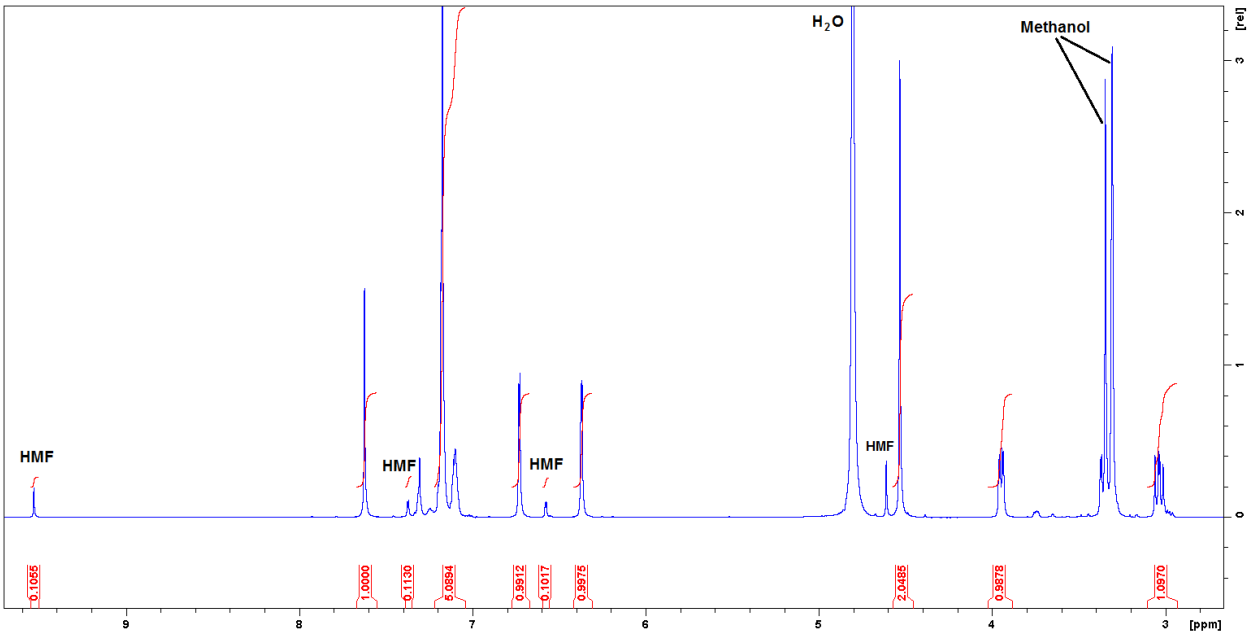
The spectrum contains peaks of compounds: **1c** (main product), HMF and glycine salt.



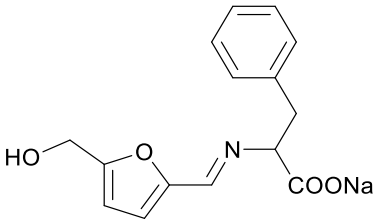
Sodium ((5-(hydroxymethyl)furan-2-yl)methylidene)aminoacetate (1c)

^{1}H NMR (500 MHz, CD_3OD) δ ppm: 4.18 (s, 2H), 4.55 (s, 2H), 6.43 (d, *J*=3.3 Hz, 1H), 6.87 (d, *J*=3.3 Hz, 1H), 8.03 (s, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 4):



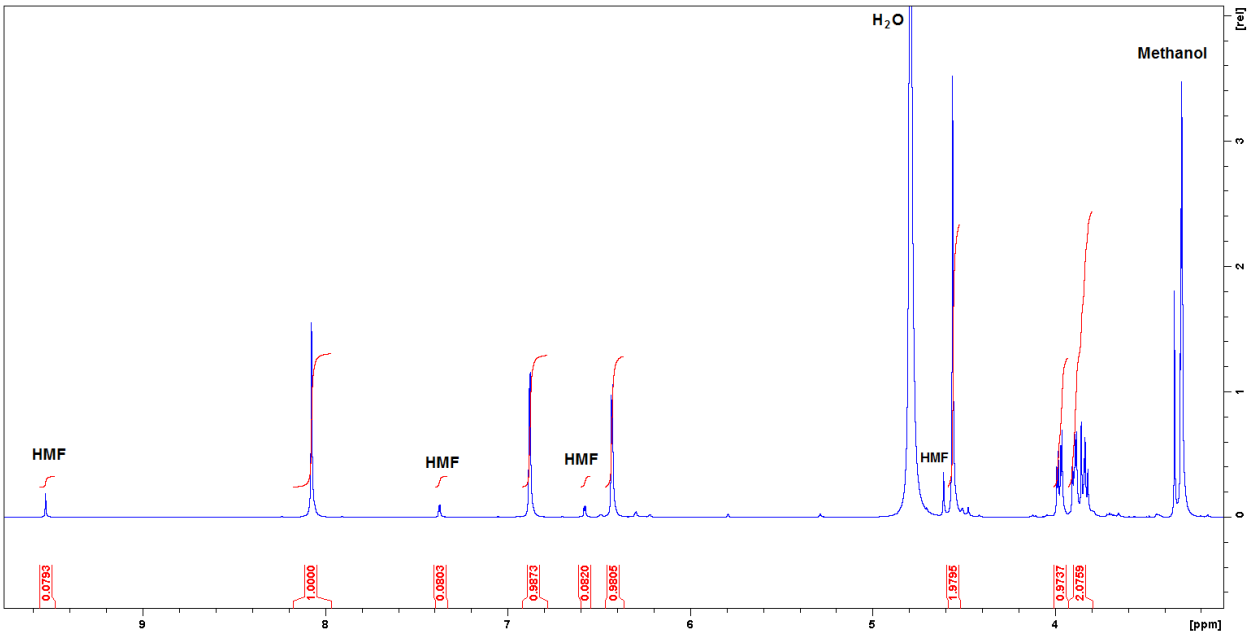
The spectrum contains peaks of compounds: **1d** (main product), HMF and phenylalanine salt.



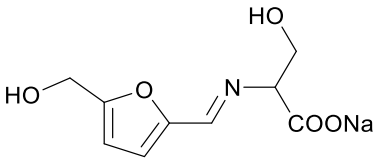
Sodium 2-(((5-(hydroxymethyl)furan-2-yl)methylidene)amino)-3-phenylpropanoate (1d)

^{1}H NMR (500 MHz, CD_3OD) δ ppm: 2.99-3.39 (m, 2H), 3.95 (dd, J_1=5.7, J_2=4.0, 1H), 4.53 (s, 2H), 6.37 (d, *J*=3.3 Hz, 1H), 6.73 (d, *J*=3.3 Hz, 1H), 7.06-7.21 (m, 5H), 7.62 (s, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 5):



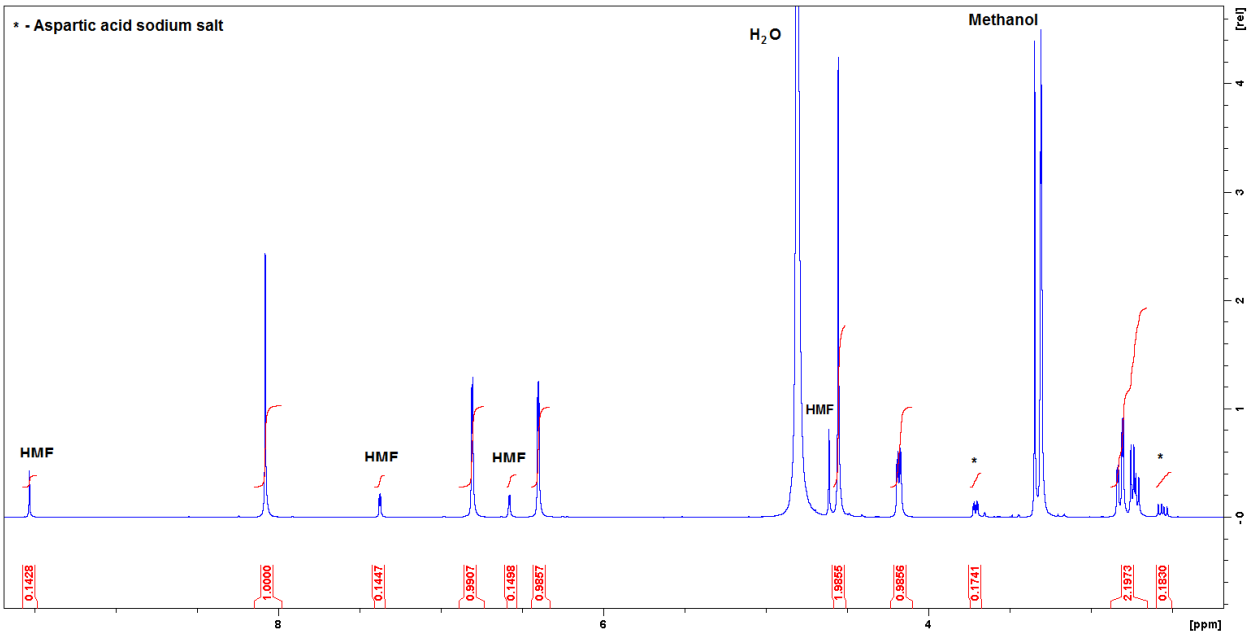
The spectrum contains peaks of compounds: **1e** (main product), HMF and serine salt.



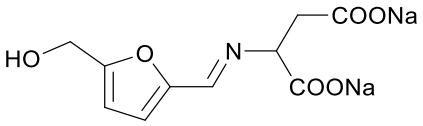
Sodium 3-hydroxy-2-(((5-(hydroxymethyl)furan-2-yl)methylidene)amino)propanoate (1e)

^{1}H NMR (500 MHz, CD_3OD) δ ppm: 3.80-3.92 (m, 2H), 3.97 (dd, J_1=6.5, J_2=4.0, 1H), 4.56 (s, 2H), 6.43 (d, *J*=3.3 Hz, 1H), 6.88 (d, *J*=3.3 Hz, 1H), 8.07 (s, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table S1 (entry 6):

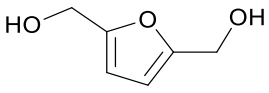


The spectrum contains peaks of compounds: **1f** (main product), HMF and aspartic acid sodium salt.



Sodium ((5-(hydroxymethyl)furan-2-yl)methylidene)amino)succinate (1f)

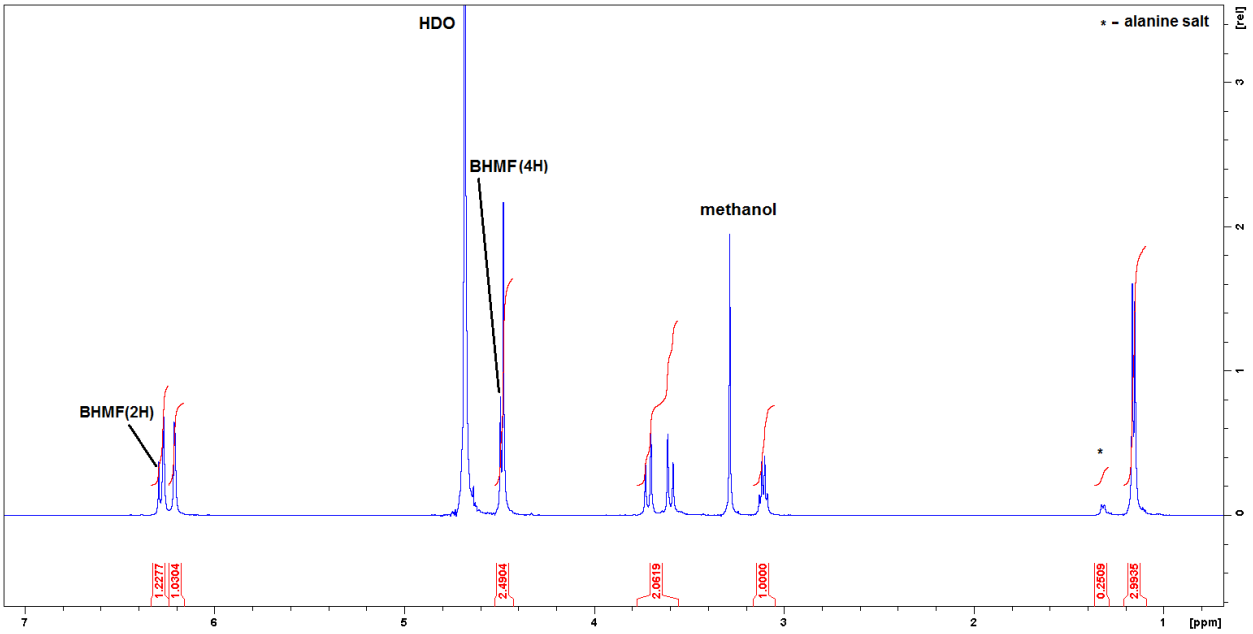
^{1}H NMR (500 MHz, CD_3OD) δ ppm: 2.67-2.86 (m, 2H), 4.18 (dd, J_1=5.1, J_2=3.9, 1H), 4.55 (s, 2H), 6.40 (d, *J*=3.3 Hz, 1H), 6.81 (d, *J*=3.3 Hz, 1H), 8.08 (s, 1H).



2,5-bis(hydroxymethyl)furan (3)

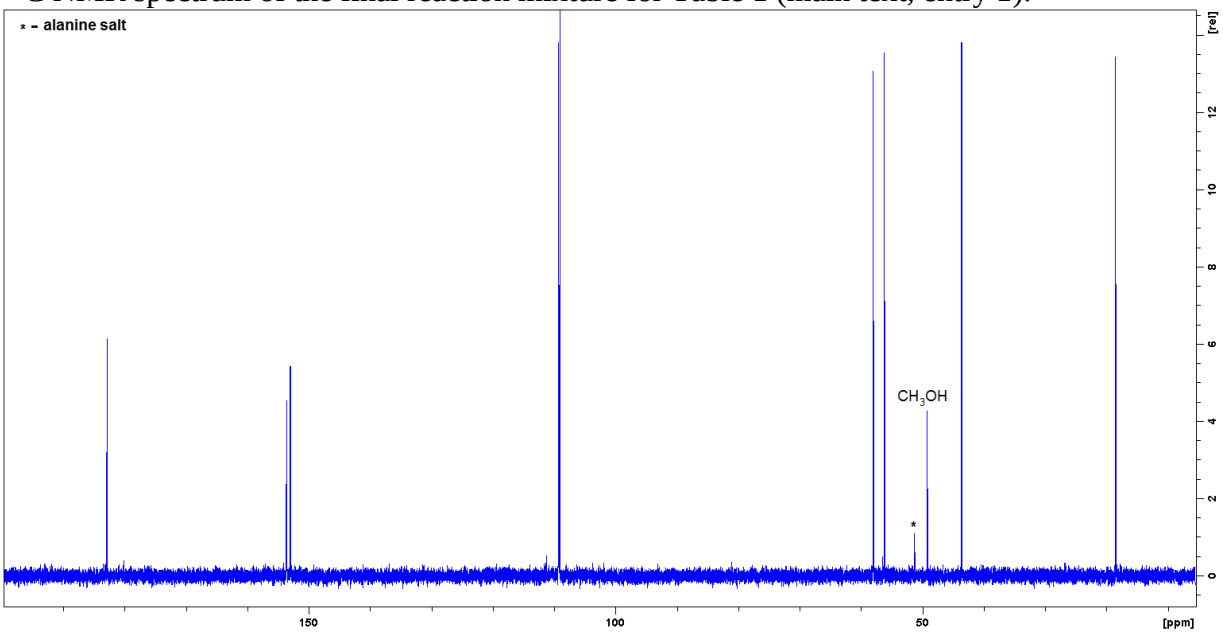
^{1}H NMR (500 MHz, D_2O) δ ppm: 4.49 (s, 4H), 6.29 (s, 2H).

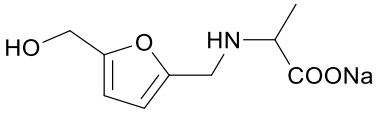
^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 1):



The spectrum contains peaks of compounds: **2a** (main product), **3** and alanine salt.

^{13}C NMR spectrum of the final reaction mixture for Table 1 (main text, entry 1):





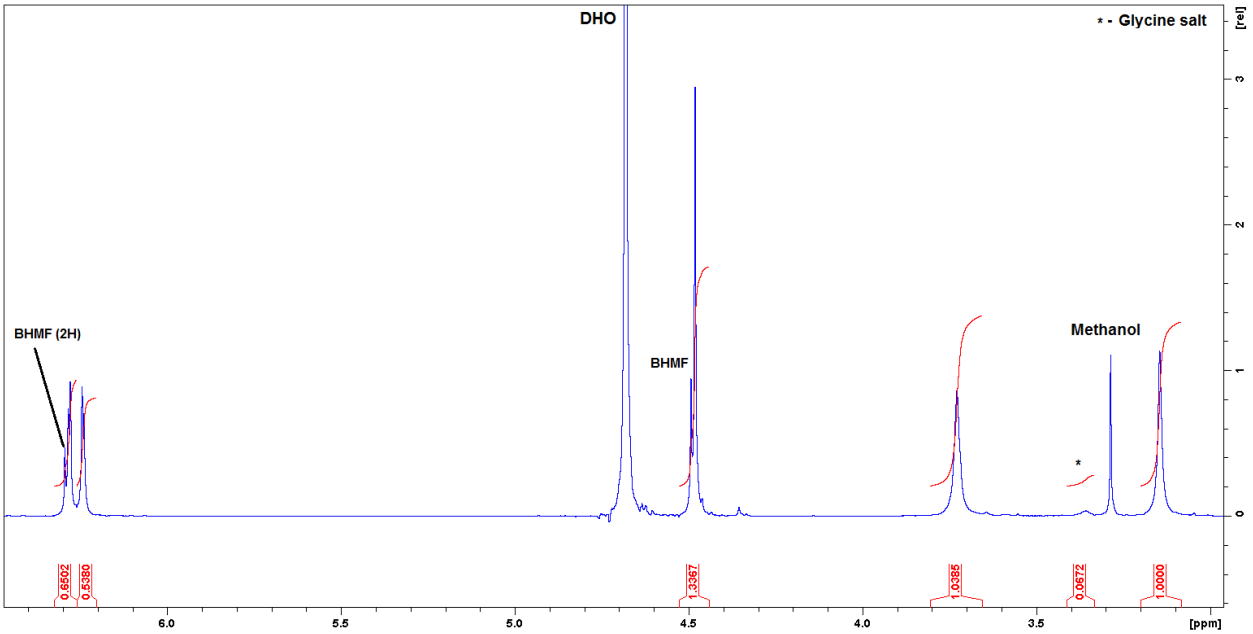
Sodium ((5-(hydroxymethyl)furan-2-yl)methyl)alaninate (2a)

^{1}H NMR (500 MHz, D_2O) δ ppm: 1.17 (d, *J*=7.0 Hz, 3H), 3.12 (q, *J*=7.0 Hz, 1H), 3.58-3.76 (dd, J_1=45.0 Hz, J_2=14.2 Hz, 2H), 4.49 (s, 2H), 6.22 (d, *J*=3.0 Hz, 1H), 6.29 (d, *J*=3.0 Hz, 1H).

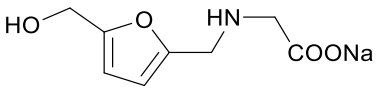
^{13}C NMR (125 MHz, D_2O) δ ppm: 18.5, 43.6, 56.2, 58.1, 109.1, 109.3, 153.0, 153.6, 182.8.

The spectral data are in good agreement with the literature [R. Villard, F. Robert, I. Blank, G. Bernardinelli, T. Soldo and T. Hofmann, *J. Agric. Food Chem.*, 2003, **51**, 4040].

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 3):



The spectrum contains peaks of compounds: **2c** (main product), **3** and glycine salt.

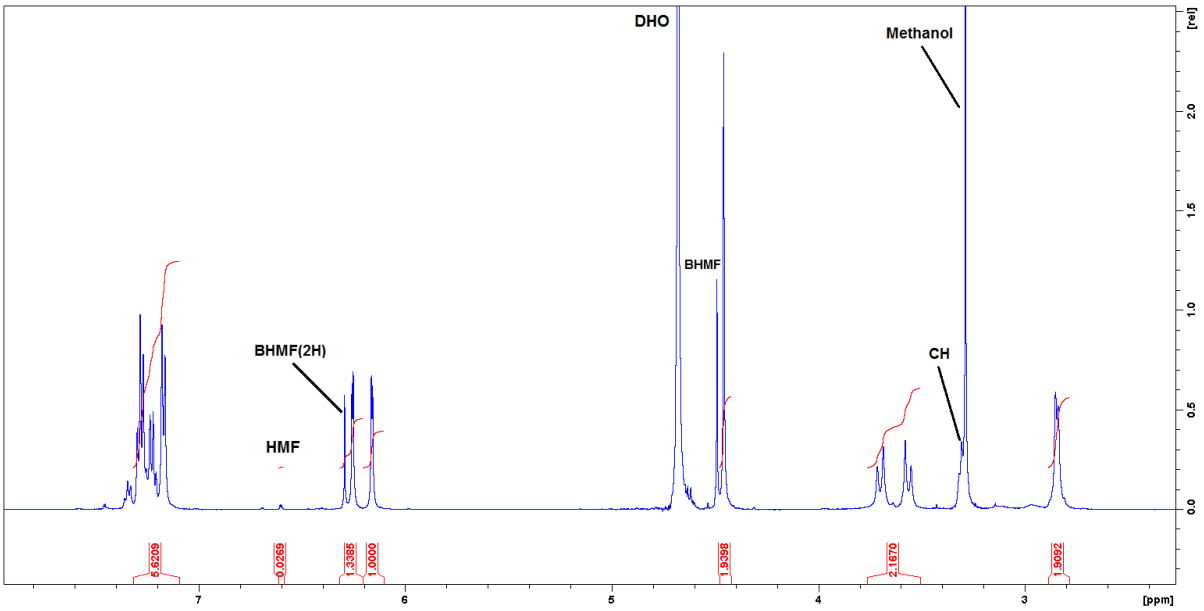


Sodium ((5-(hydroxymethyl)furan-2-yl)methyl)glycinate (2c)

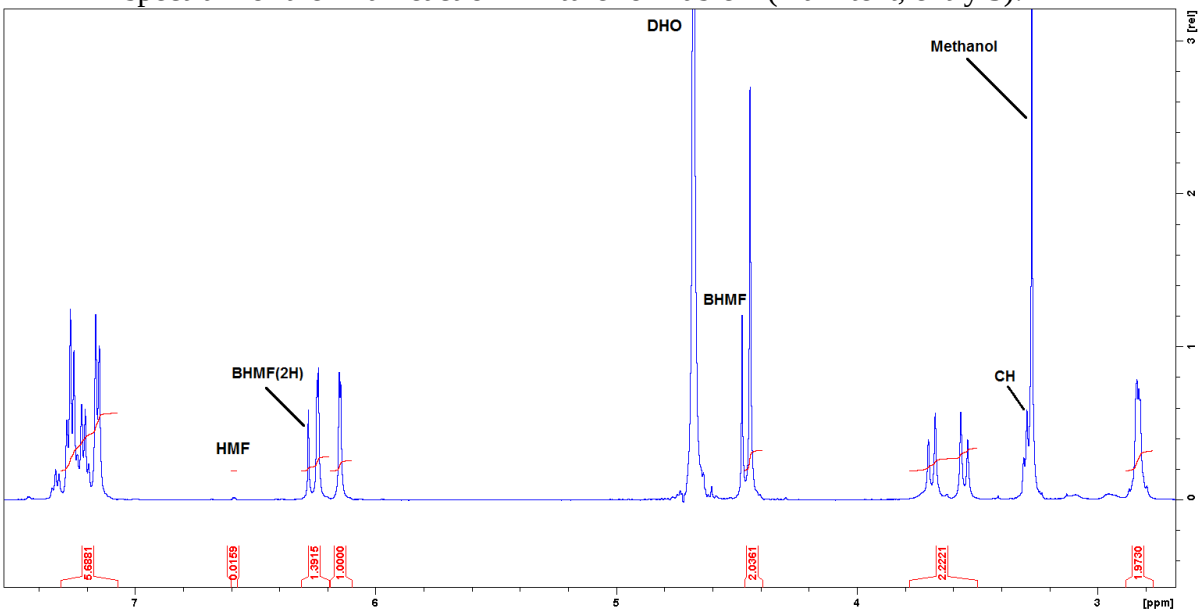
^{1}H NMR (500 MHz, D_2O) δ ppm: 3.14 (s, 2H), 3.73 (s, 2H), 4.48 (s, 2H), 6.24 (d, *J*=3.1 Hz, 1H), 6.28 (d, *J*=3.1 Hz, 1H).

The spectral data are in good agreement with the literature [V. V. Karve, D. T. Sun, O. Trukhina, S. Yang, E. Oveisi, J. Luterbacher and W. L. Queen, *Green Chem.*, 2020, **22**, 368].

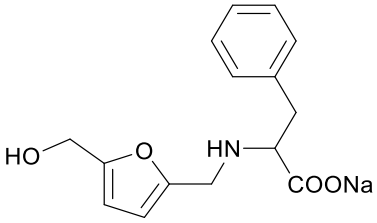
^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 4):



^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 5):



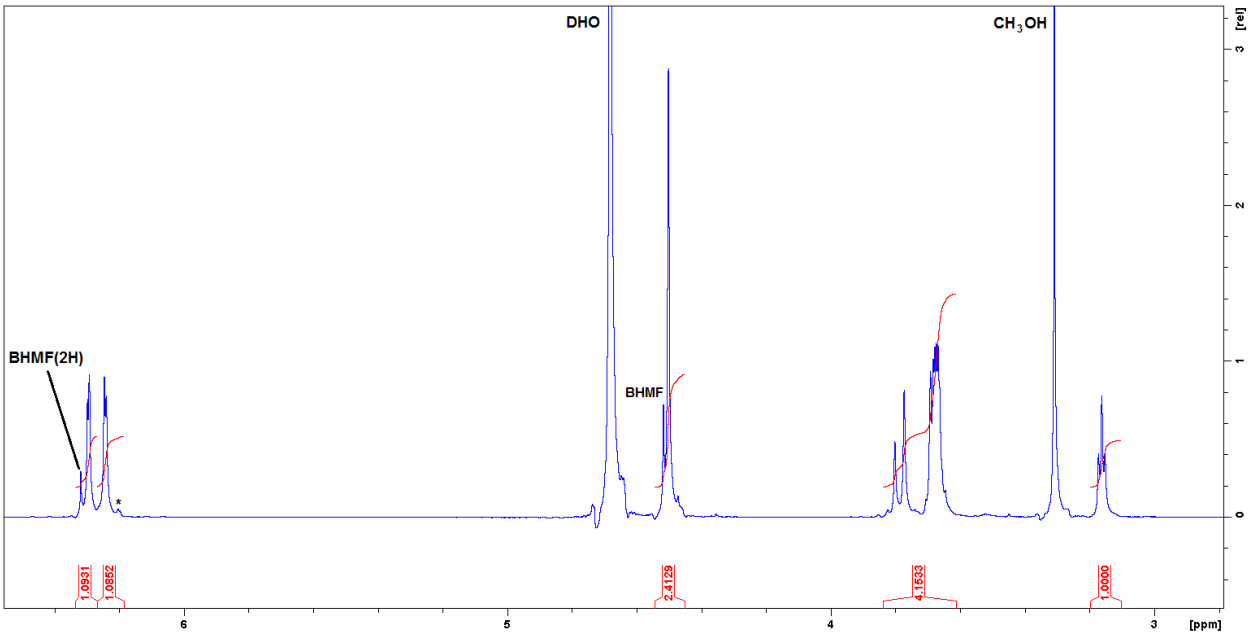
The spectra contain peaks of compounds: **2d** (main product), **3** and phenylalanine salt.



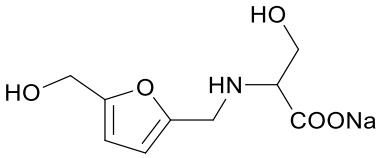
Sodium ((5-(hydroxymethyl)furan-2-yl)methyl)phenylalaninate (2d)

^{1}H NMR (500 MHz, D_2O) δ ppm: 2.78-2.88 (m, 2H), 3.29 (t, *J*=6.8 Hz, 1H), 3.50-3.77 (dd, J_1=53.0 Hz, J_2=14.3 Hz, 2H), 4.45 (s, 2H), 6.15 (d, *J*=2.9 Hz, 1H), 6.24 (d, *J*=2.9 Hz, 1H), 7.11-7.30 (m, 5H).

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 6):



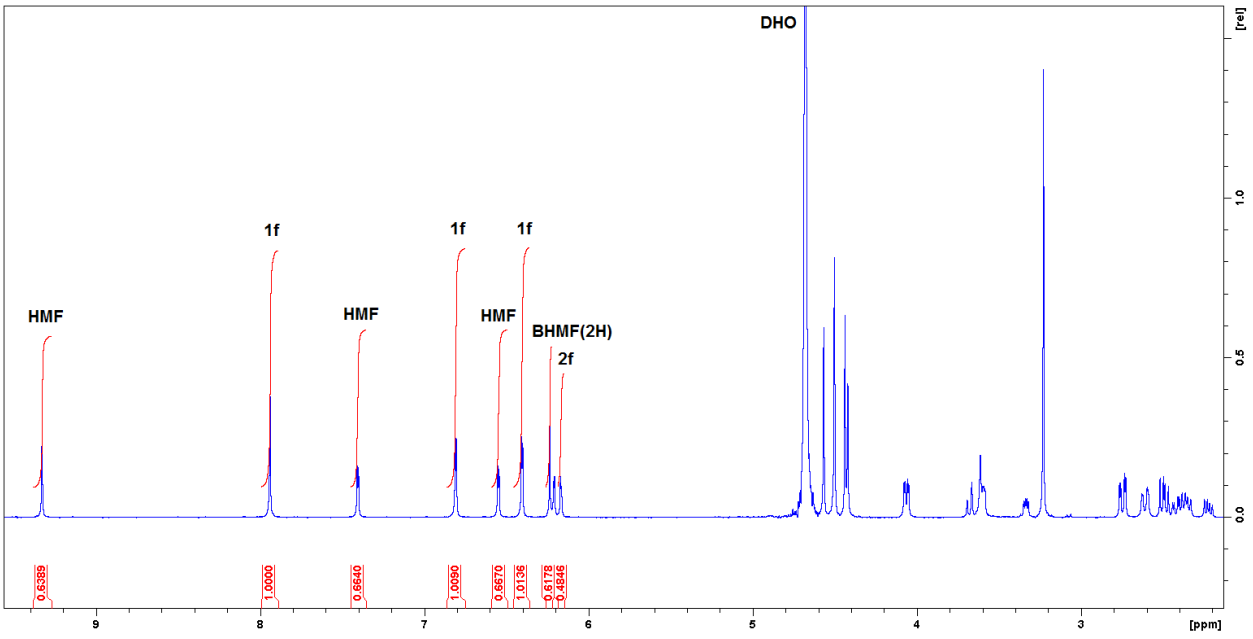
The spectrum contains peaks of compounds: **2e** (main product), **3**, serine salt and unknown product containing a furan ring (peak is marked with an asterisk).



Sodium ((5-(hydroxymethyl)furan-2-yl)methyl)serinate (2e)

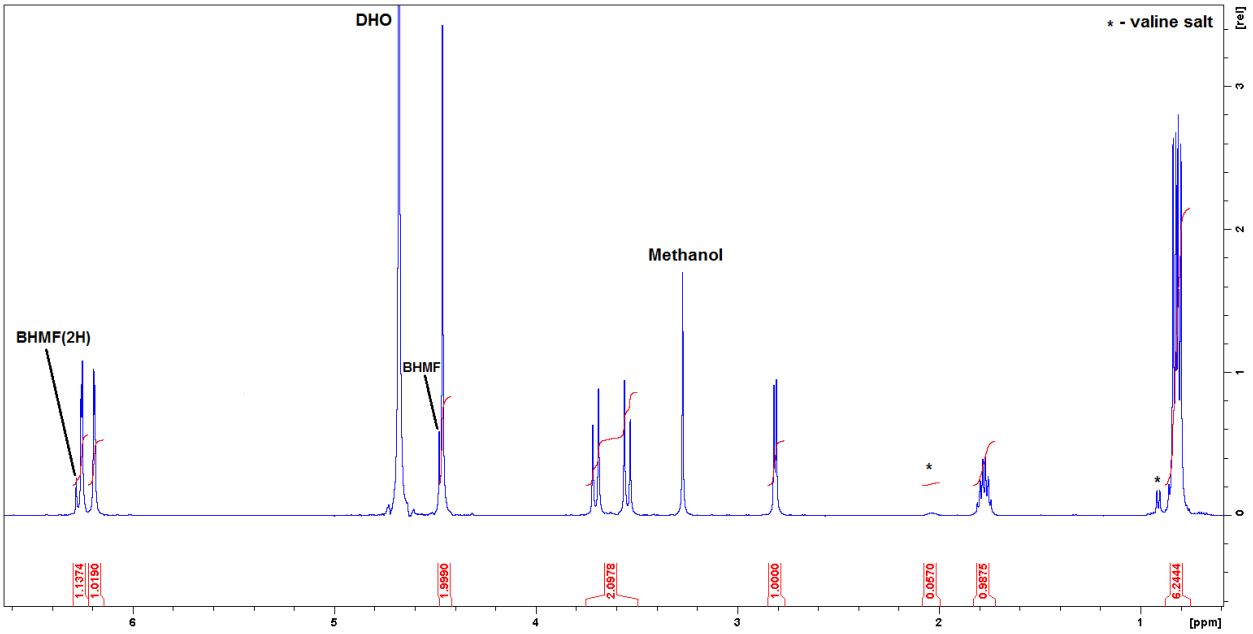
^{1}H NMR (500 MHz, D_2O) δ ppm: 3.16 (t, *J*=5.0 Hz, 1H), 3.62-3.81 (m, 4H), 4.50 (s, 2H), 6.24 (d, *J*=3.0 Hz, 1H), 6.29 (d, *J*=3.0 Hz, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 7):

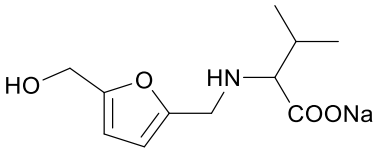


The spectrum contains peaks of compounds: **1f**, **2f**, HMF, **3** and others.

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 8):



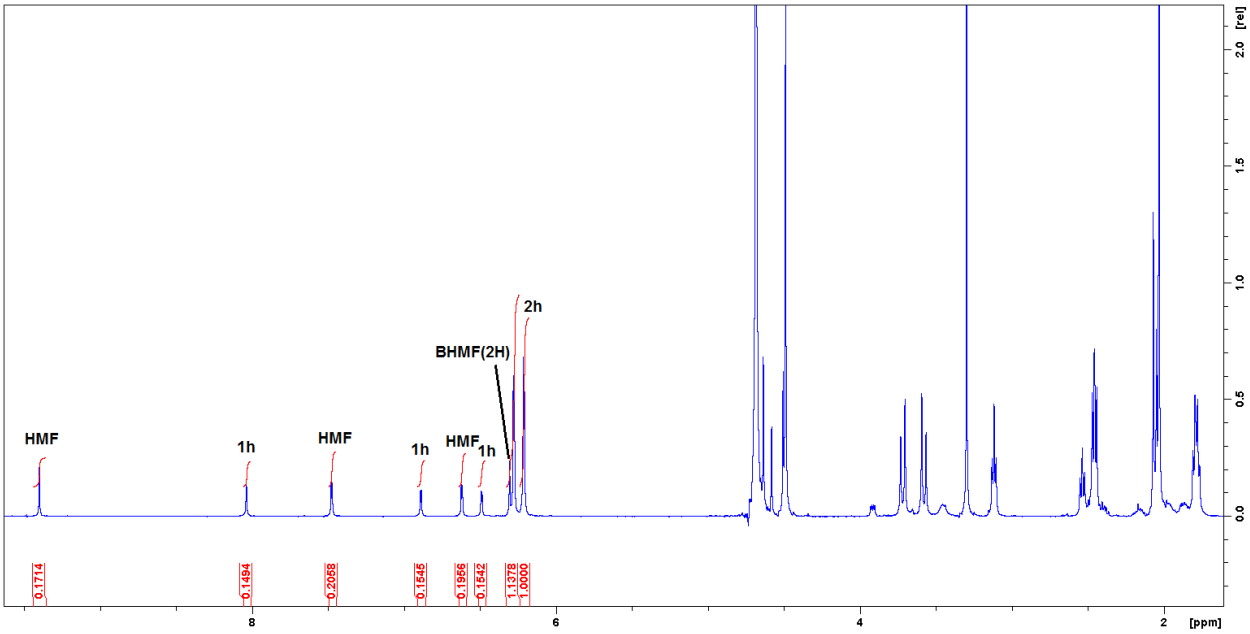
The spectrum contains peaks of compounds: **2g** (main product), **3** and valine salt.



Sodium ((5-(hydroxymethyl)furan-2-yl)methyl)valinate (2g)

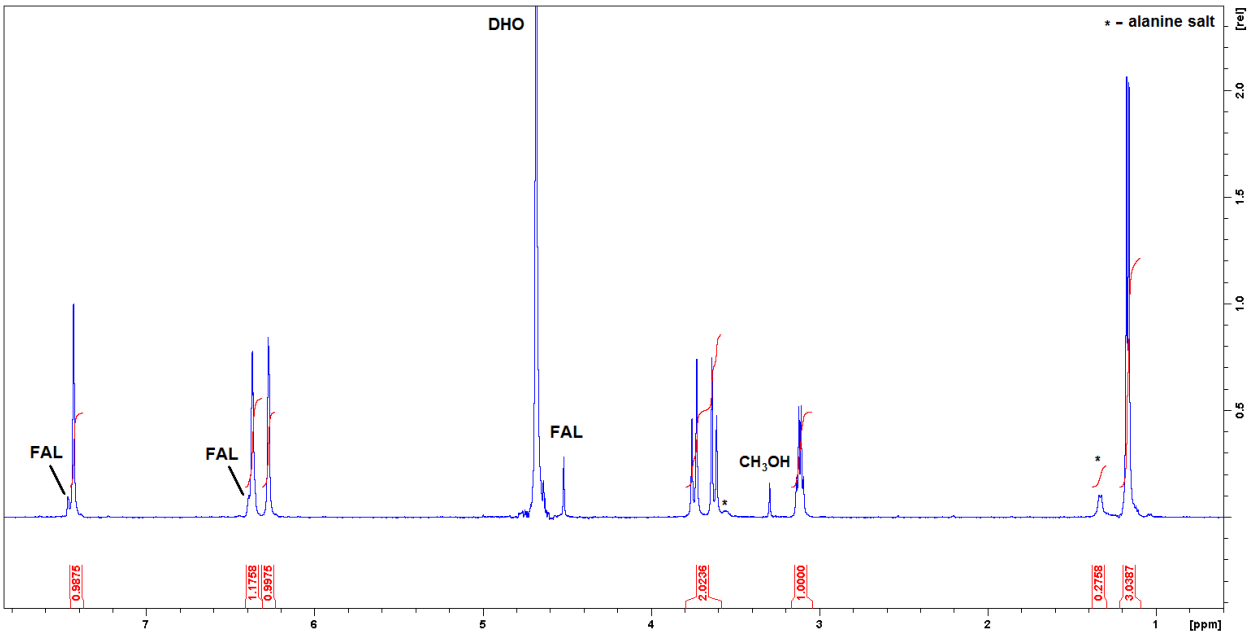
^{1}H NMR (500 MHz, D_2O) δ ppm: 0.82 (dd, J_1=6.8 Hz, J_2=5.7 Hz, 6H), 1.73-1.83 (m, 1H), 2.81 (d, J=5.7 Hz, 1H), 3.51-3.74 (dd, J_1=64.2 Hz, J_2=14.2 Hz, 2H), 4.46 (s, 2H), 6.19 (d, J=3.0 Hz, 1H), 6.25 (d, J=3.0 Hz, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 9):

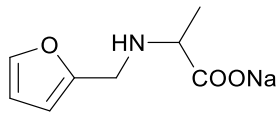


The spectrum contains peaks of compounds: **1h**, **2h**, HMF, **3** and others.

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 10):



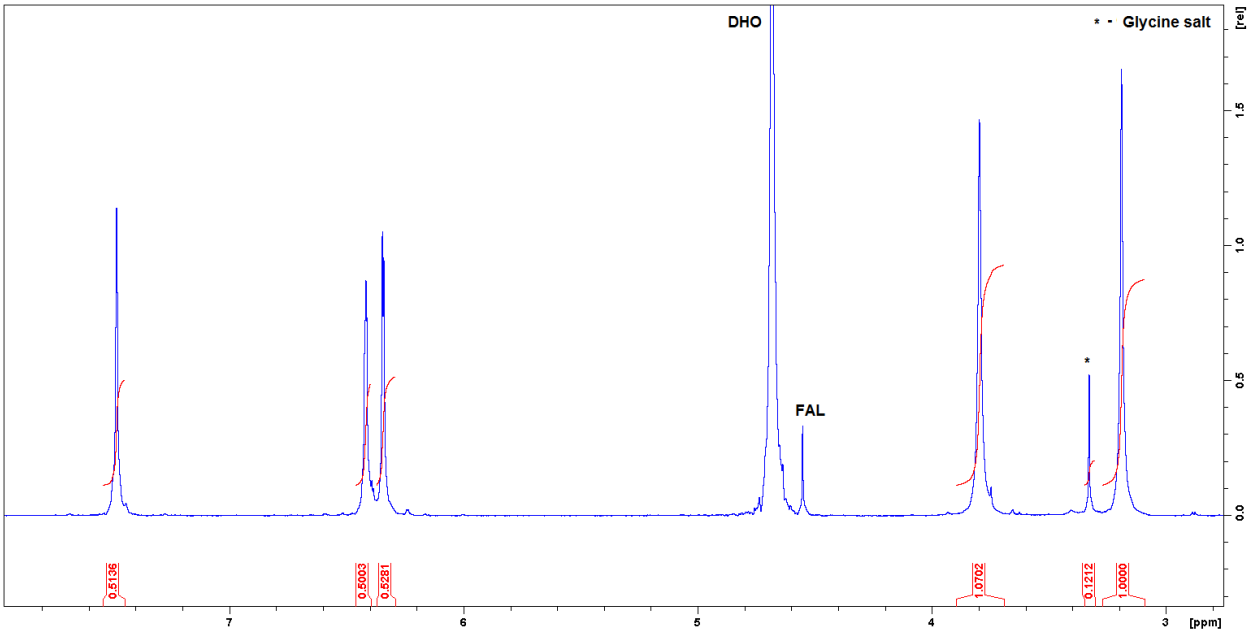
The spectrum contains peaks of compounds: **2b** (main product), furfuryl alcohol (FAL) and alanine salt.



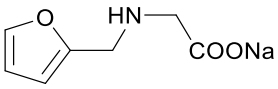
Sodium (furan-2-ylmethyl)alaninate (2b)

^{1}H NMR (500 MHz, D_2O) δ ppm: 1.17 (d, *J*=7.0 Hz, 3H), 3.11 (q, *J*=7.0 Hz, 1H), 3.58-3.78 (dd, J_1=45.0 Hz, J_2=14.2 Hz, 2H), 6.27 (d, *J*=2.4 Hz, 1H), 6.37 (q, J_1=1.1 Hz, J_2=1.8 Hz, 1H), 7.43 (d, *J*=1.1 Hz, 1H).

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 11):



The spectrum contains peaks of compounds: **2i** (main product), furfuryl alcohol (FAL) and glycine salt.

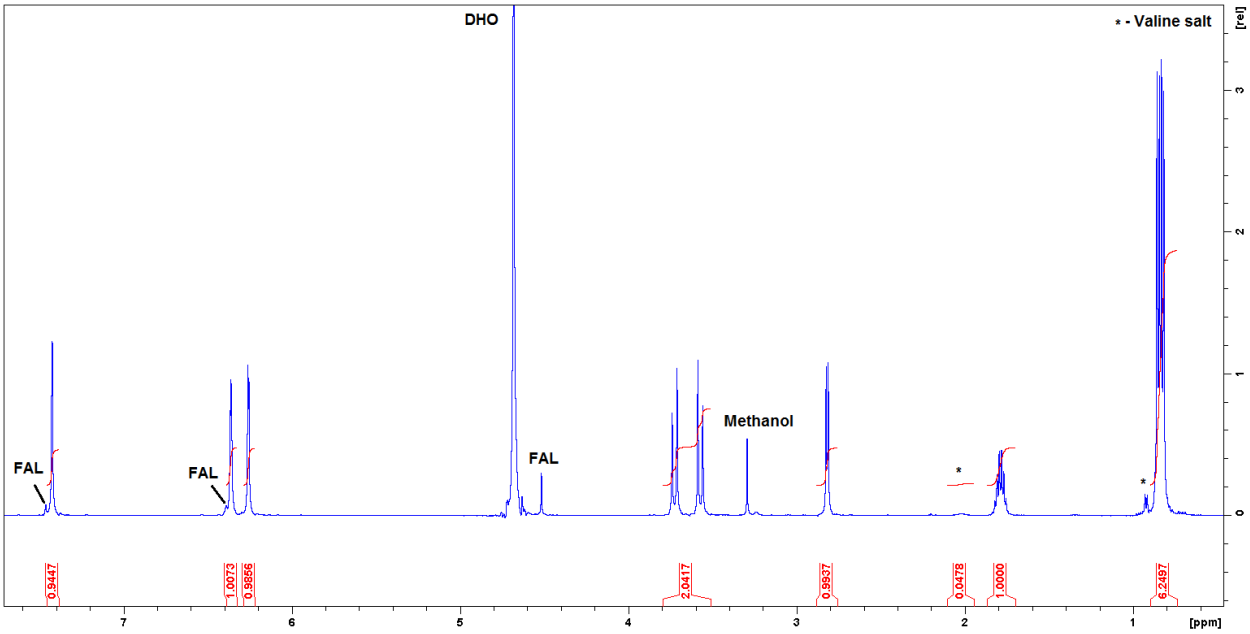


Sodium (furan-2-ylmethyl)glycinate (2i)

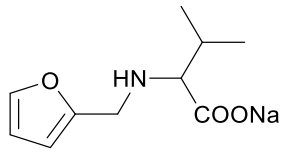
^{1}H NMR (500 MHz, D_2O) δ ppm: 3.19 (s, 2H), 3.80 (s, 2H), 6.34 (d, *J*=3.1 Hz, 1H), 6.42 (q, J_1=1.1 Hz, J_2=1.8 Hz, 1H), 7.48 (t, *J*=0.8 Hz, 1H).

The spectral data are in good agreement with the literature [A. Lawer, R. G. Epton, T. C. Stephens, K. Y. Palate, M. Lodi, E. Marotte, K. J. Lamb, J. K. Sangha, J. M. Lynam and W. P. Unsworth, *Chem. Eur. J.*, 2020, **26**, 12674].

^{1}H NMR spectrum of the final reaction mixture for Table 1 (main text, entry 12):



The spectrum contains peaks of compounds: **2j** (main product), furfuryl alcohol (FAL) and valine salt.



Sodium (furan-2-ylmethyl)valinate (2j)

^{1}H NMR (500 MHz, D_2O) δ ppm: 0.84 (dd, J_1=6.8 Hz, J_2=6.2 Hz, 6H), 1.73-1.84 (m, 1H), 2.82 (d, J=5.7 Hz, 1H), 3.54-3.76 (dd, J_1=62.5 Hz, J_2=14.2 Hz, 2H), 6.26 (d, J=3.0 Hz, 1H), 6.36 (q, J_1=1.1 Hz, J_2=1.8 Hz, 1H), 7.43 (d, J=1.0 Hz, 1H).