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

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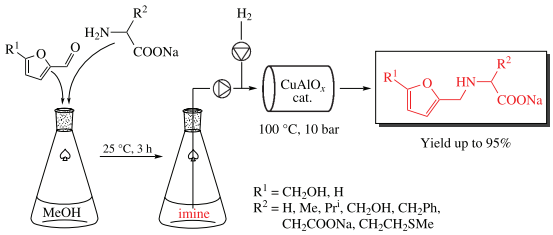
Various amino acid-based furfurylamine derivatives were synthesized by two-stage procedure, which includes the condensation of 5-hydroxymethylfurfural (or furfural) with amino acid salts in methanol followed by hydrogenation of obtained imines in a flow reactor over $CuAlO_x$ catalyst.



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N-Substituted 5-hydroxymethyl-2-furfuryl amines are known for their wide range of pharmaceutical activities.[1–5] In particular, amino acid-based furfurylamine derivatives are intermediates for the preparation of taste enhancers.[6,7] Reductive amination of 5-hydroxymethylfurfural (HMF) derived from lignocellulosic biomass[8–11] is an attractive method for the synthesis of this type of amines.[1–6]

The reductive amination of HMF with L- or D-alanine under hydrogen atmosphere over Raney nickel is documented.[6] The two-stage synthesis of furfurylamines involving the condensation of HMF with amino acid sodium salt in methanol to form an imine with its following reduction with sodium borohydride is also reported.[12] However, the stoichiometric amounts of $NaBH_4$ generate a large amount of harmful wastes, while Raney Ni is pyrophoric that makes the process potentially hazardous, especially when scaled up.

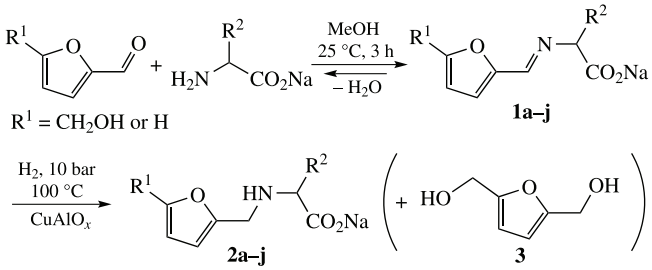
Chieffi *et al*. studied the reductive amination of HMF over carbon-supported Fe–Ni catalyst under flow conditions.[13] Advantages of continuous flow synthesis over traditional batch protocols include higher productivity, suppression of by-product formation through a better control over reaction parameters, simplified scaling, lower operational costs and limiting employee contact with toxic chemicals, which makes such processes safer and more attractive.[10,14,15] However, only sodium alaninate was used as a substrate in this work, and the yield of the target product did not exceed 78%. Unlike HMF, furfural showed lower yield for similar reaction. The use of glycine, β-alanine and leucine gave the corresponding amines with yields of 60, 50 and <10%, respectively.[13]

In our previous studies, various secondary amines were obtained in good to excellent yields by two-step reductive amination, which involved the condensation of furfural derivatives with primary amines in methanol, followed by hydrogenation in a flow reactor over Pt/Al_2O_3[16,17] or Cu–Al mixed oxide (denoted hereafter as $CuAlO_x$) derived from layered double hydroxide.[18] Herein, we investigated the efficiency of this procedure for reductive amination of HMF and furfural with amino acids through flow hydrogenation of the intermediate imines over $CuAlO_x$ catalyst.

Due to poor solubility of amino acids in methanol they were converted to salts by treament with an equimolar amount of solid NaOH. The resulting amino acid salts reacted with HMF at room temperature giving the corresponding imines **1a**,**c–h** in 88–93% yields, which were little dependent on the nature of the starting amino acid (Scheme 1, also see Online Supplementary Materials). Similar to HMF, the reaction with furfural provided close yields of imines **1b**,**i**,**j**.

The obtained reaction mixtures were further hydrogenated over pre-reduced $CuAlO_x$ catalyst in a flow reactor at 100 °C and total pressure of 10 bar.† In the case of alanine, glycine, serine,

† 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 MeOH (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. The obtained mixture was hydrogenated in a flow reactor packed with the $CuAlO_x$ material, which was prepared as previously reported.[18] Catalytic experiments were performed in H-Cube Pro setup (Thalesnano, Hungary) equipped with stainless-steel CatCart®30 cartridge (catalyst bed length of 24 mm, inner diameter of 4 mm, empty volume of 0.30 cm^3).[16–21] Before the catalytic run, the catalyst (0.17 g of 250–500 μm particles) was reduced in hydrogen flow at 120 °C for 1 h to obtain Cu^0 metal particles.[21] 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 10 bar, liquid feed rate of 0.5 ml min^{-1}, and hydrogen flow rate of 30 ml min^{-1}. The performance of the catalyst was evaluated by analysis of the samples taken in the interval of 30–33 min from the beginning of the experiment. After the reaction was complete, the catalyst was washed with MeOH flow (0.5 ml min^{-1}) for 30 min, and this could be introduced into the next reaction cycle. The composition of the reaction products was determined using ^1H NMR spectroscopy in D_2O (for details, see Online Supplementary Materials).



a $R^1 = CH_2OH$, $R^2 = Me$
b $R^1 = H$, $R^2 = Me$
c $R^1 = CH_2OH$, $R^2 = H$
d $R^1 = CH_2OH$, $R^2 = CH_2Ph$
e $R^1 = R^2 = CH_2OH$
f $R^1 = CH_2OH$, $R^2 = CH_2CO_2Na$
g $R^1 = CH_2OH$, $R^2 = Pr^i$
h $R^1 = CH_2OH$, $R^2 = (CH_2)_2SMe$
i $R^1 = R^2 = H$
j $R^1 = H$, $R^2 = Pr^i$

Scheme 1

Table 1 Two-step reductive amination of furfural derivatives with amino acid salts.[a]

Entry	R^1	R^2	Product	Conversion of aldehyde (%)	Yield (%)
1	CH_2OH	Me	**2a**	100	92
2[b]	CH_2OH	Me	**2a**	100	92
3	CH_2OH	H	**2c**	100	91
4	CH_2OH	CH_2Ph	**2d**	98	84
5[b]	CH_2OH	CH_2Ph	**2d**	99	83
6	CH_2OH	CH_2OH	**2e**	100	92
7	CH_2OH	CH_2CO_2Na	**2f**	74	20
8	CH_2OH	Pr^i	**2g**	100	95
9	CH_2OH	CH_2CH_2SMe	**2h**	86	70
10	H	Me	**2b**	100	92
11	H	H	**2i**	100	89
12	H	Pr^i	**2j**	100	95

[a] Reaction conditions: aldehyde (0.05 M), amino acid sodium salt (0.05 M), $CuAlO_x$ catalyst (170 mg), MeOH, 100 °C, 10 bar, liquid flow rate 0.5 ml min^{-1}, H_2 flow rate 30 ml min^{-1}. The conversion and yield were calculated using ^1H NMR in D_2O. [b] $T = 110$ °C.

valine and phenylalanine, imines **1a–e**,**g**,**i**,**j** are hydrogenated quantitatively that allows synthesizing furfurylamine derivatives **2** with the yield of 84–95% (see Scheme 1). Simultaneously, aspartic acid and methionine salts afford **2f** and **2h** with the lower yield of 20 and 70%, respectively, that may be explained by the strong interaction of carboxylic and sulfide group with the catalyst surface. In addition to target products, undesired 2,5-bis(hydroxymethyl)furan **3** was formed during the reaction. It should be noted that raising the reaction temperature to 110 °C has no effect on the yield of products **2** (Table 1).

The time-on-stream test in the reduction amination of HMF and furfural with sodium alanine showed a slight decrease in the yield of **2a** and **2b**, respectively, (Figure 1) that can be caused by the formation of carbonaceous deposits on the catalyst surface.[19] It was shown that the activity of the spent catalyst is completely restored after its washing by methanol flow.[20]

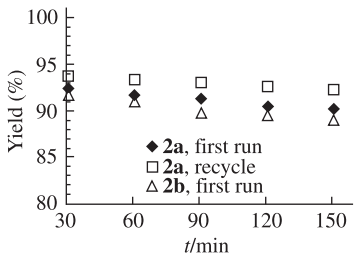


Figure 1 The time dependence of **2a** and **2b** yields in the two-step reductive amination of HMF and furfural with alanine sodium salt.

The study of the spent catalyst by atomic absorption spectroscopy (AAS) allowed us to conclude that the leaching of Cu did not occur during the reaction (see Online Supplementary Materials). Meanwhile, a decrease in the aluminum content by 0.3 and 0.6 wt% and an appearance of 0.14 and 0.37 wt% of Na were observed after one and two reaction cycles, respectively. Consequently, the limited Al leaching is probably due to the replacement of Al^{3+} ions in the $CuAlO_x$ structure with Na^+ cations. According to AAS, the liquid product obtained by reductive amination of HMF with alanine sodium salt over as-prepared $CuAlO_x$ catalyst contained 0.04 M Na, 0.0002 M Al and a negligible amount of Cu ($<10^{-5}$ M). Since the Al concentration is too low, and the Na content in the final reaction mixture is ~80% of the initial concentration, it can be concluded that sodium ions are partially replaced by protons from the surface of $CuAlO_x$.

In summary, amino acid-based furfurylamine derivatives were obtained in good to excellent yields by condensation of 5-hydroxymethylfurfural (or furfural) with amino acid sodium salts and subsequent hydrogenation over $CuAlO_x$ catalyst in a flow reactor.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.014.

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