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COMMUNICATION

Conversion of furfural to tetrahydrofuran-derived secondary amines under mild conditions

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The production of amino-containing compounds from biomass is an important goal of research programs. Starting from carbohydrate-based furfural, a simple and highly efficient system was developed for producing a library of secondary and tertiary tetrahydrofurfurylamines under mild conditions (25 °C/1 bar H₂) with excellent yields (>90%). Commercially available Pd/Al₂O₃ proved to be a suitable catalyst and exhibited outstanding performance.

Introduction

With the depletion of fossil fuel resources, transformation of renewable and abundant biomass into valuable chemicals and functional materials has become a growing field of interest.¹ To date, the production of a broad range of chemicals from lignocellulose containing C, H and O atoms, such as ethanol, hexitols, furfural, 5-hexamethylfurfural, aldehydes/ketones and acids, attracts continuous exploration.² Nonetheless, the synthesis of added-value N-compounds from biomass-derived platform molecules sugars is still limited and has become an important goal of research programs.³

Furfural (FF), issued directly from carbohydrates, is an attractive and commercial platform molecule, which has been identified as one of the top value-added chemicals with huge market potential.⁴ FF can be used for producing a variety of valuable derivatives, such as furfuryl alcohol,⁵ 2-methylfuran,⁶ succinic acid,⁷ and maleic acid.⁸ FF also can be converted into amino-compounds by reductive amination (RA). Furfurylamine

and tetrahydrofurfurylamine are important intermediates in the manufacture of pharmaceuticals (e.g. furosemide), fibers, perfumes, polymers...⁹⁻¹⁰ The synthesis of furfurylamines has been investigated from FF and 5-hydroxymethylfurfural by RA using homogeneous and heterogeneous catalysts.¹¹⁻¹² In the literature, many works are dedicated to the synthesis of furfurylamine THF-derived amines can be further generated by deep hydrogenation of the furan ring and was used as a regulator in the synthesis of polybutadiene rubber with a precise control of the microstructure,¹³ as well as for the synthesis of poly(2-vinyl-4,4-dimethylazlactone) (pVDMA)-derived (co)polymers with lower critical solution temperature.¹⁴ Alternatively, THF amines can also be synthesized through amination of furfuryl alcohol followed by the saturation of the furan ring in the presence of Raney Ni at 180 °C, an amine and 0.1 MPa H₂.¹⁵ Homogeneous catalysts such as Ru-acridine complex and triruthenium dodecacarbonyl complex have been also used for such reaction from furfuryl alcohol.¹⁶ In our group, we synthesized the THF-amines with high yields from furfural through cascade reaction combining C-C and C-N condensation reactions in the presence of Pd/Al₂O₃ and Amberlyst 26 catalysts.¹⁷ Based on these results, it was of interesting to see if this catalyst can be applied to the direct RA of furfural to THF-amines.

Scheme 1. Library of furan- and THF-derived secondary and tertiary amines that can be achieved by RA of FF with amines over Pd/Al₂O₃.

Here, we report that Pd/Al₂O₃ is an active, selective and recyclable catalyst for the direct RA of FF to secondary THF-amines at very mild conditions (Scheme 1) in the presence of

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hydrogen and different amines. This strategy was further extended to the one-pot synthesis of tertiary THF-amines using acetonitrile (ACN).

Results and Discussion

The reaction between FF and 1-butylamine (BuNH_2) was chosen as a model example. In a first set of experiments, 1 mmol of FF (20 wt% in EtOH) were reacted in EtOH with 1 mmol of BuNH_2 in the presence of 10 mg of supported Pt and Pd catalysts (5 wt% metal loading) at room temperature for 12 h and 0.1 MPa H_2 pressure (Table 1, entries 1-5). In all cases, the FF conversion was above 99% with a carbon balance higher than 90%. When 10 mg of Pt/C (5wt% Pt) was used as catalyst (10 wt% with respect to FF), the furfurylimine (**1a**) and furfurylamine (**2a**) were obtained as main products with 20% and 70% yield, respectively, whereas the target THF-derived amine (**4a**) was obtained with only 2% yield (entry 1). Pt/ Al_2O_3 exhibited a similar performance with 78% and 10% yield of **1a** and **2a**, respectively, and trace amounts of **4a** (entry 2). A drastically different behaviour was observed over 10 mg Pd catalysts (0.45 mol% with respect to FF), favouring the formation of **4a**. Pd/ Al_2O_3 exhibited the highest yield (97%) of **4a** (entry 4). For comparison, Pd/C showed 24% yield of **4a** along with product **2a** with 74% yield (entry 3). In all cases, the THF-imine (**3a**) was not detected.

The Pd/ Al_2O_3 catalyst loading was decreased from 10 to 5 mg (entry 5), a decline of the **4a** yield from 97% to 77% was observed along with an increase of the **2a** yield from <1% to 20%. These results point out that **2a** is a reaction intermediate and that depending on the catalyst loading and thus the reaction time, this product can be converted into **4a** or not. A high yield of **4a** (>95%) could be attained at shorter times (90 min instead of 12 h) by increasing the temperature and H_2 pressure to 80 °C and 1 MPa, respectively, with excellent selectivity (entry 6), and the TOF could be increased from 17.9 to 143.3 h^{-1} .

The effect of the solvent was further studied. EtOH favoured the formation of **4a** (entry 4), while THF promoted **2a** with 78% yield (entry 7). In the presence of toluene, **1a** was formed and only traces of **4a** were detected (entry 8). Finally, under neat conditions, **2a** was the main product with 85% yield (entry 9), which could be further increased under a slight excess of BuNH_2 (entry 10). This difference in the selectivity can be ascribed to the solvent properties as it is reported in the literature.¹⁸ Protic solvent (ethanol) is more active than aprotic polar and aprotic apolar solvents in such reaction. They promote the reaction between furfural and BuNH_2 , and they could decreased solvent-catalyst interactions that will inhibit the activity of the catalyst in the hydrogenation reaction.

The kinetic profile of the reaction over Pd/ Al_2O_3 was studied at room temperature and 0.1 MPa H_2 pressure (Fig. 1). Furfurylimine (**1a**) was spontaneously formed upon contacting FF with BuNH_2 . After 30 min of reaction, about 18% of product **3a** was generated along with product **1a**, **2a** and **4a** with 30%, 50% and 2% yield, respectively. Indeed, after another 30 min,

product **2a** reached a maximum yield of 72%, at the same time we could get 11% yield of **3a** and 12% yield of **4a**. The yield of **4a** increased gradually to 97% after 12 h on the benefit of **2a** as confirmed by mass/NMR analysis. The reaction rate of the conversion of **3a** to **4a** is slightly higher than the one of **2a** to **4a** (25.1 h^{-1} vs. 18.8 h^{-1}). Based on previous work^{11,12} and on control experiment, pure **2a** could be fully converted to **4a** and **3a** could be also converted to **4a**. The reaction pathway of **1a** to **4a** is depicted scheme 2. Furfuryl or THF-alcohol was not detected due to the very fast condensation between FF and BuNH_2 .

Table 1. Catalyst screening for the RA of FF with BuNH_2 ^a

Entry	Catalyst	Solvent	Yield / % ^[e]			TOF(h^{-1})
			1a	2a	4a	
1	Pt/C	EtOH	20	70	2	0.4
2	Pt/ Al_2O_3	EtOH	78	10	<1	-
3	Pd/C	EtOH	-	74	24	4.4
4	Pd/ Al_2O_3	EtOH	-	<1	97	17.9
5 ^[b]	Pd/ Al_2O_3	EtOH	-	20	77	14.2
6 ^[c]	Pd/ Al_2O_3	EtOH	-	<1	98	143.3
7	Pd/ Al_2O_3	THF	<1	78	10	1.8
8	Pd/ Al_2O_3	Toluene	27	57	<1	-
9	Pd/ Al_2O_3	neat	-	85	12	2.2
10 ^[d]	Pd/ Al_2O_3	neat	-	98	-	-

^[a] Reaction conditions: FF (100 mg, 1.04 mmol), BuNH_2 (77 mg), EtOH (5 g), 10 mg of Pd/ Al_2O_3 (0.45 mol% related to furfural), H_2 (0.1 MPa), RT, 12 h; ^[b] 5 mg for 5 wt% Pd/ Al_2O_3 (0.225 mol%); ^[c] H_2 (1 MPa), 80 °C, 90 min; ^[d] BuNH_2 (116 mg); ^[e] Yield measured on the crude mixture. The FF conversion was >99% for all the catalytic tests; ^[f] Turnover frequency (TOF) = (mol of **4a** obtained)/(mol Pd x h).

Fig. 1 (a) Representative chromatogram of the products generated along the reaction. (b) Kinetic profile of the RA of FF with BuNH₂ over Pd/Al₂O₃. Reaction conditions: FF (100 mg), BuNH₂ (77 mg), EtOH (5 g), Pd/Al₂O₃ (10 mg), RT, H₂ (0.1 MPa).

Scheme 2. Reaction pathways for **1a** hydrogenation over Pd/Al₂O₃.

The recyclability of Pd/Al₂O₃ was further investigated (Fig. 2) using the reaction conditions that lead to the highest TOF (143.3 h⁻¹). After each run, the catalyst was separated from the reaction medium by centrifugation and reused without any further pre-treatment. The yield of **4a** remained almost constant during the first 5 runs, but displayed a slight decrease after the 7th run at the expense of **2a** while keeping total selectivity to **4a** and **2a** around 95%. The spent catalyst after the 8th run was washed with EtOH and dried in an oven at 80 °C overnight.

Fig. 2 Evolution of the yield of **4a** in successive catalytic runs. Reaction conditions: FF (2 mmol, 200 mg), BuNH₂ (2 mmol, 153 mg), EtOH (10 g), Pd/Al₂O₃ (20 mg), H₂ 1 MPa, 80 °C, 90 min. The label (*) refers to a catalytic run after catalyst calcination at 500 °C for 90 min.

The spent catalyst was analyzed by thermogravimetric analysis (Fig. S1). Two weight losses were observed at 40 °C and 250 °C, which were similar to those observed on the fresh catalyst. In contrast, the spent catalyst exhibited three additional weight losses of ~1.6 wt% / 1.1 wt% / 3.4 wt% in the range of 250–500 °C, which can be attributed to coke deposits.

By calcining the spent catalyst at 500 °C for 3 h, almost 95% yield of **4a** could be recovered after 90 min (9th run).

To assess the molecular diversity of THF-amines that could be obtained through this catalytic pathway, FF was reacted over Pd/Al₂O₃ at room temperature and 0.1 MPa H₂ pressure with different amines (Table 2). For alkyl- and alcoholamines, the corresponding THF-derived amines (b-i) were obtained with 91–97% yield. Besides, with the exception of N-benzylamine (47% yield), aromatic amines afforded THF-derived amines with 90–95% yield. Overall, these results clearly show the efficient and selective one-pot synthesis of THF-derived secondary amines over Pd/Al₂O₃ at very mild conditions.

With these results in hand, we attempted the one-pot synthesis of tertiary THF-derived amines over Pd/Al₂O₃ at mild conditions. This reaction is challenging due to steric hindrance disfavoring the formation of iminium/enamine intermediates. A first experiment was carried out with FF and ethylbutylamine at 50 °C and 1 MPa H₂ pressure. A low yield of the tertiary amine (36%) was achieved after 12 h due to the formation of furfuryl and THF-alcohols as by-products (Scheme 3).

To increase the yield of tertiary THF-amines, FF was reacted with BuNH₂ over Pd/Al₂O₃ in EtOH combined with N-alkylation with ACN at a FF/BuNH₂/ACN molar ratio of 1/1/3. The kinetic profile showed that **2a** was the primary product generated, which reacted fast by deep hydrogenation of the furan ring to **4a** (Fig 3). After 100 min, **4a** reached a maximum yield of 93%, which decreased further due to N-alkylation with ACN at the expense of the N,N-butylethyl-THF-amine (**5a**). A possible reaction pathway is proposed in Scheme 4. The yield of **5a** reached a maximum yield of 84% after 12 h.

Table 2 Production of THF-derived amines from FF over Pd/Al₂O₃^[a]

	b: yield 97%
	c: yield 95%
	d: yield 97%
	e: yield 93%
	f: yield 97%
	g: yield 95%
	h: yield 93%
	i: yield 91%
	j: yield 93%
	k: yield 47%
	l: yield 95%
	m: yield 94%
	n: yield 90%
	o: yield 90%
	p: yield 90%
	q: yield 93%
	r: yield 85%

^[a] Reaction conditions: FF (1 mmol), Amine (1 mmol), EtOH (5 g), Pd/Al₂O₃ (10 mg), H₂ (0.1 MPa), RT (b-i)/80 °C (j-r), 12 h.

It is of interest to point out that the reaction temperature is a key point which can make a balance between self N-alkylation among acetonitrile and alkylation of THF-butylamine with acetonitrile to obtain a high yield of tertiary amine and high atom-economy (Fig. S2). No tertiary amine (**5a**) was observed at room temperature, affording the formation of all the products with a yield of 41%, 56% of products **2a**, **4a**, respectively. A further increase of the reaction temperature to 80 °C resulted in a decrease of product **5a** maximum yield from 84% to 69% along with 28% yield of **4a**. Furthermore, the catalytic performance of Pd/Al₂O₃ proved itself again as a suitable and efficient catalyst for facile synthesis of amines from bio-derived furfural.

Scheme 4 Proposed reaction pathway for the RA of FF with BuNH₂ combined with N-alkylation.

Fig. 3 Kinetic profile of the RA of FF with BuNH₂ and ACN to N,N-butylethyl-THF-amine over Pd/Al₂O₃. Reaction conditions: FF (1 mmol), BuNH₂ (1 mmol), EtOH (5 g), Pd/Al₂O₃ (10 mg), H₂ (1 MPa), 50 °C.

Conclusions

We presented in this study the one-pot synthesis of secondary and tertiary THF-derived amines starting from furfural and amines at very mild conditions. Commercially available Pd/Al₂O₃ was found an efficient catalyst for producing a library of amines with excellent yield by simply choosing the solvent. In particular, ethanol favoured the synthesis of tetrahydrofurfurylamine (98%). By reacting furfural, 1-butylamine and acetonitrile in ethanol, a one-pot multi-reaction could occur favouring the synthesis of N,N-butylethyl-THF-amines.

Scheme 3 C-N bond formation by RA of FF with ethylbutylamine (1) and RA of FF with BuNH₂ associated with N-alkylation with ACN (2).

Conflicts of interest

There are no conflicts to declare

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