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To cite this version:

HAL Id: hal-03015048
https://hal.science/hal-03015048
Submitted on 19 Nov 2020

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

Shi Jiang, Eric Muller, François Jerôme, Marc Pera-Titus and Karine De Oliveira Vigier

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 tetrahydrofururylamines 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. 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. 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.

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. FF can be used for producing a variety of valuable derivatives, such as furfuryl alcohol, 2-methylfuran, succinic acid, and maleic acid. FF also can be converted into amino-compounds by reductive amination (RA). Furfurylamine and tetrahydrofururylamine are important intermediates in the manufacture of pharmaceuticals (e.g. furosemide), fibers, perfumes, polymers. The synthesis of furfurylamines has been investigated from FF and 5-hydroxymethylfurfural by RA using homogeneous and heterogeneous catalysts. In the literature, many works are dedicated to the synthesis of furfurylamine THF-derived amines can also 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, as well as for the synthesis of poly(2-vinyl-4,4-dimethylazlactone) (pVDMA)-derived (co)polymers with lower critical solution temperature. 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. Homogeneous catalysts such as Ru-acridine complex and triruthenium dodecacarbonyl complex have also used for such reaction from furfuryl alcohol. In our group, we synthesized the THF-amines with high yields from furfural trough cascade reaction combining C-C and C-N condensation reactions in the presence of Pd/Al₂O₃ and Amberlyst 26 catalysts. 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...
hydrogen and different amines. This strategy was further extended to the one-pot synthesis of tertiary THF-amine using acetonitrile (ACN).

Results and Discussion

The reaction between FF and 1-butylamine (BuNH₂) 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 BuNH₂ 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 H₂ 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 (5 wt% Pt) was used as catalyst (10 wt% with respect to FF), the furylurea (1a) and furylurea (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/Al₂O₃ 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/Al₂O₃ 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/Al₂O₃ 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 (30 min instead of 12 h) by increasing the temperature and H₂ 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 BuNH₂ (entry 10). This difference in the selectivity can be ascribed to the solvent properties as it is reported in the literature.¹ Protonic solvent (ethanol) is more active than aprotic polar and aprotic apolar solvents in such reaction. They promote the reaction between furfural and BuNH₂, 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/Al₂O₃ was studied at room temperature and 0.1 MPa H₂ pressure (Fig. 1). Furylurea (1a) was spontaneously formed upon contacting FF with BuNH₂. 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 work¹¹,¹² 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 BuNH₂.

Table 1. Catalyst screening for the RA of FF with BuNH₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield / %</th>
<th>TOF(h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pt/C</td>
<td>EtOH</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Pt/Al₂O₃</td>
<td>EtOH</td>
<td>78</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Pd/C</td>
<td>EtOH</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>Pd/Al₂O₃</td>
<td>EtOH</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>Pd/Al₂O₃</td>
<td>EtOH</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Pd/Al₂O₃</td>
<td>EtOH</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>Pd/Al₂O₃</td>
<td>THF</td>
<td>&lt;1</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
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<td>Toluene</td>
<td>27</td>
<td>57</td>
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<td>9</td>
<td>Pd/Al₂O₃</td>
<td>neat</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>Pd/Al₂O₃</td>
<td>neat</td>
<td>-</td>
<td>98</td>
</tr>
</tbody>
</table>

¹ Reaction conditions: FF (100 mg, 1.04 mmol), BuNH₂ (77 mg), EtOH (5 g), 10 mg of Pd/Al₂O₃ (0.45 mol% related to furfural), H₂ (0.1 MPa), RT, 12 h; ¹² Smg for 5 wt% Pd/Al₂O₃ (0.225 mol%); ¹³ H₂ (1 MPa), 80 °C, 90 min; ¹⁴ BuNH₂ (116 mg); ¹⁵ Yield measured on the crude mixture. The FF conversion was >99% for all the catalytic tests; ¹⁶ Turnover frequency (TOF) = (mol of 4a obtained)/(mol Pd x h).

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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.

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 alcohohalines, 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 disfavouring 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 furfyl 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/ButNH₂/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-butylyleTHF-amine (5a). A possible reaction pathway is proposed in Scheme 4. The yield of 5a reached a maximum yield of 84% after 12 h.

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.

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

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

[^]: 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.

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.

**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.

**Conflicts of interest**

There are no conflicts to declare

**Acknowledgements**

The authors would like to thank the French ANR agency for the funding of FurCab Project ANR-15-CE07-0016. The authors are also grateful to the Région Nouvelle Aquitaine for the funding of this project through the FR CNRS INCREASE 3707, the chair TECHNOGREEN and FEDER.

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