NaBH₄/PhCO₂H: An Efficient system for Reductive Amination of Aldehydes

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ABSTRACT

NaBH₄/PhCO₂H system has been used for the reductive amination of a variety of aldehydes with anilines. The reductive amination reactions have been performed within 60-120 min in THF under reflux conditions in high to excellent yields of products (85-95%).

Key words: NaBH₄, PhCO₂H, Reductive amination, Aldehydes, Amines.

INTRODUCTION

Amines can be synthesized from their corresponding aldehydes. So much method has been used for this purpose such as: the reduction of nitro, cyano, azide, carboxamide compounds or the alkylation of amines. These methods have problems such as: harsh reaction conditions, overalkylation, low chemical selectivity and generally poor yields. Another method is the reductive amination. This reaction has been carried out by sodium borohydride with different reducing system. Previously, we have reported some systems for this achievement. In continuing our efforts for the development of new reducing systems, in this context, we have reported the reductive amination reaction of aldehydes with anilines by NaBH₄ in the presence of benzoic acid in THF.

RESULTS AND DISCUSSION

The model reaction has been performed by reductive amination of benzaldehyde and aniline. This reaction was carried out with different molar ratio of the benzaldehyde/aniline/PhCO₂H/NaBH₄ in different solvents for the optimization reaction conditions. Our experiments have been shown that using 1 eq. of benzoic acid in THF (5 mL) under reflux conditions is the best conditions to complete the reductive amination of benzaldehyde (1 mmol) and aniline (1 mmol) to N-benzylaniline. The reductive amination was completed within 60 min with 92% yields of product as shown in scheme 1.
Table 1. Reductive Amination of Aldehydes (1 mmol) with Anlines (1 mmol) by NaBH₄ (1 mmol) in the presence of benzoic acid (1 mmol) in THF (5 mL) under reflux conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>Anilines</th>
<th>Products</th>
<th>Time/min</th>
<th>Yield a/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>NH₂</td>
<td>CH₂-NH</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>BrNH₂</td>
<td>CH₂-NH-Br</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>MeNH₂</td>
<td>CH₂-NH-Me</td>
<td>60</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>O₂N NH₂</td>
<td>CH₂-NH-NO₂</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>BrCHO</td>
<td>NH₂</td>
<td>BrCH₂-NH</td>
<td>60</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>BrCHO</td>
<td>MeO NH₂</td>
<td>BrCH₂-NH-OMe</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>MeO-CHO</td>
<td>BrNH₂</td>
<td>MeOCH₂-NH-Br</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>MeCHO</td>
<td>NH₂</td>
<td>MeCH₂-NH</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>CHO</td>
<td>OMe</td>
<td>CH₂-NH-OMe</td>
<td>120</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>MeCHO</td>
<td>OMe NH₂</td>
<td>MeCH₂-NH-OMe</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>BrCHO</td>
<td>BrNH₂</td>
<td>BrCH₂-NH-Br</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

a Yields refer to isolated pure products (±5%).
A variety of aldehydes and anilines have been used by this reducing system. Experiments have been shown the corresponding secondary amines were obtained in excellent yields (85-95%) within 60-120 min as shown in Table 1. The influence of benzoic acid is not clear but we have observed sodium borohydride is slowly decomposed by activated benzoic acid. Consequently, it is liberated hydrogen gas in situ. Thus, the generated molecular hydrogen accelerates the reduction reaction.

![Scheme 1](image)

**EXPERIMENTAL**

The products were characterized by their 1H NMR (400 MHz Bruker) or IR (PerkinElmer FT-IR RXI) and comparison with authentic samples (melting or boiling points). TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F$_{254}$ aluminum sheet.

Reductive amination of benzaldehyde and aniline with NaBH$_4$/Benzoic acid system (typical procedure)

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, 1 mmol), aniline (0.093 g, 1 mmol) and activated benzoic acid (0.122 g, 1 mmol) was prepared in THF (5 mL). Then the NaBH$_4$ (0.036 g, 1 mmol) was added to the reaction mixture and stirred under reflux conditions. TLC monitored the progress of the reaction (eluent; CCl$_4$/Ether: 5/2). The reaction was filtered after completion within 60 min. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent; CCl$_4$/Ether: 5/2) afforded the N-benzylaniline (0.166 g, 92% yield, Table 1, entry 1).

**CONCLUSION**

In this context, we have shown that the NaBH$_4$/benzoic acids convenient system for the reductive amination of a variety of aldehydes and anilines to their corresponding secondary amines. The reduction reactions were accomplished with NaBH$_4$ (1 mmol) and activated benzoic acid (1 mmol) in THF under reflux conditions. High efficiency of the reduction reactions and easy work-up procedure makes an attractive new protocol for reductive amination of aldehydes.

**ACKNOWLEDGEMENTS**

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**REFERENCES**