INTRODUCTION

The reduction of nitro, cyano, azide, carboxamide compounds is common routes for the synthesis of amines. Also, this goal has been achieved by the alkylation of amines. These methods for the preparation of secondary amines are often problems such as harsh reaction conditions, overalkylation, low chemical selectivity and generally poor yields. Other approach is reductive amination reaction in a single operation. The reductive amination has been carried out by sodium borohydride under different reducing system such as: NaBH₄/cellulose sulfuric Acid/ EtOH¹, NaBH₄-amberlyst15², NaBH₄-silica chloride³, NaBH₄-silica-gel-supported sulfuric acid⁴, NaBH₄-H₃PO₄·H₂O⁵, NaBH₄/guanidine hydrochloride/H₂O⁶, NaBH₄/Bronsted acid ionic liquid (1-butyl-3-methyl imidazoli umtetrafluoroborate [(BMIm)BF₄])⁷, NaBH₄ or LiAlH₄/LiClO₄/diethyl ether⁸ NaBH₄-PhCO₂H⁹, NaBH₄-NiCl₂·Ti(O-i-Pr)₄-NaBH₄¹₀, NaBH₄-wet-clay-microwave¹², NaBH₄/Mg(ClO₄)₂¹³, NaBH₄/B(OH)₃ or Al(OH)₃¹⁴ NaBH₄/Ga(OC)³¹⁵. In continuing our efforts for the development of new reducing systems¹⁶-²⁶, in this context, we have carried out the reductive amination reaction of aldehydes with anilines by NaBH₄/NaH₂PO₄·H₂O system in THF.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>Anilines</th>
<th>Products</th>
<th>Time/min</th>
<th>Yield(^\text{a})%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>benzaldehyde</td>
<td>aniline</td>
<td>(N)-benzylaniline</td>
<td>55</td>
<td>92</td>
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<tr>
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<td>benzaldehyde</td>
<td>4-bromoaniline</td>
<td>(N)-benzyl-4-bromoaniline</td>
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<td>87</td>
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<tr>
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<td>benzaldehyde</td>
<td>4-methylaniline</td>
<td>(N)-benzyl-4-methylaniline</td>
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<tr>
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<td>aniline</td>
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<tr>
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<td>4-bromobenzaldehyde</td>
<td>4-methoxyaniline</td>
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<td>85</td>
<td>90</td>
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<tr>
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<td>8</td>
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<tr>
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<tr>
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<td>(N)-(4-nitrobenzyl)-4-bromoaniline</td>
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<td>14</td>
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<td>4-methylaniline</td>
<td>(N)-(2-methoxybenzyl)-4-methylaniline</td>
<td>100</td>
<td>91</td>
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</tbody>
</table>

\(^{a}\) Yields refer to isolated pure products (±5%).
RESULTS AND DISCUSSIONS

The model reaction has been selected by reductive amination of benzaldehyde with aniline. This reaction was performed with different molar ratio of the benzaldehyde/aniline/NaH$_2$PO$_4$.H$_2$O/NaBH$_4$ in different solvents for the selection of appropriate conditions. Experiments have been shown that using 1 eq. of NaH$_2$PO$_4$.H$_2$O in THF (3 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 completes within 55 min with 92% yields of product as shown in scheme 1. By using the various structurally different aldehydes and anilines, the efficiency of this protocol was further examined. Experiments have been shown the correspondingsecondary amines were obtained in excellent yields (85-92%) within 55-100 min as shown in Table 1. The influence of NaH$_2$PO$_4$.H$_2$O is not clear but we observed sodium borohydride slowly is liberated hydrogen gas in situ in the presence of NaH$_2$PO$_4$.H$_2$O. Consequently, the generated molecular hydrogen combines with more easily hydride attack, thus accelerates the rate of reduction reaction.

EXPERIMENTAL

IR and $^1$H NMR spectra were recorded on PerkinElmer FT-IR RXI and 400 MHz Bruker spectrometers, respectively. The products were characterized by their $^1$H NMR or IR spectra 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.

Scheme 1:

Reductive amination of benzaldehyde and aniline with NaBH$_4$/NaH$_2$PO$_4$.H$_2$O 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 NaH$_2$PO$_4$.H$_2$O (0.14, 1 mmol) was prepared in THF (3 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 55 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$_4$/NaH$_2$PO$_4$.H$_2$O as reducing system is efficient for the reductive amination of a variety of aldehydes and anilines to their corresponding secondary amines. Reduction reactions were carried out with NaBH$_4$ (1 mmol) and NaH$_2$PO$_4$.H$_2$O (1 mmol) in THF under reflux conditions. High efficiency of the reduction reactions and easy work-up procedure makes as an attractive new protocol for reductive amination of aldehydes.

ACKNOWLEDGEMENTS

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REFERENCES