Note

**Sodium borohydride-iodine, an efficient reagent for reductive amination of aromatic aldehydes**

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Reactions of aromatic aldehydes with primary amines give the corresponding secondary amines in the presence of iodine and sodium borohydride in methanol.

The reductive amination process is a significant transformation in synthetic organic chemistry. It may be judged from the enormous number of its uses in various synthetic schemes¹. The commonly used direct methods of reductive amination mostly use either catalytic hydrogenation procedure or a hydride reducing agent². In case of hydride reducing agent, sodium cyanoborohydride³ is so far the reagent of choice for this transformation. Many more new and modified hydride reagents like borane-pyridine⁴, borohydride exchange resin⁵, sodium borohydride in acidic medium⁶, zinc-acetic acid⁷, zinc borohydride-zinc chloride⁸, sodium cyanoborohydride-titanium isoproxide⁹, sodium borohydride magnesiumchlorate¹⁰, sodium cyanoborohydride-zinc chloride¹¹ had been developed later on. In a recently reported method sodium triacetoxyborohydride had been used for this process.¹² Due to the importance of solid phase reactions in combinatorial chemistry, a few solid supported reagents and reactions are also developed for this transformation¹³.

Although several reagents are available for reductive amination yet most of the reagents have one or the other drawback. Hydrogenation is not compatible with compounds that contains a double or a triple bond and several other reducible functional groups; sodium cyanoborohydride requires up to five fold excess of the amine and may result in the contamination of the product with cyanide. Moreover this reagent is highly toxic and generates toxic byproducts HCN and NaCN upon work up. Although sodium triacetoxy-

borohydride is free from these drawbacks, yet it is very expensive in comparison to sodium borohydride. Recently, we had introduced nickel boride as a reagent for direct reductive amination¹⁴. In continuation of our work, herein we wish to present a new direct reductive amination method using sodium borohydride and iodine.

In the present method sodium borohydride was used in combination with catalytic amount of iodine for reductive amination of aromatic aldehydes. This reagent combination is selective only for reductive amination of aromatic aldehydes with primary amines. Aliphatic aldehydes and ketones were converted into alcohols only. When sodium borohydride alone was used for this transformation, the yield was found to be very low and the major product obtained was the corresponding alcohol.¹⁵ Literature report¹⁶ shows the use of sodium borohydride only for indirect amination of carbonyls through their Schiff’s bases under acidic medium. In the present method four different aldehydes were reductively aminated with n-butyl amine, benzyl amine and aniline, respectively to get the corresponding secondary amines within few minutes. Our observations are reported in the Table 1.

It is clear from Table 1 that both aliphatic and aromatic primary amines react with aromatic aldehydes to give appreciable yield of the corresponding secondary amines. The secondary amines were found to remain inert in this system. A blank reaction of the aldehyde and the amine in presence of catalytic amount of iodine was found to give the corresponding Schiff’s base or imine in almost quantitative yield. Hence it may be concluded that sodium borohydride actually reduces the *in situ* generated imine to the corresponding amine. Iodine catalyzes the formation of imine from aldehyde and amine.

**Experimental Section**

*A typical procedure.* To a solution of 1 mmole of 4-nitrobenzaldehyde in 3 mL of methanol was added 1.2 mmoles of benzyl amine and 0.2 mmole (50.8 mg)
NOTES

Table I—Reductive amination with NaBH₄

<table>
<thead>
<tr>
<th>Carbonyl compounds</th>
<th>Amines</th>
<th>Time (min)</th>
<th>Products</th>
<th>Yield (%)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>PhCHO</td>
<td>n-BuNH₂</td>
<td>10</td>
<td>PhCH₂NH₂Bu⁺</td>
<td>70</td>
<td>17</td>
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<tr>
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<td>PhNH₂</td>
<td>10</td>
<td>PhCH₂NHPh</td>
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<tr>
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<td>10</td>
<td>PhCH₂NHCH₂Ph</td>
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<tr>
<td>4-CIC₆H₄CHO</td>
<td>n-BuNH₂</td>
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<td>4-CIC₆H₄CH₂NH₂Bu⁺</td>
<td>82</td>
<td>14</td>
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<tr>
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<td>PhNH₂</td>
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<td>4-CIC₆H₄CH₂NHPh</td>
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<tr>
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<td>n-BuNH₂</td>
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<tr>
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<td>PhNH₂</td>
<td>10</td>
<td>4-MeOC₆H₄CH₂NHPh</td>
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<td>14</td>
</tr>
<tr>
<td>4-MeOC₆H₄CHO</td>
<td>PhCH₂NH₂</td>
<td>10</td>
<td>4-MeOC₆H₄CH₂NHCH₂Ph</td>
<td>65⁺</td>
<td>17</td>
</tr>
</tbody>
</table>

In all the products were characterized by spectroscopic (NMR, IR, MS) methods as well as direct comparison (TLC, mmp’s) with authentic samples.

Minor amount of corresponding alcohol was obtained as a side product.

of iodine with stirring at room temperature. To the stirred solution 1.5 mmoles (55 mg) of sodium borohydride was added slowly. Stirring was continued for 10 minutes (monitored on TLC). The reaction mixture was diluted with water and extracted with chloroform (3 x 25 mL). The organic layer was washed again with water, dried over anhydrous sodium sulfate and evaporated at reduced pressure to get the crude product. Purification in preparative TLC yielded 126 mg (85%) of the secondary amine.

Acknowledgement

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References

15 Schellenberg K A, J Org Chem, 28, 1963, 2359, here the reductive amination was done with amine salt in acetic acid medium.