Chapter 4

Facile Catalytic Transfer Hydrogenation of Imines to Secondary Amines Using Inexpensive Commercial Zinc Dust and Ammonium Formate

4.1 INTRODUCTION

The conversion of carbonyl derivatives to secondary amines via imines is a useful transformation in the synthesis of numerous organic compounds. Although addition to the C=N bonds of imines, hydrazones and oximes are well known [1], the development of such reaction is often limited by the poor electrophilicity of the C=N carbon. Numerous reagents have been developed for the reduction of imines to amines such as NaBH₄ [2,3], LiAlH₄ [4,5], NH₃/Ra-Ni [6], NH₄Cl/PtO₂ [7], isopropyl alcohol/aluminum isopropoxide/Ra-Ni [8], CH₃CO₂NH₄/Ra-Ni [9]. Eventhough, some of these systems are widely used, still they pose limitations based on chemo-selectivity, low yield and economic considerations. Catalytic hydrogenation is also commonly used [10,11], but, the success of reaction is sensitive towards catalyst, solvent and substrate. Further, catalytic hydrogenation employs highly diffusible, low molecular weight, flammable hydrogen gas and requires pressure equipment. Electrolytic reduction of imines to amines, in acid solution has also been reported [12], but this system offers very low yield.
Catalytic transfer hydrogenation using a stable hydrogen donor in conjunction with a metal catalyst is emerging as a viable tool for the reductive functional group transformation in organic synthesis [13-16]. Several CTH systems have been reported for the reduction of imines [17-20]. However, these systems require long reaction time at reflux and also expensive and pyrophoric catalysts such as Pd/C, Ra-Ni and Pd(OAc)$_2$. Recently, zinc has been successfully utilized as a safe and low-cost alternative to Pd/C and/or Ra-Ni for the reduction of nitro compounds, azo compounds, azides and also for the synthesis of biaryls [21-24]. In this context, for the first time, we utilized zinc and ammonium formate systems for the reduction of imines to the corresponding secondary amines. The present system is rapid and selective, carried out at room temperature in methanol (Scheme 4.1).

\[ \text{Zn/HCOONH}_4 / \text{MeOH, r.t} \]

**Scheme 4.1**

### 4.2 RESULTS AND DISCUSSION

The results given in Table 4.1 reveal the viability of using Zn and ammonium formate systems for the reduction of imines. The course of reaction was monitored by TLC and IR spectra. The work-up and isolation of the products were easy. Thus, the imines reduced by this system were obtained in good yields and most of the reactions were completed within 30 minutes. The products were characterized by comparison of their boiling points or melting points, TLC, IR, elemental analysis and $^1$H NMR spectra with authentic samples. The disappearance of strong absorption bands between 1690 and 1640 cm$^{-1}$ due to C=N stretching and appearance of one strong absorption bands between 3500 and 3200 cm$^{-1}$ for the -NH group clearly shows that the imines were reduced to corresponding secondary amines. Furthermore, in the case of nitro imines, the nitro group at aryl residue and also imine group undergo reduction to yield primary and secondary amines respectively at room temperature.
A control experiment carried out using imines with ammonium formate, but without zinc dust, does not yield any reduced product and the starting material is recovered in 100%. This confirms the role of zinc dust as catalyst. Further, another control experiment was carried out by refluxing imines with zinc dust in methanol and in the absence of ammonium formate yielded no desired product. Even after long duration we could not obtain any reduced product. This clearly confirms that methanol serves only as solvent and not as hydrogen source. A plausible mechanism for the reduction of imines to secondary amines is proposed (Scheme 4.2).

Plausible Mechanism of Reduction of Imines to Secondary Amines using Zn/HCO$_2$NH$_4$

\[
\begin{align*}
\text{Zn} & \quad \text{HCO}_2\text{NH}_4 \quad \text{Zn} \\
& \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{H} \\
& \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{H} \\
& \quad \text{Ar} \quad \text{Ar}' \quad \text{Ar} \quad \text{Ar}' \quad \text{Ar} \quad \text{Ar}' \\
& \quad \text{Zn} \quad \text{Zn} \quad \text{Zn} \quad \text{Zn} \quad \text{Zn} \quad \text{Zn} \\
& \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\end{align*}
\]

Scheme 4.2
Table 4.1: Zinc Catalyzed Reduction of Imines to Secondary Amines Using Ammonium Formate

<table>
<thead>
<tr>
<th>SI No.</th>
<th>Imines (1)</th>
<th>Secondary amines (2)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
<th>Found</th>
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<tr>
<td>1</td>
<td>NH</td>
<td>1a</td>
<td>2a</td>
<td>21</td>
<td>84</td>
<td>182-184</td>
<td>184-185</td>
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<tr>
<td></td>
<td>1b</td>
<td>1b</td>
<td>2b</td>
<td>25</td>
<td>85</td>
<td>36-37</td>
<td>37-38</td>
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<tr>
<td></td>
<td>1c</td>
<td>1c</td>
<td>2c</td>
<td>28</td>
<td>80</td>
<td>45-46</td>
<td>46-48</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>1d</td>
<td>2d</td>
<td>30</td>
<td>80</td>
<td>Liquid</td>
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<tr>
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<td>1e</td>
<td>1e</td>
<td>2e</td>
<td>43</td>
<td>76</td>
<td>165-167</td>
<td>184-189</td>
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<td>1f</td>
<td>1f</td>
<td>2f</td>
<td>30</td>
<td>80</td>
<td>34-35</td>
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Table 4.1 continued...
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<td><img src="image" alt="Structure 1g" /></td>
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<td><img src="image" alt="Structure 1j" /></td>
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*Table 4.1 continued...*
<table>
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<th>No.</th>
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<th>1m</th>
<th>Yield (ºC)</th>
<th>Product</th>
<th>Note</th>
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<tr>
<td>13</td>
<td>13</td>
<td>MeO</td>
<td>2m</td>
<td>75</td>
<td>Oily</td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td>Cl</td>
<td>2n</td>
<td>80</td>
<td>34-36</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td>Cl</td>
<td>2o</td>
<td>81</td>
<td>n. d.</td>
</tr>
</tbody>
</table>

*a* Isolated yields are based on single experiment and the yields were not optimized.

*b* Not determined due to high boiling point.
Figure 4.1: IR Spectra of N-phenylbenzylamine
Figure 4.2: $^1$H NMR Spectra of N-Phenylbenzylamine
Figure 4.3: $^1$H NMR Spectra of N-(4-methylphenylmethyl)aniline
In conclusion, the reduction of imines can be accomplished at room temperature in short duration with Zn instead of expensive Pd or Raney-Ni etc., without affecting the reduction of any other reducible or hydrogenolysable substituents. The yields were virtually quantitative and the compounds obtained were analytically pure. In addition, the easy availability of the reagents, operational simplicity, mild reaction condition and cost-effectiveness make this procedure extremely attractive.

4.3 EXPERIMENTAL

The imines were either commercially available or prepared from the corresponding carbonyl compound by standard methods. In cases where the imines was obtained as an E/Z-mixture, no attempts were made to separate such mixtures and were used as such for the reduction. The details of instruments used have been described in chapter 2.

**General Procedure for Reduction of Imines**

To a solution of the substrate (1 mmol) in methanol or in any other suitable solvent (10 mL) were added ammonium formate (2 mmol) and Zinc powder (1 mmol). The mixture was stirred under nitrogen atmosphere at room temperature. The reaction was exothermic and effervescent. After the completion of reaction (monitored by TLC), the reaction mixture was filtered through celite. The organic layer was evaporated and dissolved the residue in chloroform or dichloromethane or ether and washed with saturated sodium chloride solution to remove excess of ammonium formate. The organic layer was dried over anhydrous sodium sulphate and evaporated the organic layer followed by purification either by preparative TLC or by column chromatography.

2a. IR (neat): \( \nu = 3375, 3295, 2930, 1620, 1465, 1072, 752 \text{ cm}^{-1} \); \(^1\text{H NMR} \) (400 MHz, TMS, CDCl\(_3\)): \( \delta = 8.06 \text{ (s, -NH}_2\text{, 2H)}, 7.33-7.34 \text{ (m, 2H)}, 7.23-7.26 \text{ (m, 6H)}, 4.36 \text{ (s, -CH}_2\text{-, 2H)} \). Anal. Calcd for C\(_7\)H\(_9\)N: C, 78.46; H, 8.47; N, 13.07; Found: C, 78.58; H, 8.54; N, 13.15.

2b. IR (neat): \( \nu = 3418, 2927, 1468, 1340, 1303 \text{ cm}^{-1} \); \(^1\text{H NMR} \) (400 MHz, TMS, CDCl\(_3\)): \( \delta = 7.37 \text{ (m, 4H)}, 7.28 \text{ (m, 2H)}, 7.18 \text{ (t, 2H)}, 6.72 \text{ (t, 1H)}, \)
6.64 (d, 2H), 4.33 (s, -CH$_2$-, 2H), 4.04 (s br, -NH-, 1H). Anal. Calcd for C$_{13}$H$_{13}$N: C, 85.21; H, 7.15; N, 7.64; Found: C, 85.29; H, 7.20; N, 7.69.

2c. IR (neat): $\nu$ = 3402, 2925, 2863, 1462, 1339, 1298, 725 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.27 (d, 2H), 7.23 (d, 4H), 6.71 (tt, 1H), 6.54 (dd, 2H), 4.35 (s, -CH$_2$-, 2H), 4.12 (s br, -NH-, 1H). Anal. Calcd for C$_{13}$H$_{12}$ClN: C, 71.72; H, 5.56; N, 6.43; Found: C, 71.81; H, 5.67; N, 6.53.

2d. IR (neat): $\nu$ = 3408, 2960, 2921, 2869, 2852, 1457, 1336, 1288 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.27 (d, 2H), 7.16 (d, 4H), 6.71 (tt, 1H), 6.64 (dd, 2H), 4.28 (s, -CH$_2$-, 2H), 3.98 (s br, -NH-, 1H), 2.35 (s, -CH$_3$, 3H). Anal. Calcd for C$_{14}$H$_{15}$N: C, 85.24; H, 7.66; N, 7.10; Found: C, 85.31; H, 7.67; N, 6.53.

2e. IR (neat): $\nu$ = 3400, 2910, 2850, 1460, 1340, 1275, 550 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.48 (d, 1H), 7.12-7.15 (m, 2H), 7.23-7.27 (m, 3H) 6.77-6.83 (m, 3H), 4.30 (s, -CH$_2$-, 2H), 4.15 (s br, -NH-, 1H). Anal. Calcd for C$_{13}$H$_{12}$BrN: C, 59.56; H, 4.61; N, 5.34; Found: C, 59.69; H, 4.67; N, 5.43.

2f. IR (neat): $\nu$ = 3401, 2900, 2852, 1460, 1341, 1270, 552 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.58 (d, 1H), 7.32-7.33 (m, 2H), 7.23-7.26 (m, 3H), 7.17-7.19 (m, 1H) 6.65-6.68 (m,1H), 6.49 (d, 1H), 4.32 (s, -CH$_2$-, 2H), 4.10 (s br, -NH-, 1H). Anal. Calcd for C$_{13}$H$_{12}$BrN: C, 59.56; H, 4.61; N, 5.34; Found: C, 59.65; H, 4.70; N, 5.46.

2g. IR (neat): $\nu$ = 3401, 3369, 1650, 1485, 1345 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.23 (m, 2H), 7.08 (t, 1H), 6.77-6.83 (m, 3H), 6.55-6.59 (m, 2H), 6.44 (m, 1H), 4.35 (s, -CH$_2$-, 2H), 4.10 (s br, -NH-, 1H), 3.32 (s, -NH$_2$, 2H). Anal. Calcd for C$_{13}$H$_{14}$N$_2$: C, 78.75; H, 7.12; N, 14.13; Found: C, 78.87; H, 7.22; N, 14.25.

2h. IR (neat): $\nu$ = 3398, 2930, 2852, 1463, 1341, 1255, 1041, 820 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.18 (m, 2H), 7.10 (m, 3H), 6.55 (m, 2H, CH), 6.30 (m, 2H), 4.32 (s, -CH$_2$-, 2H), 3.92 (s, NH, 1H), 3.70 (s, -OCH$_3$, 3H); Anal. Calcd for C$_{14}$H$_{15}$NO: C, 78.84; H, 7.09; N, 6.57; Found: C, 77.96; H, 6.88; N, 6.62.

2i. IR (neat): $\nu$ = 3402, 2933, 2850, 1458, 1345, 1253, 1037, 821, 710 cm$^{-1}$; $^1$H NMR (400 MHz, TMS, CDCl$_3$): $\delta$ = 7.32-7.37 (m, 4H), 6.77 (s, 4H),
4.35 (s, -CH\textsubscript{2}-, 2H), 4.12 (s, NH, 1H), 3.83 (s, -OCH\textsubscript{3}, 3H). Anal. Calcd for C\textsubscript{14}H\textsubscript{14}ClNO: C, 67.88; H, 5.70; N, 5.65; Found: C, 67.97; H, 5.81; N, 5.78.

2j. IR (neat): \(\nu = 3413, 2918, 2860, 1475, 1334, 820, 723\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.33-7.36\) (m, 4H), 7.27 (m, 2H), 6.54 (dd, 2H), 4.31 (s, -CH\textsubscript{2}, 2H), 4.09 (s, NH, 1H). Anal. Calcd for C\textsubscript{13}H\textsubscript{11}Cl\textsubscript{2}N: C, 61.93; H, 4.40; N, 5.56; Found: C, 62.16; H, 4.51; N, 5.68.

2k. IR (neat): \(\nu = 3405, 2930, 2870, 2845, 1463, 1343, 1256, 1039\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.11\) (s, 4H), 7.01 (d, 2H), 6.48 (d, 2H), 4.29 (s, -CH\textsubscript{2}, 2H), 4.02 (s, NH, 1H), 2.34 (s, -2CH\textsubscript{3}, 6H). Anal. Calcd for C\textsubscript{15}H\textsubscript{17}N: C, 85.26; H, 8.11; N, 6.63; Found: C, 85.30; H, 8.18; N, 6.72.

2l. IR (neat): \(\nu = 3406, 2925, 2850, 1470, 1334, 1291, 1255, 1041, 810\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.14\) (m, CH, 2H), 7.06 (m, CH, 4H), 6.92 (m, CH, 1H), 6.52 (m, 1H, CH), 6.37 (m, CH, 1H), 4.32 (s, -CH\textsubscript{2}, 2H), 3.80 (s, -NH, 1H); Anal. Calcd for C\textsubscript{13}H\textsubscript{12}ClN: C, 71.72; H, 5.56; N, 6.43; Found: C, 71.55; H, 5.66; N, 6.40.

2m. IR (neat): \(\nu = 3401, 2936, 2856, 1460, 1336, 1289, 1251, 1025, 841\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.14\) (m, CH, 2H), 7.06 (m, CH, 3H), 6.60 (m, CH, 1H), 6.55 (m, CH, 1H), 6.47 (m, CH, 1H), 6.32 (m, CH, 1H), 4.12 (s, -CH\textsubscript{2}, 2H), 3.85 (s, NH, 1H), 3.75 (s, -OCH\textsubscript{3}, 3H); Anal. Calcd for C\textsubscript{14}H\textsubscript{15}NO: C, 78.84; H, 7.09; N, 6.57; Found: C, 77.86; H, 6.93; N, 6.49.

2n. IR (neat): \(\nu = 3408, 2930, 2916, 2870, 2863, 2856, 1454, 1336, 720\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.35\) (m, 4H), 7.23 (m, 2H), 7.19 (m, CH, 2H), 6.90-7.12 (m, CH, 4H), 4.21 (s, CH\textsubscript{2}, 2H), 3.78 (s, NH, 1H), 2.42 (s, -CH\textsubscript{3}, 3H); Anal. Calcd for C\textsubscript{14}H\textsubscript{14}ClN: C, 72.57; H, 6.09; N, 6.04; Found: C, 72.25; H, 6.13; N, 5.98.

2o. IR (neat): \(\nu = 3400, 2935, 2948, 1650, 1461, 1146, 730\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, TMS, CDCl\textsubscript{3}): \(\delta = 7.33\) (m, 4H), 7.23-7.26 (m, 6H), 3.76 (s, 2CH\textsubscript{2}, 4H), 4.2 (s, NH, 1H). Anal. Calcd for C\textsubscript{14}H\textsubscript{15}N: C, 85.24; H, 7.66; N, 7.10; Found: C, 85.29; H, 7.82; N, 7.18.
4.4 References


