Novel and Efficient Synthesis of Hydrazoarenes by Tin Mediated Controlled Reduction of Azoarenes

3.1 INTRODUCTION:

Since nitro and azo compounds are reduced to their corresponding amines under mild conditions, the controlled reduction of these functionalities to hydrazo compounds is still a great challenge in organic synthesis. Although a variety of reagents including NaBH₄, LAlH₄ have been reported for the reduction of azoarenes to hydrazoarenes, limitations include the use of harsh conditions and or costly reagents [1]. Catalytic hydrogenation [2] has also been used, although further reductive cleavage of the -NH-NH- bond can occur. Zinc and other metals have also been used for reduction but strongly acidic conditions have to be avoided in order to prevent the benzidine rearrangement of the hydrazoarenes.

Metal catalysed hydrogen transfer using hydrogen donors such as hydrazine hydrate, formic acid, formate salts, cyclohexene and cyclohexadiene is emerging as a useful tool for reductive functional group transformation in organic synthesis [3-11]. This approach involves mild reaction conditions, easy bulk management, minimal effluents, and facile product separation. The hydrogen transfer reduction of nitro and azo
compounds using various metal catalysts such as Pd-C [3,4,12], Raney Ni [3,4,13], Zn [14,15], Mg [16,17] PdMCM-41 and NiMCM-41 molecular sieves [18,19] has been reported. However, all these metal catalysts in conjunction with hydrogen donors reduce both nitro and azo compounds to their corresponding amino derivatives. Although tin and organotin compounds are widely employed in organic synthesis [20-23] to the best of our knowledge, tin has not been used in conjunction with hydrazine hydrate for reduction reactions. We investigated the reduction of azoarenes using tin and hydrazine hydrate. Azoarenes underwent smooth reduction to hydrazoarenes at room temperature in methanol without further reduction to aniline derivatives (Scheme 3.1).

![Scheme 3.1](image)

\( R \text{ or } R' = \text{halogen, OH, OCH}_3, \text{COOH, CH}_3, \text{COCH}_3 \text{ etc.} \)

### 3.2 RESULTS AND DISCUSSION:

A wide range of azoarenes underwent reduction by this procedure to furnish the corresponding hydrazoarenes. The results are summarised in Table 3.1. All the products were characterised by comparison of their TLC, melting points, IR spectra, and \(^1\)H NMR spectra with authentic samples. The reactions are reasonably fast and high yielding. This procedure is found to be compatible with several sensitive functionalities such as halogens, NO\(_2\), OH, OMe, COOH. However, this system was not useful for the reduction of azoarenes containing carbonyl functionality due to the formation of hydrazone derivative with hydrazine hydrate. It should be emphasised that in the absence of tin, the reaction did not proceed and mainly resulted in the recovery of the starting materials. Similarly, the reduction of azoarenes in the absence of hydrazine hydrate did not yield the product. This clearly confirms that methanol serves only as a solvent but not as a hydrogen source.
Attempts were also made to reduce nitroarenes using large excess of tin and hydrazine hydrate in methanol. Even after prolonged time (24 h) the starting material was recovered quantitatively (Table 3.1; entries 14 and 15). This distinguishes the present system from other metal-aided hydrogen transfer reductions in which both nitroarenes and azoarenes undergo easy reduction to yield the corresponding amines [3,4,12-19]. Thus, tin in conjunction with hydrazine hydrate provides a system for the controlled, rapid reduction of azoarenes to hydrazoarenes in high yield without further cleavage of N-N bond. In addition, unlike organotin compounds, tin powder is non-toxic, widely available and inexpensive. The ease of product isolation, high selectivity and low cost of the reagents make this procedure attractive. A plausible mechanism for tin mediated controlled reduction of azoarenes to hydrazoarenes is proposed (Scheme 3.2 & Scheme 3.3).

Plausible Mechanism of Synthesis of Hydrazo compounds using Sn and H$_2$NNH$_2$·H$_2$O

1. Reduction by Hydrazine.

\[
\text{H}_2\text{NNH}_2 + \text{Sn} \rightarrow \text{H-Sn-N-NH}_2 \rightarrow \text{H-Sn-N-NH}_2 \rightarrow \text{R-N=N-R'}
\]

\[\text{H-Sn-N-NH}_2 \rightarrow \text{R-N=N-R'} \rightarrow -\text{Sn}, -\text{HN=NH}\]

Scheme 3.2

2. Reduction by Diimide.

\[
\text{HN=NH + Sn} \rightarrow \text{H-Sn-N=NH} \rightarrow \text{H-Sn-N=NH} \rightarrow \text{R-N=N-R'}
\]

\[\text{H-Sn-N=NH} \rightarrow \text{R-N=N-R'} \rightarrow -\text{Sn}, -\text{N}_2\]

Scheme 3.3
### Table 3.1: Tin-Mediated Controlled Reduction of Azoarenes to Hydrazoarenes using Hydrazine Hydrate

<table>
<thead>
<tr>
<th>Sl No.</th>
<th>Azoarenes (1)</th>
<th>Hydrazoarenes (2)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
</tr>
<tr>
<td>1</td>
<td><img src="image" alt="Azobenzene" /></td>
<td><img src="image" alt="Hydrazobenzene" /></td>
<td>20</td>
<td>95</td>
<td>125-127</td>
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<td>2</td>
<td><img src="image" alt="Azodibromoaniline" /></td>
<td><img src="image" alt="Hydrazodibromoaniline" /></td>
<td>15</td>
<td>92</td>
<td>96-98</td>
</tr>
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<td><img src="image" alt="Hydrazodimethylaniline" /></td>
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<td>92</td>
<td>133-136</td>
</tr>
<tr>
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<td><img src="image" alt="Hydrazodibromoaniline" /></td>
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<td>106-107</td>
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<td>20</td>
<td>95</td>
<td>89-92</td>
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<tr>
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<td><img src="image" alt="Hydrazodimethylaniline" /></td>
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<td>93</td>
<td>oil</td>
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<td>100$^\circ$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 1o" /></td>
<td>24h</td>
<td>100$^\circ$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Starting material was recovered almost quantitatively.
Figure 3.1: IR Spectra of Hydrazobenzene
Figure 3.2: IR Spectra of 3,3'-Dichlorohydrazobenzene
Figure 3.3: \(^1\text{H} \text{NMR} \) Spectra of Hydrazobenzene
3.3 Experimental

The details of instruments used have been described in chapter 2. The substrates were either commercial products and were used as purchased or were prepared according to literature procedures.

General Procedure for Reduction of Imines
The azoarene (5 mmol) in methanol (10 mL) was treated with tin powder (5 mmol) and hydrazine hydrate (10 mmol). The mixture was stirred at room temperature for the specified time under nitrogen (Table 3.1). After consumption of the starting material, as monitored by TLC, the reaction mixture was filtered through celite. The filtrate was evaporated under reduced pressure and the residue was taken into chloroform or ether, washed twice with 80% saturated brine solution and finally with water. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was found to be analytically pure in most cases. Where necessary, the crude product was purified by SiO₂ column chromatography.

2a. IR (neat): ν = 3327, 1599, 1512, 1478, 1306 cm⁻¹; ¹H NMR (400 MHz, TMS, CDCl₃): δ = 7.24-7.26 (m, 4H), 6.87-6.91 (m, 6H), 5.63 (s, NH, 2H). Anal. Calcd for C₁₂H₁₂N₂: C, 78.23; H, 6.57; N, 15.21; Found: C, 78.42; H, 6.61; N, 15.28%.

2b. IR (neat): ν = 3405, 1340, 1269, 575 cm⁻¹; ¹H NMR (400 MHz, TMS, CDCl₃): δ = 7.72 (d, 2H), 7.29-7.33 (m, 2H), 6.76-6.79 (m, 2H), 6.72-6.70, (m, 2H), 5.89 (s, NH, 2H). Anal. Calcd for C₁₂H₁₀Br₂N₂: C, 42.14; H, 2.95; N, 8.19; Found: C, 42.18; H, 2.99; N, 8.25%.

2c. IR (neat): ν = 3341, 2927, 2865, 1339, 1255 cm⁻¹; ¹H NMR (400 MHz, TMS, CDCl₃): δ = 7.15 (d, 4H), 6.71 (d, 4H), 5.64 (s, NH, 2H), 2.34 (s, 4,4'-CH₃, 6H). Anal. Calcd for C₁₄H₁₆N₂: C, 79.21; H, 7.60; N, 13.20; Found: C, 79.25; H, 7.61; N, 13.27%.

2d. IR (neat): ν = 3392, 1320, 1271, 581 cm⁻¹; ¹H NMR (400 MHz, TMS, CDCl₃): δ = 7.11-7.19 (m, 2H), 7.04-7.07 (m, 2H), 6.96-7.00 (m, 2H), 6.89 (s, 2H), 5.58 (s, NH, 2H). Anal. Calcd for C₁₂H₁₀Br₂N₂: C, 42.14; H, 2.95; N, 8.19; Found: C, 42.19; H, 3.01; N, 8.22%.
2e. **IR** (neat): $\nu = 3356, 3076, 1335, 1685, 1420, 1223, 935 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 11.5$ (s, br, -COOH, 1H), 7.58 (d, 2H), 6.37 (t, 2H), 7.04-7.06 (m, 4H), 6.90 (m, 1H), 5.30 (s, NH, 2H). Anal. Calcd for C$_{13}$H$_{12}$N$_2$O$_2$: C, 68.41; H, 5.30; N, 12.27; Found: C, 68.50; H, 5.35; N, 12.32%.

2f. **IR** (neat): $\nu = 3382, 1594, 1519, 1494, 1318, 875, 743, 688 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 11.5$ (s, br, -COOH, 1H), 7.58 (d, 2H), 6.37 (t, 2H), 7.04-7.06 (m, 4H), 6.90 (m, 1H), 5.30 (s, NH, 2H). Anal. Calcd for C$_{12}$H$_{10}$Cl$_2$N$_2$: C, 56.94; H, 3.98; N, 11.07; Found: C, 57.08; H, 4.04; N, 11.13%.

2g. **IR** (neat): $\nu = 3357, 2910, 2867, 1330, 1287 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 7.25$ (t, 2H), 6.87-6.89 (m, 2H), 6.75 (s, 2H) 6.66–6.69 (m, 2H), 5.25 (s, NH, 2H). Anal. Calcd for C$_{14}$H$_{16}$N$_2$: C, 79.21; H, 7.60; N, 13.20; Found: C, 79.32; H, 7.56; N, 13.28%.

2h. **IR** (neat): $\nu = 3395, 1338, 1260, 1280, 1040 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 7.26$ (t, 2H), 6.61–6.63 (m, 2H), 6.38–6.44 (m, 4H), 5.66 (s, 2NH, 2H). Anal. Calcd for C$_{14}$H$_{16}$N$_2$O$_2$: C, 68.83; H, 6.60; N, 5.59; Found: C, 68.85; H, 6.64; N, 11.59%.

2i. **IR** (neat): $\nu = 3350, 1337, 1278 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 9.41$ (s, 2OH, 2H), 7.20 (t, 2H), 6.57-6.61 (m, 2H), 6.34–6.40 (m, 4H), 5.59 (s, 2NH, 2H). Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_2$: C, 66.65; H, 5.60; N, 12.96; Found: C, 68.71; H, 6.64; N, 12.89%.

2j. **IR** (neat): $\nu = 3394, 1325, 1267, 550 \text{ cm}^{-1}$; **$^1H$ NMR** (400 MHz, TMS, CDCl$_3$): $\delta = 7.74$ (d, 4H), 6.95 (d, 4H), 4.21 (s, 2NH, 2H). Anal. Calcd for C$_{14}$H$_{16}$N$_3$NaO$_2$: C, 53.66; H, 5.15; N, 13.41; Found: C, 52.55; H, 5.31; N, 13.26%.
3.4 References