The efficient reduction of oximes to amines with Zn and acetic acid under ultrasonic irradiation

Yu-Qing Cao*, Rui-Yan Liu, An-Li Qu, Yuan-Yuan Jin
College of Pharmacy, Hebei University, Baoding-071002, (P. R. CHINA)
E-mail: pharm_hbu@yahoo.com
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ABSTRACT

Zn and Acetic acid, as a kind of reducing system can easily reduce a variety of aromatic aldoximes or ketoximes to their corresponding amines in high to excellent yields under ultrasonic irradiation at room temperature. As against the conventional methods, the reaction times were shortened by 1h-4h.

INTRODUCTION

Amines are very important organic compounds widely used as intermediates for the synthesis of a diversity of pharmaceutical[1] and polymeric products[2]. Therefore, synthetic methodologies for amines have evolved through the years from diverse precursors[3]. The transformation of oximes into amines is a synthetically important process and its value has been well established. A variety of oximes can easily be prepared from the corresponding aldehydes or ketones in excellent yields[4,5], which provides a feasible approach for preparing amines. Numerous new reagents have been developed for the reduction of oximes to amines, such as Lithium aluminum hydride[6], Sodium- Liquid Ammonia or Sodium- ethanol[7], Sodium amalgam[8], Catalytic hydrogenation[9]. However, these methods suffer from drawbacks, such as requiring anhydrous condition and the reaction conditions greatly depend on the structures of oximes. For example, the reduction of benzaldoxime to benzylamine goes in the presence of catalyst Raney nickel under the harsh reaction condition of 10.1MPa, 100°C. Thus, development of a simple and efficient method for synthesizing amines is very desirable.

High-power ultrasound can generate cavitation within a liquid and through cavitation provide a source of energy which can be used to enhance a wide range of chemical processes[10]. The use of high-intensity ultrasound to enhance the reactivity of metals has become an important synthetic technique for many heterogeneous organic reactions, especially those involving reactive metals, such as magnesium, lithium and zinc[11-14]. The mechanism of the rate enhancements in reactions of metals has been unveiled by monitoring the effect of ultrasonic irradiation on the kinetics of the chemical reactivity of the solids, examining the effects of irradiation on surface structure and size distributions of powders and solids[15]. Ultrasonic irradiation of liquid, nickel, zinc, and copper powders leads to dramatic changes in structure, ultrasonic irradiation effectively removed the inactive surface oxide coating. The removal of such passivating coatings dramatically improves reaction rates. Based on this, we now report the applica-
Application of ultrasonic technology to the reduction of oximes to amines. The results showed that the reaction times were shortened by 1h-4h with yields of 93%-98% (Scheme 1). The simplified condition of the reaction is adaptable to the industrialized production.

**RESULTS AND DISCUSSION**

A variety of aldoximes and ketoximes were reduced to their primary and secondary amines, respectively, in the presence of Zn and acetic acid under ultrasonic irradiation with excellent yields. The reaction times and isolated yields of the products were summarized in TABLE 1. Compared with the classic methods reported in the relevant literatures, it not only shortened the reaction times, but also led to higher yields. By comparison, benzylamine was obtained from benzaldehyde oxide in the presence of Zn under reflux in acetic acid for 4hr, with 90% yield was provided. The reaction was completed in 60min under ultrasonic irradiation at room temperature and gave yield of 94%. It is easy to see that ultrasonic irradiation can significantly promote the reaction.

Substitution pattern on the aromatic ring has an influence on the reaction rate. The reduction of aryl aldoximes with electron donating substituents like dimethylamino group (entry 8) and methoxy group (entries 9, 10) was slow and with electron withdrawing substituents, such as chloro group (entries 2, 3 and 4) and nitro group (entry 5) were readily reduced. Aryl aldoxime with a substituted nitro group showed a selectivity and was readily reduced with 1.2 molar amounts of reducing agent without affecting the nitro group (entry 5), but with further molar amounts of reducing agent the simultaneous reduction of the nitro group took place (entry 6). 1-Naphthalene aldoxime (entry 13) shows further reactivity relative to others with consumption of lower molar of equivalents of the reducing reagent (1: 0.8).

In anticipating Fe and Acetic acid reduction, experiments were also performed by using Oximes with Fe and Acetic acid under ultrasonic irradiation for 1.5h. Even after a longer period the yields were only 10-15%, which clearly indicated that reducing Oximes to Amines with Fe and acetic acid under ultrasonic irradiation was not feasibility.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Molar Ratio</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Mp or Bp(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅CH=NOH</td>
<td>1:1.2</td>
<td>C₆H₅CH₂NH₂</td>
<td>1h</td>
<td>94%</td>
<td>183-184</td>
</tr>
<tr>
<td>2</td>
<td>3-ClC₆H₅CH=NOH</td>
<td>1:1.2</td>
<td>3-ClC₆H₅CH₂NH₂</td>
<td>0.8h</td>
<td>93%</td>
<td>110-112</td>
</tr>
<tr>
<td>3</td>
<td>4-ClC₆H₅CH=NOH</td>
<td>1:1.2</td>
<td>4-ClC₆H₅CH₂NH₂</td>
<td>0.9h</td>
<td>96%</td>
<td>215-216</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Cl₂C₆H₄CH=NOH</td>
<td>1:1.2</td>
<td>2,4-Cl₂C₆H₄CH₂NH₂</td>
<td>0.7h</td>
<td>98%</td>
<td>257-259</td>
</tr>
<tr>
<td>5</td>
<td>4-O₂NC₆H₄CH=NOH</td>
<td>1:1.2</td>
<td>4-O₂NC₆H₄CH₂NH₂</td>
<td>0.6h</td>
<td>93%</td>
<td>266</td>
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<tr>
<td>6</td>
<td>4-O₂NC₆H₄CH=NOH</td>
<td>1:2</td>
<td>4-O₂NC₆H₄CH₂NH₂</td>
<td>1.3h</td>
<td>95%</td>
<td>101/0.05</td>
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<tr>
<td>7</td>
<td>2-HOC₆H₅CH=NOH</td>
<td>1:1.2</td>
<td>2-HOC₆H₅CH₂NH₂</td>
<td>0.5h</td>
<td>96%</td>
<td>129-130</td>
</tr>
<tr>
<td>8</td>
<td>4-(CH₃)₂N-C₆H₄CH=NOH</td>
<td>1:1.2</td>
<td>4-(CH₃)₂N-C₆H₄CH₂NH₂</td>
<td>1.7h</td>
<td>96%</td>
<td>149-150</td>
</tr>
<tr>
<td>9</td>
<td>4-CH₃OC₆H₄CH=NOH</td>
<td>1:1.2</td>
<td>4-CH₃OC₆H₄CH₂NH₂</td>
<td>1.5h</td>
<td>94%</td>
<td>235-236</td>
</tr>
<tr>
<td>10</td>
<td>2-CH₃OC₆H₄CH=NOH</td>
<td>1:1.2</td>
<td>2-CH₃OC₆H₄CH₂NH₂</td>
<td>2h</td>
<td>96%</td>
<td>226/724</td>
</tr>
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<td>11</td>
<td>C₆H₅(CH₃)C=NOH</td>
<td>1:1.2</td>
<td>C₆H₅(CH₃)CH₂NH₂</td>
<td>1.1h</td>
<td>95%</td>
<td>186-188</td>
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<tr>
<td>12</td>
<td>Fururaldoxime</td>
<td>1:1.2</td>
<td>Furufurylamine</td>
<td>1.4h</td>
<td>94%</td>
<td>145-147</td>
</tr>
<tr>
<td>13⁺</td>
<td>C₁₀H₈CH=NOH</td>
<td>1:0.8</td>
<td>C₁₀H₈CH₂NH₂</td>
<td>0.3h</td>
<td>98%</td>
<td>290-292</td>
</tr>
</tbody>
</table>

* The structure of the compound (entry 13) is
In Conclusion, we have described an efficient and convenient method to reduce Oximes to Amines with Zn and acetic acid under ultrasonic irradiation, which bring some practical values with mild reaction conditions, cleaner reactions, and simple experimental procedures.

EXPERIMENTAL

All reagents were commercially available. Oximes were prepared according to literature procedure[4,5]. TLC was used to monitor the reaction process. TLC was GF$^{254}$ thin layer chromatography with Carbon tetrachloride / ether(5/2) used as eluent. IR spectra were recorded on a IR Prestige-21/FTIR-8400S spectrometer. 1H-NMR spectra were obtained on a Brucker ADVANCE(400MHz) spectrometer using TMS as internal standard and DMSO as solvent. The products were also characterized by comparison of their melting points and boiling points with literature values.

General Procedure for Preparation of Benzylamine (entry 1)

Benzaldehyde oxime (1.21g, 0.01mol), acetic acid (5ml), zinc powder (0.78g, 0.012mol) were respectively added in a dry 50ml conical flask and treated under Ultrasonic Irradiation at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with dichloromethane (3 x 10ml), the extract was dried with anhydrous sodium sulfate. Then it was evaporated under reduced pressure afforded the crude product. The product was purified by recrystallization. Selected spectral data of some of the products are given below:

C$_6$H$_5$CH$_2$NH$_2$ (entry 1) $^1$HNMRCDCI$_3$: δ: 7.33(s, 5H), 3.90 (s, 2H), 1.41 (s, 2H); IR (v, neat): 3367, 3278, 3039, 2940, 2857, 1600, 1492, 1450, 1388, 1052, 1025, 854, 780, 775, 730, 695 cm$^{-1}$.

C$_8$H$_7$CH$_2$NH$_2$ (entry 4) $^1$HNMR(CDCI$_3$): δ: 7.45-7.11 (m, 3H), 3.90 (s, 2H), 1.52 (s, 2H); IR (v, neat): 3390, 3300, 3090, 3070, 2940, 2880, 1590, 1562, 1470, 1392, 1260, 1200, 1098, 1100, 1050, 865, 820, 732, 740, 715, 700, 650 cm$^{-1}$.

C$_6$H$_4$CH$_2$NH$_2$ (entry 5) $^1$HNMR(DMSO-d$_6$): δ: 8.90 (bs, 3H), 8.37 (d, 2H), 7.81(d, 2H), 4.36(s, 2H).

C$_6$H$_4$CH$_2$NH$_2$ (entry 6) $^1$HNMR(CDCI$_3$): δ: 7.16(d, 2H), 6.63(d, 2H), 4.38-3.53 (b, 2H), 1.74(s, 2H); IR (v, neat): 3390, 3300, 3090, 3070, 2940, 2880, 1590, 1562, 1470, 1392, 1260, 1180, 1085, 1030, 880, 825 cm$^{-1}$.

REFERENCES