Solvent free synthesis of 1,5-benzodiazepines catalyzed by zirconium nitrate

Ambika¹ Pradeep Pratap Singh²*

¹ Department of Chemistry, Hansraj College, University of Delhi, Delhi-110007, India; ² Department of Chemistry, Swami Shraddhanand College, University of Delhi, Delhi-110036, India.

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ABSTRACT

1,5-benzodiazepines are synthesized by the condensation of o-phenylenediamine and various ketones in the presence of Zr(NO₃)₄ under solvent free condition. The method offers mild reaction conditions, less reaction time, easy workup, high yields, easy product isolation, selectivity of the reaction and reusability of catalyst.

Keywords: Benzodiazepines, Solvent free, Zirconium nitrate

INTRODUCTION

Benzodiazepines represent an important class of bioactive compounds and possess anticonvulsant, analgesic, hypnotic, sedative, and antidepressent activity.¹⁻⁶ They are used as intermediates for the synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furano-benzodiazepines.⁷,⁸ In addition they also find commercial use as dyes for acrylic fiber, in photography industry and industrial scale production of anti-inflammatory agents. Benzodiazepines have been synthesized by the condensation of o-phenylenediamines with α,β-unsaturated carbonyl compounds, β-haloketones or with ketones. Different catalyst such as BF₃-etherate, polyphosphoric acid, NaBH₄, SiO₂, Yb(OTf)₃, InBr₃, acetic acid under microwave conditions, zirconia and ionic liquids have been utilized for the synthesis of benzodiazapines.⁹⁻¹⁷ All of the above processes suffer from one or more limitations, such as long reaction times, drastic reaction conditions, low yields, and tedious work-up procedures.

Catalysis has played a significant role in reducing pollution in the environment. Catalysis, can make the reactions more efficient and selective thereby eliminating large amounts of by-products.¹⁸ Solid acids have many advantages in both research and industry.¹⁹,²⁰ Zirconium salts have emerged in the recent years as "eco-friendly" reagents suitable for green chemistry.²¹,²² Recently, Zr(NO₃)₄ have been used to carry out an array of organic transformations.²³,²⁴

Scheme 1.

In this communication, we report a facile method for the synthesis of 1,5-benzodiazepines by the condensation of o-
phenylenediamine with ketones under solvent free conditions catalyzed by Zr(NO₃)₄ (Scheme 1).

Table 1. Synthesis of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (3a) in different reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Catalyst</th>
<th>Time (min.)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>Zr(NO₃)₄</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>H₂O:EtOH (1:1)</td>
<td>Zr(NO₃)₄</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Zr(NO₃)₄</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>Zr(NO₃)₄</td>
<td>5</td>
<td>98</td>
</tr>
</tbody>
</table>

Notes: All reactions were carried out using o-phenylenediamine (1, 2.1 mmol) and acetone (2a, 1.0 mmol); a Isolated yields

Table 2: Condensation of o-phenylenediamine (1) with various ketones (2a-g) catalyzed by Zr(NO₃)₄.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obs.</td>
<td>Litt.</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>3a</td>
<td>5</td>
<td>98</td>
<td>137</td>
</tr>
<tr>
<td>2b</td>
<td>3b</td>
<td>10</td>
<td>97</td>
<td>138</td>
</tr>
<tr>
<td>2c</td>
<td>3c</td>
<td>15</td>
<td>95</td>
<td>150</td>
</tr>
<tr>
<td>2d</td>
<td>3d</td>
<td>15</td>
<td>97</td>
<td>152</td>
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<td>2e</td>
<td>3e</td>
<td>15</td>
<td>94</td>
<td>111</td>
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<tr>
<td>2f</td>
<td>3f</td>
<td>10</td>
<td>95</td>
<td>136</td>
</tr>
<tr>
<td>2g</td>
<td>3g</td>
<td>10</td>
<td>94</td>
<td>136</td>
</tr>
</tbody>
</table>

Note: All reactions were carried out using o-phenylenediamine (1, 2.1 mmol), ketones (1.0 mmol) and catalytic amount of Zr(NO₃)₄; a Isolated yields

The reaction of o-phenylenediamine (1, 2.1 mmol) and acetone (2a, 1.0 mmol) in the presence of catalytic amount of Zr(NO₃)₄ with stirring at ambient temperature afforded 98% yield of 2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (3a) in 5 min. (Table 1). The above reaction in different solvents such as H₂O, EtOH:H₂O (1:1) and EtOH, gave 3a in 57, 69 and 82% yields respectively in 30 min. (Table 1). In the absence of the catalyst the desired product was not obtained even after 24h stirring at ambient temperature. Hence all the reactions were carried out using Zr(NO₃)₄ under solvent free conditions.

Similarly the reaction of other ketones (2b-g) with 1 in the presence of Zr(NO₃)₄ gave fused ring 1,5-benzodiazepine derivatives in excellent to good yields (Table 2). Unsymmetrical ketones such as butanone (2b) underwent ring closure selectively to give a single product. Substituted acetophenones carrying either electron releasing (2d) or electron withdrawing (2e) substituents afforded good yields of benzodiazepines (Table 2). One of the salient features of this method is that all aliphahtic (2a-b), aromatic (2c-e) and cyclic ketones (2f-g) used gave the corresponding benzodiazepines in good to excellent yields with high purity.

Further, the recovery of the products is relatively simple under solvent free conditions as compared to the solvents. The benzodiazepines are easily separated by simple extraction with dichloromethane followed by recrystallisation with a suitable solvent. The reaction of 1 with 2a in the presence of recovered Zr(NO₃)₄ afforded 3a in 94, 92, 87 and 84% yields. Thus, the catalyst can be used for at least four successive runs without significant loss of activity (Table 2).

The mechanism of the condensation reaction probably involves an intramolecular imine-enamine cyclization promoted by Zr(NO₃)₄ (Scheme 2). The amine group of 1 attacks the carbonyl group of the ketone (2), giving the intermediate diimine (4). A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine (5), which cyclizes to afford the seven-membered ring (3).

In conclusion, we describe a mild and efficient method for the synthesis of 1,5-benzodiazepines using Zr(NO₃)₄. The method offers easy workup, low reaction time, mild reaction conditions, good yields, easy product isolation, selectivity and reusability of the catalyst.

**Scheme 2.**
EXPERIMENTAL

All melting points were determined on a Thomas Hoover Unimelt melting point apparatus and uncorrected. IR spectra ($\nu_{\text{max}}$, cm$^{-1}$) were recorded on a Shimadzu IR 435 spectrometer. $^1$H NMR spectra were recorded on a Bruker Avance 300 spectrometer using TMS as internal standard (chemical shift in ppm).

GENERAL PROCEDURE

A mixture of o-phenylenediamine (1.0 mmol) and ketone (2.1 mmol) was stirred at ambient temperature in the presence of catalytic amount of Zr(NO$_3$)$_4$. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the reaction mixture was diluted with water and dichloromethane (1:1, v/v). The organic layer was separated, dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was recrystallized using alcohol to afford the pure product. All reactions were completed within 15 min. After work-up procedure, the catalyst remaining in the filtrate was recovered by removing the solvent through heating and then dried under vacuum for 4h.

The spectroscopic data of selected compounds is given below:

3a: IR (KBr, cm$^{-1}$): 3334, 1645, 1594; $^1$H NMR (300 MHz, DMSO-$d_6$, δ in ppm): 1.18 (s, 6H), 2.10 (s, 2H), 2.20 (s, 3H), 4.62 (bs, 1H), 6.40-6.86 (m, 4H); ESI-MS: 190.163 (M + 1).
3c: IR (KBr, cm$^{-1}$): 3352, 1648, 1597; $^1$H NMR (300 MHz, DMSO-$d_6$, δ in ppm): 1.60 (s, 3H), 2.81 (d, 1H, J = 14 Hz), 3.22 (d, 1H, J = 14 Hz), 5.62 (bs, 1H), 6.78-6.82 (m, 1H), 6.98 (d, 2H, J = 7.4 Hz), 7.04 (dd, 2H, J = 1.4 & 2.6 Hz), 7.12 (t, 2H, J = 8.0 Hz), 7.18-7.28 (m, 3H), 7.48 (d, 2H, J = 7.2 Hz), 7.58 (d, 2H, J = 7.4 Hz); ESI-MS: 314.248 (M + 1).
3g: IR (KBr, cm$^{-1}$): 3268, 1665, 1588; $^1$H NMR (300 MHz, CDCl$_3$, δ in ppm): 0.90 (d, 6H, J = 7.5), 1.10 (s, 3H), 1.40 (d, 6H, J = 7.4), 1.82 (m, 1H), 2.1 (m, 1H), 2.44-2.52 (d, 1H, J = 16 Hz), 2.57-2.64 (d, 1H, J = 16 Hz), 3.67 (bs, 1H), 6.62-7.32 (m, 4H); ESI-MS: 245.183 (M + 1).

REFERENCES AND NOTES

2 J.R. de Baun, F.M. Pallos, D.R. Baker. 5-furoyl-2,2,4-trimethyl-1,4-dihydro-1H-1,5-benzodiazepine as an antiinflammatory agent. Chemical Abstracts, 1977, 86, 5498d.
8 A.M. El-Sayed, H. Abdel-Ghany, A.M.M. El-Saghier. A novel synthesis of pyrano (2,3-C)-1,3-oxazino (2,3-b)-1,2,4-triazolo(3,4-b)-oxazole (2,3-b)- furano (2,3-e)-, and 3-substituted-(1,5) benzodiazepin-2-ones. Synth. Commun. 1999, 29, 3561–3572.