One pot Solvent-free synthesis of 1,5-benzodiazepine derivatives

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ABSTRACT

Zinc oxide has been used for the synthesis of 1,5-benzodiazepines from o-phenylenediamine and ketones. This method is simple, effective and environmentally friendly and gives better yields.

Keywords: 1,5-benzodiazepines, Zinc oxide, solvent free condition

INTRODUCTION

Benzodiazepines are biologically active compounds with anti-inflammatory [1], antianxiety, anticonvulsant, and hypnotic activity [2,3]. Due to its wide biological utility, the syntheses of these types of compounds have gained much importance in last few years. Benzodiazepines have been synthesized by the condensation of o-phenylenediamines with α,β-unsaturated Difffpounds, β-haloketones or ketones. These compounds have been used for this type of condensation which majorly includes like lead nitrate [4], L-proline [5], BF$_3$-etherate [6], polyphosphoric acid [7], NaBH$_4$ [8], SiO$_2$ [9], MgO/POCl$_3$ [10], acetic acid under microwave conditions [11] and in ionic liquids [12]. Many of these processes suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedure. Therefore, the search continues for a better catalyst for the synthesis of 1,5-benzodiazepines in terms of mild reaction conditions, operational simplicity, economic viability and selectivity.

We are herewith reporting simple, efficient and practical method for the synthesis of 1,5-benzodiazepines using ZnO catalyst.

Initially, we studied the catalytic properties of Zinc Oxide for the synthesis of 1,5-benzodiazepines (3a-3h) using o-phenylenediamine (1) and the ketone (2) substrates (Scheme –1) and varying the mol % of Zinc Oxide (Table 1). Among the results obtained, use of 20 mol % gave better yield (94%) for synthesis of 3a.

We investigated the reaction of number of ketones with o-phenylenediamine to get the corresponding 1,5-benzodiazepines (Table 2). All synthesized derivatives were characterized using mass and $^1$H NMR.

In conclusion, we have developed an efficient and simple alternative for the preparation of substituted 1,5-benzodiazepines via solvent-free condensation of o-phenylenediamine and the ketone using zinc oxide catalyst.
General procedure for preparation of 1,5-benzodiazepines:
A mixture of o-phenylenediamine (1mmol), ketone (2mmol) and Zinc oxide (0.1mmol) was stirred at 80°C untill completion of the reaction (as indicated by TLC). Then the reaction mixture was poured in water. The solid was filtered and dried. The crude compound was purified by silica gel column chromatography.

Spectral data of compound 3a: yellow solid, mp 137-139°C ¹H NMR (CDCl₃): 1.29 (S, 6H), 2.22 (S, 2H), 2.33 (S, 3H), 3.08 (br S, 1H, NH), 6.69-7.26 (M, 4H arom); MS: 189 (M-H), 190,

All the synthesized compounds were characterized using mass, and ¹H NMR. Also the melting points of synthesized compounds were compared with the corresponding reported melting points in literature [8,14,15].

Scheme 1

Table 1. Optimization of reaction conditions and the concentration of ZnO for the synthesis of 3a:

<table>
<thead>
<tr>
<th>Mol % of ZnO</th>
<th>Reaction time (min)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>120</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 2. Zinc Oxide Catalyzed synthesis of 2,3-dihydro-1H-1,5-benzodiazepines

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Time</th>
<th>M.P. ºC</th>
</tr>
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<tbody>
<tr>
<td>3a</td>
<td></td>
<td>100</td>
<td>137-139</td>
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<tr>
<td>3b</td>
<td></td>
<td>110</td>
<td>198-140</td>
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<tr>
<td>3c</td>
<td></td>
<td>100</td>
<td>144-145</td>
</tr>
</tbody>
</table>
REFERENCES

[2] (a) H. Schultz, Benzodiazepines (Springer: Heidelberg, 1982);