Synthesis of 1, 5-Benzodiazepine Derivatives Using Sulphated Tin Oxide as Solid Super Acid Catalyst

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Abstract: A competent protocol for synthesis of benzodiazepine derivatives has been developed by condensation of o-phenylenediamine and various ketones using sulphated tin oxide as heterogenous solid super acid catalyst in ethanol water (1:1-v/v) at reflux condition. The synthesized catalyst was validated by Infrared spectra, X-ray powder diffraction, Scanning electron microscopic images and EDS maps. The optimization of reaction was carried for different solvents and loading of catalyst. The Synthesized compounds were confirmed by spectral analysis. The method is advantageous in accordance with environmentally benign procedure, short reaction time, easy work up, reusable catalyst and high yields.

Index Terms: sulphated tin oxide, o-phenylenediamine, ketones, reflux

I. INTRODUCTION

Benzodiazepines are crucial nitrogen containing heterocyclic compounds that own a varied array of pharmacological and therapeutic properties. It’s substantial central nervous system (CNS) depressant characteristic make benzodiazepines highly used psychotropic [1]. These are broadly worked as antianxiety, sedative, anticonvulsant, analgesic, hypnotic agents, anti-depressive and anti-inflammatory agents [2]. The 1, 5-dibenzodiazepines have been narrated to inhibit inhibitory activities towards HIV-1 protease [3–4]. Fused ring structures like triazole, oxazino, and furanobenzodiazepines can be prepared from 1,5-benzodiazepines synths [5]. The compounds of 1, 5 benzodiazepines are moreover employed in Photography as dyes for acrylic fibers [6]. Due to their extensive applications, numerous approaches for the construction of benzodiazepines have been described by reaction between o-phenylenediamines (OPDAs) and enones, ketones, or β-halo ketones using several homogenous catalysts such as BF3-etherate [7], NaBH4 [8], polyphosphoricacid [9], solvent free under microwave irradiation [10], ZnCl2 [11], Yb(OTf)3 [12], ionic liquids [13]. Along with that various solid acid as well as solid supported catalysts have been used for the synthesis of 1,5-benzodiazepines that includes sulfated zirconia [14], amberlyst-15 [15], stannic oxide NPs [16], polymer-supported FeCl3 [17], Al2O3/P2O5 [18], Zeolite [19], H-MCM-22 [20], and Hg(OTf)2 [21]. However, all of these procedures have difficulties, which include costly reagents, extreme reaction conditions, comparatively extended reaction period, low yields, generation of unwanted products and difficulty in retrieval and reuse of the catalysts. Consequently, developing a novel approach for the scheming of 1,5-benzodiazepines in terms of being eco-friendly, simple and economically feasible is still of prime importance. To overcome all those limitations, development of green and environmentally sustainable synthetic methods is extremely required. Usually, heterogeneous catalysts offer various advantages such as modest reaction conditions, prodigious selectivity, great yields and ease of work-up processes. Recently organic transformations by using solid super acid catalyst are receiving a great importance. Among the several solid acid catalysts studied, sulphated tin oxide has fascinated much courtesy because of its low cost, super-acidity, and non-toxicity [22].

As a part of our research, here we validate the scheming of 1,5-benzodiazepines by applying sulphated tin oxide as catalyst through condensation of orthophynelene diamines with various ketones in ethanol: Water at reflux condition (Scheme 01).

II. EXPERIMENTAL

2.1 Materials and Methods

All the reagents used were brought from Sigma Aldrich, SD Fine. Solvents utilized for chromatography were distilled to make them pure. The reactions were reviewed with TLC using aluminum plates coated by silica gel. Melting points of produced derivatives were assessed on Fisher John’s apparatus. The synthesized derivatives were examined by 1H NMR spectroscopy, Infrared spectra, 13C NMR and Mass Spectrometry. IR spectra were invaded from a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. 1H NMR was documented on a Bruker Advance II 400MHz Spectrometer (SAIF,
Punjab University, Chandigarh) using tetramethysilane as standard in CDCl₃. SEM images were observed from Quanta 200 from FEI and Carl Zeiss LSM 710. EDX were procured from Oxford instrument.

2.2 Synthesis of Sulphated Tin Oxide Catalyst

Sulphated tin oxide was produced ensuing literature process [23]. 50 g of stannous chloride was dissolved in 150 ml water. The solution pH was attuned to 8 with addition of 20% ammonia drop wise with continuous stirring. The precipitate developed then appended in 200 ml cold ammonium acetate solution (1 to 5%). The solid generated was salvaged through filtration and dried at 100 °C for 24-30 h. 20 ml concentrated H2SO4 was added slowly to obtained tin oxide and allowed to stand for 1 h. The solid obtained was filtered and dried at 100 °C, then further heated at 500 °C for 4 h and potted in a closed sample bottle.

2.3 General Procedure for Synthesis of Substituted Benzodiazepine Derivatives

Sulphated tin oxide catalyst (20 mol %) was added to a mixture containing o-phenylene diamine (10 mmol) and ketones (25 mmol) in ethanol: water (1:1, 25 ml), and heated at 80 °C for proper time given in a table 3. The reaction progress was observed by using TLC, the mobile phase employed was ethyl acetate: pet ether (2:8). Succeeding the accomplishment of the reaction, ethyl acetate was added to reaction blend and catalyst was salvaged as residue through filtration, dried and reused. The organic layer was condensed under pressure and dried using sodium sulphate. The purity of product was improved via column chromatography (silica gel) employing ethyl acetate: pet ether (2:8) as eluent.

III. RESULTS AND DISCUSSION

3.1 Characterization of Synthesized Sulphated Tin Oxide

The synthesized sulphated tin oxide was inverterate by FTIR [Fig. 1]. The peaks at 941, 1035, 1155, 1190, and 1385 cm⁻¹ clearly indicates the presence of sulphated groups attached to tin. Super acidity of STO is due to the attached sulphated groups. [Fig. 2] XRD study of STO catalyst shown that, it has the formula SnO2·2H2O. The catalyst possess crystalline structure with decrease crystal size due to adsorbed sulphate groups and consequently increase in surface area. XRD patterns observed are of pure SnO2 having tetragonal structure at 2θ= 27.30, 35.35 and 52.85. Cubic morphology and Nano size of STO was illustrated by SEM analysis [Fig.3]. The EDS report authenticates the occurrence of Oxygen, tin and sulphur in estimated stoichiometric extent [Fig.4].

![Infra-Red Spectrum of Sulphated Tin Oxide (STO)](image1)

**Figure 1:** Infra-Red Spectrum of Sulphated Tin Oxide (STO)

![XRD of Sulphated Tin Oxide (STO)](image2)

**Figure 2:** XRD of Sulphated Tin Oxide (STO)
3.2 Spectral data for selected compound

[1] 2,3-Dihydro-2-methyl-2,4-diphenyl-1H-1,5-benzodiazepine,(Entry 3) Yellow solid; MP: 150–152 °C; FT-IR (KBr): (in Cm⁻¹) 3430, 3018, 1645, 1470, 1220; ¹H NMR (400 MHz, CDCl₃): δ (ppm): 1.75 (s, 3H), 3.0–3.20 (d, 1H, J = 12.8 Hz), 3.11–3.15 (d, 1H, J = 12.8 Hz) 3.50 (br s, NH), 6.80–7.35 (m, 10H), 7.55–7.65 (m, 4H); ¹³C NMR (50 MHz, CDCl₃) δ(ppm): 167.6, 147.5, 140.1, 139.5, 138.1, 129.7, 128.3, 128.0, 127.1, 125.4, 121.7, 121.4, 73.6, 43.1, 29.8.; MS: [M+Na]⁺ = 335.

[2] 2,3-Dihydro-2-methyl-2,4-bis(4-nitrophenyl)-1H-1,5-benzodiazepine,(Entry 5) Yellow solid; MP: 150–152 °C; FT-IR (KBr): (in Cm⁻¹) 3460, 3018, 1645, 1550, 1470,1350, 1220; ¹H NMR (400 MHz, CDCl₃): δ (ppm): 2.40 (s, 3H), 2.69 (s, 2H), 3.72 (br s, NH), 6.65–6.85 (m, 4H),7.02 (m, 4H), 8.10–8.45 (m, 4H); ¹³C NMR (50 MHz, CDCl₃) δ(ppm): 164.6, 148.6, 144.9, 141.3, 138.5, 136.1, 129.3, 126.3, 125.8, 123.1, 118.4, 115.7, 27.0, 17.8.; MS: [M+Na]⁺ = 425.

3.3 Optimization of reaction conditions

Owing to the pharmacological and biological prominence of benzodiazepines derivatives, we have synthesized it by condensation of o-phenylenediamine and various ketones using sulphated tin oxide as catalyst in ethanol: water (1:1-v/v) at reflux condition. In the calibration experiment, to decide the optimization conditions of the reaction we have taken OPDA and acetophenone as a characteristic reaction and vetted it for different solvents, results are outlined in Table 1. From this, it was noticed that ethanol: water (1:1-v/v) is the best solvent for the synthesis of required benzodiazepine compounds in relation with reaction yield and time (Entry 7, Table 1).
Table 1: Solvent optimization for synthesis of benzodiazepines by using sulphated tin oxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>3.8</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>4.0</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>4.2</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>Chloroform</td>
<td>3.8</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol</td>
<td>2.2</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol water (1:1-v/v)</td>
<td>2.0</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>Methanol</td>
<td>2.4</td>
<td>80</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield

The impact of catalyst quantity on time and yield for the same reaction was analyzed (Table 2). Initially, we performed the catalyst free reaction of OPDA with acetophenone at reflux, we observed no reaction for 3 hr, got only 20% yield after 5 hours at reflux condition. Subsequently we have carried out the same reaction for 5.0 wt.%, 10 wt.%, 15 wt.%, 20 wt.% and 25 wt.% of solid heterogenous sulphated tin oxide catalyst under uniform conditions and found that all the reactions progressed nicely but it was found that 25 mol % of sulphated tin oxide gives best yield in briefer reaction time. In addition to this, we also processed the same reaction applying other heterogenous catalyst providing less yields. (Entry 5, Table 2).

Table 2: Optimization of catalyst for synthesis of benzodiazepines by using sulphated tin oxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst amount in mol%</th>
<th>Time (hr)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No catalyst</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>05</td>
<td>3.4</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<td>76</td>
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<tr>
<td>3</td>
<td>15</td>
<td>2.6</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>2.3</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>2.0</td>
<td>88</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields

Owing to promising reactivity of sulphated tin oxide, it has been exercised in varied organic transformations. We have advanced effective and green approach for synthesis of biologically important benzodiazepines by employing sulphated tin oxide in ethanol: water. To study the synthetic dimensions and effectiveness of the protocol, a series of unsymmetrical and symmetrical ketones were reacted with di-amino-arenes and substituted diaminoarenes under the standard reaction conditions. The outcomes are précised in Table 3.
Table 3: Synthesis of substituted benzodiazepine derivatives by using Sulphated tin oxide as catalyst at reflux condition in ethanol: water media.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Ketone</th>
<th>Product</th>
<th>Yield%</th>
<th>Time (h)</th>
<th>M.P. °C</th>
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<tr>
<td>1</td>
<td></td>
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<td><img src="image1" alt="Product Image" /></td>
<td>90</td>
<td>2.0</td>
<td>136-138</td>
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<td>2</td>
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<td><img src="image2" alt="Product Image" /></td>
<td>88</td>
<td>2.1</td>
<td>138-140</td>
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<td>3</td>
<td></td>
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<td><img src="image3" alt="Product Image" /></td>
<td>88</td>
<td>2.0</td>
<td>150-152</td>
</tr>
<tr>
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<td>83</td>
<td>2.4</td>
<td>137-139</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td><img src="image5" alt="Product Image" /></td>
<td>80</td>
<td>2.5</td>
<td>146-148</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td><img src="image6" alt="Product Image" /></td>
<td>89</td>
<td>2.2</td>
<td>126-128</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td><img src="image7" alt="Product Image" /></td>
<td>86</td>
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<td>92-94</td>
</tr>
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<td>9</td>
<td></td>
<td></td>
<td><img src="image8" alt="Product Image" /></td>
<td>81</td>
<td>2.5</td>
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<tr>
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<td></td>
<td><img src="image9" alt="Product Image" /></td>
<td>80</td>
<td>2.6</td>
<td>158-160</td>
</tr>
</tbody>
</table>

*Yields refer to the pure isolated product

IV. CONCLUSION

A solid acid heterogenous catalyst of sulphated tin oxide was prepared and was exercised in the catalytic scheming of 1,5-benzodiazepines in ethonolic aqueous medium under reflux condition. The offered catalytic scheme revealed 80-90 % yield of 1,5-benzodiazepines at reflux condition using 25 mole% of sulphated tin oxide catalyst. The sulphated tin oxide catalyst was salvaged by a simple filtration following the completion of the reaction and reprocessed for five cycles with no substantial loss of catalytic action and selectivity. The results reveal that sulphated tin oxide is an exceptional and environmentally moderate solid acid catalyst for the synthesis of 1,5-benzodiazepines. The protocol developed was mild, clean, high yielding and environmentally affable.
ACKNOWLEDGEMENT

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