One-Pot Solvent-Free Synthesis of Polyhydroquinolines Promoted by In/SiO<sub>2</sub> Composite Catalyst

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INTRODUCTION

Hantzsch multicomponent reaction has been recognized as an important synthetic method to access the 1,4-dihydropyridines (1,4-DHPs) with high atomic economy. These compounds exhibit a wide range of biological activities, specially as calcium channel blockers and useful drugs for the treatment of heart diseases. Polyhydroquinolines (PHQs) derivatives are structurally related compounds that can be obtained via a non-symmetrical Hantzsch reaction.

The utilization of Lewis acid catalysts in these syntheses is an alternative to surpass drawbacks such as long reaction times, harsh conditions and low yields. Moreover, heterogeneous catalysts are easy handling and fast isolation from the reaction, minimizing additional work-up procedures.

In the present work we describe the preparation of a novel In/SiO<sub>2</sub> composite and its application as heterogeneous Lewis acid catalyst in a solventless multicomponent Hantzsch reaction.

RESULTS AND DISCUSSION

The Indium/Silica hybrid composite was prepared by the Sol-Gel method using InCl<sub>3</sub> as metal source (Scheme 1). The process of gelification was carried out on air at room temperature followed by thermal treatment and washes with H<sub>2</sub>O and EtOH.

![Scheme 1. Sol-Gel Synthesis of hybrid In/SiO<sub>2</sub> composite.](image)

The hybrid material was analyzed by EDS which showed 1:18 atomic ratio of In/Si (0.94 mmols of In/g of composite). The specific surface area was determined by the BET method as being 326 ± 10 m<sup>2</sup>·g<sup>-1</sup>. The range of pore diameter minor than 2 nm was determined by BJH method. Two known bioactive 1,4-DHPs, Nifedipine (1) and Nemadipine B (2) were synthesized by mixing the reagents in presence of 10 mol% of In/SiO<sub>2</sub> under neat condition, at 100°C over 30 minutes period (Scheme 2). The catalyst was isolated from the crude mixture by a simple filtration process.

![Scheme 2. Bioactive 1,4-DHPs via In/SiO<sub>2</sub> composite.](image)

We extended the same methodology to the synthesis of a series of PHQs 7a-f with different aromatic substituents (Scheme 3). The results are shown in Table 1, below.

![Scheme 3. Synthesis of Polyhydroquinolines 7a-f.](image)

### Table 1. Synthesis of Polyhydroquinolines.

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Ar</th>
<th>PHQ (7)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>7a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>7b</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>3,4-(MeO)&lt;sub&gt;2&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>7c</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>2,3,4-(MeO)&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7d</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>3-NO&lt;sub&gt;2&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>7e</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>1-Naphthyl</td>
<td>7f</td>
<td>84</td>
</tr>
</tbody>
</table>

Recycle experiments with the recovered catalyst were performed for the synthesis of 7b for additional three times affording the product in similar yields.

CONCLUSION

The synthesized new In/SiO<sub>2</sub> hybrid composite material proved to be an efficient and recyclable Lewis acid heterogeneous catalyst to the synthesis of 1,4-DHPs and PHQs through the Hantzsch multicomponent reaction in solvent-free conditions.

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REFERENCES