**L-PROLINE-CATALYZED SYNTHESIS OF FUSED DIHYDROPYRIDINES THROUGH HANTZSCH REACTION**

Farahnaz K. Behbahani[a] and Mahsa Mohammadloo[a]

**Keywords:** Synthesis; Polyhydroquinoline; L-proline; Catalyst; Four components

An efficient Hantzsch four-component condensation reaction for the synthesis of polyhydroquinolines was found to proceed in the presence of L-proline in ethanol at room temperature. The method is really simple and environmentally benign. The keys features of this protocol are the use of a bio, organic and reusable catalyst, high yields of products, using nontoxic solvent and short reaction times from the principles of green chemistry point of view.

**Introduction**

Among various biologically active heterocyclic scaffolds, Hantzsch 1,4-dihydropyridines (1,4-DHPs) are an important class of biologically active heterocycles.1,4-Dihydropyridines are analogues of NADH coenzymes and an important class of drugs.1 These compounds possess a variety of biological activities such as curing the disordered heart ratio as the chain-cutting agent of factor IV channel and having the calcium channel agonist–antagonist modulation activities.2–6

Classical method for the synthesis of 1,4-dihydropyridines is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohol.7 This method, however, involves long reaction time, harsh reaction conditions or generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs and the progress in this field is remarkable including recently the promotion of microwave,8 TMSCl,[10] ionic liquid,9 polymer,10,[11] Yb(OTf)3,12 silica sulfuric acid,13 Sc(OTf)3,14 MCM-41,15 sulfamic acid,16 hafnium(IV) bis(perfluoro-octanesulfonyl)imide,17 guanidine hydrochloride (GuHCl),18 grinding till,19 fluoro alcohols,20 cerium(IV) ammonium nitrate,21 and Cs2.5H0.5PW12O40...22 However, the use of high temperatures, expensive metal precursors and catalysts those are harmful to environment, and longer reaction times limit the use of these methods. Therefore, the search for a better method for the synthesis of polyhydroquinolines is still the need of the day.

In recent years, L-proline has gained importance as versatile catalyst for effecting various organic transformations such as the synthesis of coumarins in ionic liquid23 and density functional study of the L-proline-catalyzed á-aminoxylaution of aldehydes.24 Moreover, L-proline and L-proline derivatives were successfully used as organo catalysts in asymmetric aldol and Michael addition reactions.25

On the other hand, a part of our program aiming at developing selective and environmental friendly methodologies for the preparation of fine chemicals,[26] therefore in this paper, we wish to disclose our finding about the L-proline catalyzed four-component Hantzsch reaction of aldehydes, dimedone, ethylacetoacetate and ammonium acetate in the presence of L-proline as an inexpensive, eco-friendly and recyclable catalyst in ethanol at room temperature (Scheme 1).

**Results and discussion**

Firstly, the mixture of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate was chosen as the model reaction to detect whether the use of L-proline was efficient and investigate the optimized conditions. Thus, we selected the optimized reaction condition to exam the universality of this catalyst’s application. Various aromatic aldehydes were selected to undergo the Hantzsch reaction in the presence of catalytic amount of L-proline in ethanol at room temperature. The results of this study are summarized in Table 1. It was indicated that both electron-rich and electron-deficient aldehydes giving high yields of products with little difference.

---

**Scheme 1**

---

**Table 1**

---


916
Table 1: Synthesis of polyhydroquinolines using L-proline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time, h</th>
<th>Yield, %</th>
<th>MP., °C</th>
<th>MP., °C (Lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>O</td>
<td>3.5</td>
<td>96</td>
<td>196-198</td>
<td>202-204^27</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>Cl</td>
<td>3.0</td>
<td>90</td>
<td>210-212</td>
<td>214-216^27</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>Cl</td>
<td>2.5</td>
<td>91</td>
<td>238-241</td>
<td>244-246^27</td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td>NO2</td>
<td>3.0</td>
<td>93</td>
<td>178-180</td>
<td>178-180^27</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>OMe</td>
<td>3.5</td>
<td>90</td>
<td>190-195</td>
<td>197-199^27</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>Cl</td>
<td>2.0</td>
<td>85</td>
<td>204-206</td>
<td>208-209^27</td>
</tr>
<tr>
<td>7</td>
<td>CHO</td>
<td>Me</td>
<td>3.0</td>
<td>88</td>
<td>254-256</td>
<td>265-268^27</td>
</tr>
</tbody>
</table>

Experimental

General procedure for the synthesis of polyhydroquinoline derivatives

To a mixture of benzaldehyde (1.0 mmol), dimedone (1.5 mmol), ethyl acetoacetate (1.0 mmol), and ammonium acetate (1.0 mmol) in ethanol (4.0 ml), L-proline (10 mol%) was added at room temperature. The progress of the reaction was monitored by TLC and the spot were detected either UV light. After completion of the reaction, ethanol was removed, ethyl acetate and water was added and the product was extracted. The crude product was obtained recrystallized from ethanol and water. Next, extracted aqueous layer containing catalyst was washed with 10 ml of dichloromethane twice and was used for three times (Table 2).

Table 2: Reusability of the catalyst^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield, %^b</td>
<td>96</td>
<td>93</td>
<td>93</td>
<td>90</td>
</tr>
</tbody>
</table>

^aReaction condition: benzaldehyde (1.0 mmol), dimedone (1.5 mmol), ethylacetoacetate (1.0 mmol) and ammonium acetate (1.0 mmol) at r.t.; ^bIsolated yield.

Synthesis of fused dihydropyridines through Hantzsch reaction

Section A-Research Paper

Conclusion

The use of inexpensive L-proline in a catalytic quantity is a general practical alternative to existing procedures for multicomponent Hantzsch synthesis of polyhydroquinolines. The procedure offers several advantages including increased variations of substituent in the product with high yields, operational simplicity, minimum environmental effects and above all, the ease in purification of products simply by crystallization.

References


Synthesis of fused dihydropyridines through Hantzsch reaction


Received: 30.06.2013.
Accepted: 21.07.2013.