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Multicomponent synthesis of dihydropyridines catalyzed by L-proline

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Abstract

Multicomponent synthesis of mono and bis 4-substituted-1,4-dihydropyridines from aldehydes, dimedone and ammonium acetate in the presence of an efficient recyclable catalyst, L-proline, in high yield and short reaction time is reported.

Keywords: Multicomponent; Dihydropyridines; Dimedone; L-Proline

In recent years, an increasing interest has been focused on the synthesis of 1,4-dihydropyridine compounds owing to their significant biological activity [1]. In particular, dihydropyridine drugs such as nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension [2]. 4-Aryl-1,4-dihydropyridines have been known for their calcium channel activity and this heterocyclic ring is found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antidiabetic, antitumor and anti-inflammatory agents [3]. Moreover studies have discovered that these compounds exhibit diverse medical functions such as neuroprotectants, platelet antiaggregators and chemosensitizers [4].

1,4-DHPs are generally synthesized by Hantzsch method. This method involves one-pot condensation of aldehyde with ethylacetoacetate and ammonium acetate in refluxing alcohol [5]. Starting from Hantzsch, a number of modified methods for the synthesis of DHPs have been reported, which comprise the use of microwave [6], ionic liquid [7], at high temperature in refluxing solvent [8], TMSCl–NaI [9], metal triflates [10], I_2 [11] and CAN [12]. However, these methods suffer from several disadvantages such as longer reaction times, excess of organic solvent, lower product yield, harsh refluxing condition, use of high temperatures, expensive reagents, occurrence of several side products and difficulty in recovery and reusability of the catalyst. Thus, the development of a simple, efficient and versatile method for the preparation of dihydropyridines is an active area of research and there is a scope for further improvement towards milder reaction condition and higher product yields.

Small organic molecules like L-proline and its derivatives are readily commercially available catalysts and they have been used in various transformations with excellent yields [13,14]. L-Proline has been found to be very effective in enamine based direct catalytic asymmetric aldol [15,16], Mannich [17,18], Michael [19,20], Diels–Alder [21] and

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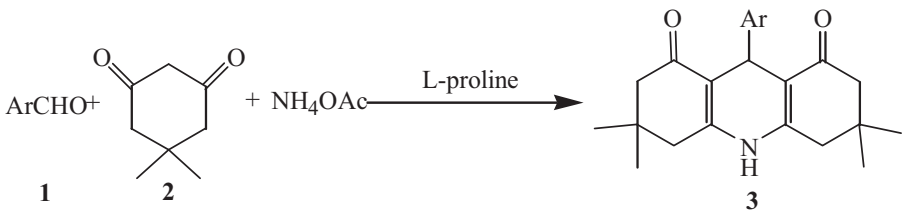

Ar: C_6H_5, 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-$CH_3OC_6H_4$, 4-HOC_6H_4

Scheme 1. Synthesis of 1,4-dihydropyridines catalyzed by L-proline.

unsymmetrical Biginelli reaction [22,23]. Therefore, we are interested in investigating the activity of L-proline in synthesis of fused dihydropyridines (Scheme 1).

Initially, the multicomponent reaction of substituted benzaldehyde, dimedone and ammonium acetate in the classical condition and in the presence of catalytic amount of L-proline in a green solvent, H_2O, was done and the results are listed in Table 1.

As expected, the reaction time and the product yield in the presence of L-proline were improved. On the other hand, both substituted benzaldehyde containing electron-releasing and electron-withdrawing substituent gave the corresponding products in high yields and short reaction time (Table 1).

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the reaction solution offer a significant advantage. Because L-proline is soluble in H_2O and the desired products are insoluble in H_2O, therefore, the products can be directly separated by filtration and the remaining reaction solution can be recycled. Studies using **1d** as model substrates showed that the recovered reaction solution could be successively recycled in subsequent reactions without any decrease of yields. It is shown that the reaction solution has been recycled in sixth rounds, but the catalytic efficiency of L-proline in reaction solution not be decreased even in the seventh round.

It is interesting, not only, we synthesized mono dihydropyridines **3a–j**, but also, we concentrated on the synthesis of bis dihydropyridines **3k–q** (Scheme 2).

All of compounds summarized were characterized by spectroscopic methods (IR, ^{1}H NMR and ^{13}C NMR) and elemental analysis.

Finally, we develop an efficient and convenient procedure for the synthesis of 1,4-dihydropyridines through three component synthesis of aldehydes, dimedone and ammonium acetate by L-proline. This procedure offers advantages such as reduced reaction time, mild reaction condition, productivity and higher yield, ease of execution and economic viability of the catalyst. This simple process combined with easy of recovery and reuse of catalyst makes this procedure economic, benign and a waste free chemical process for the synthesis of dihydropyridines.

Table 1
Synthesis of fused 1,4-dihydropyridine derivatives (**3a–j**) using L-proline.

Entry	Aldehyde	Time (min)	Yield (%)[a]
a	C_6H_4CHO	180 (360)[b]	85 (67)[b]
b	2-NO_2 C_6H_4CHO	130	93
c	3-NO_2 C_6H_4CHO	150	84
d	4-NO_2 C_6H_4CHO	130 (360)[b]	92 (65)[b]
e	2-ClC_6H_4CHO	150	88
f	4-ClC_6H_4CHO	150	82
g	3-BrC_6H_4CHO	130	90
h	4-FC_6H_4CHO	140	85
i	4-$CH_3OC_6H_4CHO$	200	78
j	4-HOC_6H_4CHO	200	80

[a] Isolated yield.
[b] Classical method without L-proline.