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Zn[(*L*)-proline], as a Recyclable and Green Catalyst for Efficient and One-pot Three-Component Synthesis of 1,4-Dihydro- pyridines Under Solvent-Free and Microwave Irradiation Conditions

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ABSTRACT

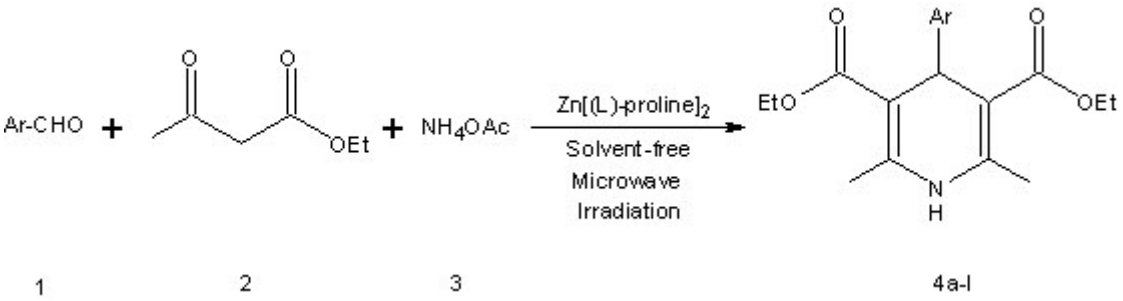
Zn[(*L*)-proline], was faund to be efficient, green, and recyclable catalyst for the synthesis of 1,4-dihydropyridines by condensation reaction of aldehydes, ethyl acetoacetate, and ammonium acetate in high to excellent yields under solvent-free and microwave irradiation conditions. The present methodology offers several advantages, such as a simple procedure with an easy work-up, high yields, and the absence of any volatile and hazardous organic solvent. Morever, the catalyst can be easily recovered and reused at least three time with only slight reduction in its catalytic activity.

Key words: 1,4-Dihydropyridines, Zn[(*L*)-proline], Solvent-Free conditions, Green and Recyclable catalyst.

INTRODUCTION

Multicomponent reaction (MCRs) have manifested as an powerful tool for the rapid introduction of molecular diversity. The design and development of MCRs for the generation of heterocycles receives growing interest[1-3]. MCRs contribute to the requirments of an environmentally friendly process by reducting the number of synthetic steps, energy consumption, and wast production. One such reaction is the synthesis of 1,4-dihydropyridines. 1,4-dihydropyridines (1,4-DHPs) are an important class of heterocycles with a wide rang of pharmacological and biological activities such as anti-hypertensive, anti-anginal[4-6],antitumor[7], anti-inflammatory activity[8-9], anti-tubercular activity[10], analgesic activity[11], anti-thrombotic[12,13]. Other activities like anti-convulsant[14], stress protective effect[15], cardio depressant activity[16]. 1,4-dihydropyridines are generally synthesized by classical Hantzsch reaction, which involves the condensation of an aldehyde, α – ketoester and ammonia or ammonium acetate in refluxing ethanol or acetic acid for a longer time[17]. There are several efficient methods developed for the synthesis of 1,4-dihydropyridines which comprise the use of

ionic liquid[18,19], high temperature in refluxing solvents[20], silica sulfuric acid[21], TMSCl-NaI[22], and metal triflates[23]. However, most of these procedures, have significant drawbacks such as high temperature, long reaction times, low yields of the products, harsh reaction conditions, and difficult work-up. Therefore, the development of simple, green, efficient, clean, high-yielding, and environmentally friendly approaches for the synthesis of these compounds is an important task for organic chemists. The development of heterogeneous catalysts for organic synthesis has become major area of research. The potential advantages of these materials over homogeneous systems could lead to novel, environmentally benign chemical procedures for academia and industry[24]. Microwave irradiation has proved to be an efficient method of heating that cause to some facilities in performing reaction and improvement of yields[25]. The use of microwave irradiation in organic synthesis has become increasingly popular with in the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development[26-28]. Recently, Darbre's group have showed that Zn-amino acids complexes such as Zn[(*L*)-proline], are efficient and enantioselective catalysts for the direct aldol reaction[29]. There are also a few reports that show Zn[(*L*)-proline], can act as an efficient recyclable and inexpensive lewis acid (LA) catalyst for the preparation of heterocyclic compounds[30-32]. As a finding of our ongoing research projects on the synthesis of heterocyclic compounds[33-35], and in continuations of our previous works on the applications of solid acid catalysts in organic reactions[36-41], herein, we want to report a new and efficient synthesis of 1,4-dihydropyridines in the presence of Zn[(*L*)-proline], as a lewis acid (LA) catalyst under solvent-free and microwave irradiation conditions (sheme1).



Scheme 1: Synthesis of 1,4-dihydropyridines

EXPERIMENTAL

Melting points were recorded on Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300-shimadzu spectrophotometer in KBr disks. The ^{1}H NMR (500 MHz) spectra were recorded on a Bruker - Ac - 500 spectrometer. All reactions were carried out in a CEM MARS 5™ microwave oven. The catalyst was synthesized according to the literture[42].

Preparation of the catalyst (Zn[(*L*)-proline],)

(*L*)-proline (20 mmol) was dissolved in absolute ethanol (50 ml) containing potassium hydroxide (20mmol) and magnetically stirred for 15 min in a round- bottomed flask at room temperature. $Zn(NO_3)_2.6H_2O$ (10 mmol) was dissolved in a small quantity of double distilled water and added in drops to the (*L*)-proline solution. The contents were vigorously stirred at room temperature for 6h by using a magnetic stirrer. The Zn[(*L*)-proline], complex was obtained as a white solid. It was collected by filtration and dried at 70°C in vacuum for 6h[42].

General procedure for the synthesis of 1,4-dihydropyridines (4a-l)

A mixture of $CuCl_2$ (0.4mmol) aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and Zn[(*L*)-proline], (0.25 mmol) was subjected to microwave irradiation at 300W for indicated time. The progress of reaction

was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, water was added and the mixture stirred for 2 min. The preeipitate was filtered off and recrystallized from ethanol to give compounds 4a-m in high yields (see table 2). The structures of the products were confirmed by ^{1}H NMR, IR spectra and comparison with authentic samples prepared by reported methods.

Recycling and reusing of the catalyst

The catalyst is soluble in water and could therefore be recycled as the filtrate. The catalyst was recovered by evaporation of the water, washed with chloroform, dried at 70°C under vacuum for 1h and reused in another reaction without appreciable reduction in the catalytic activity.

RESULTS AND DISCUSSION

Zn[(*L*)-proline], is an efficient, stable, inexpensive, recyclable, lewis acid catalyst which is not dissociated under reaction conditions[43]. This complex is soluble in water but insoluble in organic solvent, which allows simple and quntitaive recovery of the catalyst. Solvent-free heterogeneous catalysts has received much attention among the researches and has forced them to seek solvent-free heterogenous reactions. Due to the increasing demand in modern organic processes for avoiding expensive purification, we decided to investigate the efficiency of Zn[(*L*)-proline], as catalyst in the synthesis of 1,4-dihydropyridines under solvent-free and microwave irradiation conditions. In order to find an suitable conditions for the microwave-assisted Hantzsch reaction under solvent-free conditions, one-pot, three- component condensation of benzaldehyde, ethyl acetoacetate, and ammonium acetate, catalyzed with Zn[(*L*)-proline], was first investigated as a model reaction. Therefore, a mixture of benzaldehyde(1 mmol), ethyl acetoacetate (2 mmol) and ammonium acetate (1 mmol) in the presence of various amount of the Zn[(*L*)-proline], was irradiated in the microwave oven under solvent-free conditions at 300W (Table 1).

We were pleased to see that the synthesis of compound 4a was efficiently catalyzed by Zn[(*L*)-proline], in solvent- free and microwave irradiation conditions at 300W (Entries 2-7). In the absence of the catalyst, 4a was obtained in a low yield after 10 min (Entry1). The best catalytic activity of Zn[(*L*)-proline], was optimized to be 25 mol % during less than 5 min (Entry 6) and any excess of the catalyst, beyond this proportion, did not show any further increase in the conversion and yield (Entry 7). To evaluate the generality of this model reaction we then prepared a rang of 1,4-dihydropyridines under optimized reaction conditions. In all cases, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups

Table 1: Effect of Zn[(*L*)-proline], amount on the model reaction[a]

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	None	10	38
2	5	10	45
3	10	8	57
4	15	8	68
5	20	7	80
6	50	5	89
7	30	6	88

[a]2mmol ethyl acetoacetate, 0.4mmol $CuCl_2$ 1mmol benzaldehyde, and 1mmol ammonium acetate in the presence of various amount of Zn[(*L*)-proline], under solvent-free and microwave irradiation conditions at 300W. [b]Isolated yieldes.

Table 2: Synthesis of 1,4-dihydropyridines 5a-l [a]

Entry	Aromatic Aldehyde	Product[b]	Time(min)	Yield(%)[c]	m.p(°C)	
					Found	Reported
1	C_6H_5	4a	5	89	155-157	158-160[18]
2	4-ClC_6H_4	4b	4	93	145-146s	145-146[18]
3	4-$MeOC_6H_4$	4c	4	91	153-156	153-155[18]
4	3-$NO_2C_6H_4$	4d	5	87	164-165	165-167[18]
5	4-BrC_6H_4	4e	4	92	162-163	162-164[18]
6	4-$NO_2C_6H_4$	4f	4	95	126-128	128[21]
7	2-$NO_2C_6H_4$	4g	5	87	171-172	170[21]
8	4-HOC_6H_4	4h	4	90	224-226	227[21]
9	2-HOC_6H_4	4i	5	88	121-123	121[21]
10	3-ClC_6H_4	4j	4	94	139-140	141[21]
11	2-ClC_6H_4	4k	5	89	216-217	216[21]
12	3,4-$(MeO)_2C_6H_3$	4l	4	96	160-162	161[21]

[a] 2mmol ethyl acetoacetate, 0.4mmol $CuCl_2$ 1mmol NH_4OAc and 25 mol% Zn[(*L*)-proline], under solvent-free and microwave irradiation conditions at 300W. [b]All the products were characterized by comparision of their spectroscopic and physical data with authentic samples synthesized by reported procedures. [c] Isolated yields.

reacted successfully and gave the products in good yields. The type of aldehydes had no significant effect on the reaction. The results are summarized in table 2.

Reusability of the catalyst was also investigated. For this purpose, the synthesis of compound **4a** was again studied under the optimized conditions. After completion of the reaction, the catalyst was recovered according to the procedure mentioned in experimental section and reused for a similar reaction. The catalyst could be used at least three times with only slight reduction the catalytic activity (89% for 1st use, 86% for 2nd use, 85% for 3rd use).

CONCLUSIONS

In conclusion, we have successfully demonstrated the catalytic activity of Zn[(*L*)-proline], in the synthesis of 1,4-dihydropyridines. The catalyst can be reused after a simple work-up, with a gradual decline for its activity being observed. Other advantages of this protocol are high yield, short reaction times, easy work-up and omitting any volatile and hazardous organic solvents.

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