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Rapid and Cleaner Synthesis of 1,4-Dihydropyridines in Aqueous Medium

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ABSTRACT: *The present investigation deals with a novel water soluble Lewis acid complex, $Zn[(L)proline]_2$ catalyzed Hantzsch 1,4-dihydropyridine derivatives syntheses in aqueous medium assisted by microwave irradiation. The microwave promoted syntheses in aqueous medium afforded moderate to excellent yield (up to 98%) within short reaction time and allowed the reaction to take place with low microwave power (200 W). This synthetic methodology provides easier separation of products and the catalyst exhibits recycling ability without loss of its catalytic activity up to five reaction cycles.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:267–271, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20197

INTRODUCTION

The development of benign synthetic methodology for fine and specialty chemicals is of great interest because of growing environmental awareness. The basic principles of green chemistry have recognized organic synthesis in aqueous medium through replacing utilization of toxic organic solvents [1]. The use of water as a solvent has been accepted for a wide range of organic transformations including stereo selective Diels–Alder reactions [2], Claisen rearrangements [3], aldol reactions [4], allylation reactions [5], oxidations including asymmetric epoxidation [6], and hydrogenation of alkenes [7].

Dihydropyridine (DHP) derivatives are important class of organic compounds in view of its vast application in pharmaceuticals. These derivatives are widely known as calcium channel blockers and emerge as one of the most substantial classes of drugs for treatment of cardiovascular diseases including hypertension [8]. 1,4-DHP heterocyclic ring is an essential nucleus in various bioactive compounds such as vasodilator, bronchodilator, geroprotective, and hepatoprotective [9]. Conventionally, 1,4-DHPs were prepared by one pot three-component condensation of an aryl or alkyl aldehyde, a β-dicarbonyl compound and ammonia in the presence of a mineral acid catalyst under reflux condition. Although numerous methods with improved conditions have been reported, many of them are suffering from serious drawbacks such as low catalyst life cycle, occurrence of side reactions, unsatisfactory yield, high temperatures, and longer reaction times [10–29]. Hence, the development of an efficient and versatile method for the preparation of Hantzsch 1,4-DHPs is an important approach, and essential to pharmaceutical industries for scale-up process [30,31]. Microwave-assisted organic synthesis in aqueous medium enhances reaction rate and yield due to high absorbance of microwave power by polar medium and also provides easier separation of products from water-soluble catalysts in low microwave power compared to solid phase reactions

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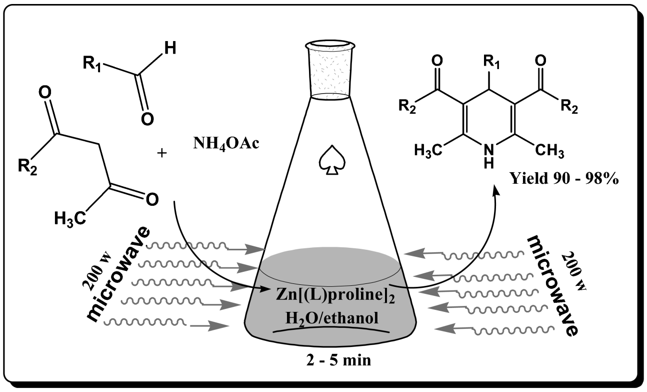

SCHEME 1 Synthesis of 1,4-dihydropyridine.

[32]. We report herein the synthesis of Hantzsch 1,4-DHP derivatives catalyzed by Zn[(L)proline]$_2$ complex in aqueous medium assisted with microwave irradiation (Scheme 1).

RESULTS AND DISCUSSION

All the materials used in this study were extrapure quality and purchased from E-Merck (Germany). The melting point of products was determined using Raga Hot stage apparatus and are uncorrected. The FTIR spectra of products were recorded on a Nicolet 360 FTIR using KBr pellet technique. The elemental analyses were carried out in a Heraeus CHNO-rapid analyzer. The mass spectra were recorded on a Finnigan Mat 8230 MS spectrometer.

Synthesis and Characterization of Zn[(L)proline]$_2$ Complex

Zn[(L)proline]$_2$ complex has been successfully synthesized and characterized by FTIR, ^{1}H NMR, MS, and elemental analysis. The results are in accordance with our earlier report [33].

Catalytic Studies [34]

The effect of substituents on the reactivity of Zn[(L)proline]$_2$ catalyst is presented in Table 1. The results reveal that electronic effect of substituents has no significant effect on the catalytic activity. The microwave-irradiated reactions rendered excellent yield in aqueous medium. The presence of polar medium such as water is capable of absorbing more microwave energy within less energy input ($<$200 W) than solid-phase solvent-free condition. All the reactions were carried out in 200 W microwave power range with a pulse of 10 s. The progress of reaction was monitored by TLC analysis. After completion of the reaction, the reaction mixture was allowed to stand overnight at 10–15°C and the product separated as fine crystals. The product was filtered and dried in vacuum for 6 h at 75°C. This methodology provides easier separation of products from the

TABLE 1 Synthesis of Hantzsch 1,4-Dihydropyridine Derivatives

Entry	*R*$_1$	*R*$_2$	*Time*^{a} *(min)*	*Yield*^{b,c} *(%)*	*Reference*
1	4-NO_2—C_6H_4	OC_2H_5	2	93	25
2	3-NO_2—C_6H_4	OC_2H_5	3	95	20
3	4-CH_3O—C_6H_4	OC_2H_5	2	98	20
4	4-HO—3-CH_3O—C_6H_3	OC_2H_5	3	95	20
5	3,4-$(CH_3O)_2$—C_6H_3	OC_2H_5	2	98	18
6	2-Furyl	OC_2H_5	3	92	19
7	3-Indolyl	OC_2H_5	4	90	25
8	4-NO_2—C_6H_4	CH_3	2.5	90	25
9	3-NO_2—C_6H_4	CH_3	3	95	20
10	4-CH_3O—C_6H_4	CH_3	2	98	20
11	4-HO—3-CH_3O—C_6H_3	CH_3	2.5	90	20
12	3,4-$(CH_3O)_2$—C_6H_3	CH_3	4	95	18
13	2-Furyl	CH_3	3.5	94	19
14	3-Indolyl	CH_3	5	92	25
15	3-NO_2—C_6H_4	OCH_3	3	95	20
16	4-CH_3O—C_6H_4	OCH_3	2	98	20
17	4-NO_2—C_6H_4	OCH_3	2	93	25
18	4-HO—3-CH_3O—C_6H_3	OCH_3	2.5	95	20
19	3,4-$(CH_3O)_2$—C_6H_3	OCH_3	3	96	18
20	2-Furyl	OCH_3	4	93	19
21	3-Indolyl	OCH_3	5	90	25

[a] Reaction time monitored by TLC analysis.
[b] Isolated yield after column chromatography.
[c] The products were confirmed by FTIR, MS, and elemental analysis.

TABLE 2 Catalyst Recycling Studies[a]

	Microwave Irradiation	
Catalyst Recycle	*Time[b] (min)*	*Yield[c] (%)*
I	3	90
II	3	85
III	3	80
IV	3	80
V	3	80
VI	3	68

[a] Model reaction: 5 mmol of 2-furfuraldehyde, 11 mmol of acetylacetone and 10 mmol of ammonium acetate in presence of 0.2 mmol of catalyst.
[b] Reaction progress monitored by TLC analysis.
[c] Isolated yield.

water-soluble catalyst with acceptable purity. Mixture of water and ethanol (65:35) has been used in all the reactions in order to achieve homogeneity of water and insoluble organic compounds [1].

Catalyst Recycling Studies

The results of catalyst recycling studies under the same reaction conditions are given in Table 2. The reaction of 2-furfuraldehyde and acetylacetone in presence of 0.2 mmol of catalyst in water–ethanol mixture (65:35) was taken as model reaction for recycling studies. The reaction mixture was irradiated in a microwave oven with 200 W input power [35]. The results reveal that the catalyst exhibits good catalytic activity up to five cycles. The reduction of yield in the sixth cycle is due to decomposition of metal complex upon microwave irradiation. The decomposition of catalyst was confirmed by atomic adsorption spectroscopy.

Effect of Water–Organic Solvents

The reaction of aromatic aldehyde and ethyl acetoacetate in presence of 0.2 mmol of catalyst was taken as a model reaction for all catalytic studies. The values in Table 3 show the influence of water with various organic solvents on reaction time and yield. The results reveal that water with ethanol and methanol show higher efficiency than other solvents such as tetrahydrofuran, 1,4-dioxan, and acetonitrile. The results confirm enhancement of absorption of MW power even in low input by polar medium. The present methodology afforded 1,4-DHPs in excellent yield in comparison to solid-phase microwave irradiated reactions, and also increases the solubility of organic components in aqueous medium. Table 4 shows the effect of water to ethanol ratio. Low water–ethanol ratio like 80:20 causes insoluble nature of organic components, whereas high ethanol–water ratio and in pure ethanol takes longer time for precipitation of products and also utilize more amount of organic solvents. Water to ethanol ratio of 65:35 is the optimized solvent medium to obtain maximum yield of the expected product within a short reaction time and also utilizes low amount of organic solvents.

TABLE 3 Effect of Water and Organic Solvent

S. No.	*Solvents[a]*	*Time[b] (min)*	*Yield[c] (%)*
1	Methanol	4	92
2	Ethanol	3	98
3	Acetonitrile	5	90
4	Tetrahydrofuran	5	85
5	1,4-Dioxan	4.5	85

[a] 50:50 Water–organic solvent ratio. Reactions carried out with 200 W MW power.
[b] Reaction time monitored by TLC analysis.
[c] Isolated yield.

TABLE 4 Effect of Water and Ethanol Ratio

S. No.	*Ratio[a]*	*Time[b] (min)*	*Yield[c] (%)*
1	20 (ethanol):80 (water)	5	85
2	35:65	4	95
3	50:50	4	96
4	65:35	4	96
5	80:20	3.5	95
6	Ethanol (100%)	3	93

[a] Reactions carried out with 200 W MW power.
[b] Reaction time monitored by TLC analysis.
[c] Isolated yield.

Effect of Microwave Power

Figure 1 illustrates the effect of microwave power on reaction time and yield. The results reveal that even with low microwave power (200 and 350 W),

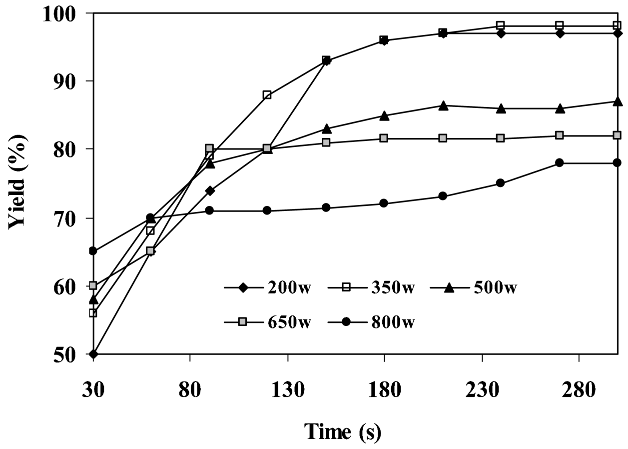

FIGURE 1 Effect of microwave power.

maximum yield of the expected product could be obtained within short reaction time. Medium and high microwave power gave low yield, which may be due to rapid heating of reaction medium that cause evaporation of solvent medium and lead to precipitation of unreacted compounds. The results have proved that the present investigation is a new green protocol for the preparation of 1,4-DHPs by utilizing low microwave power.

CONCLUSIONS

Zn[(L)proline]$_2$ complex is proved to be an efficient catalyst for the preparation of 1,4-DHP derivatives using Hantzsch synthetic route in aqueous medium. This catalyst can be used for the synthesis of 1,4-DHPs using a wide range of aldehydes and β-dicarbonyl compounds. The microwave irradiated reactions in aqueous medium in the presence of catalyst afforded moderate to excellent yield (98%) within short reaction periods (<5 min). The Zn[(L)proline]$_2$ exhibits greater catalytic activity even with low MW power (≈200 W) and it can be reusable up to five cycles without appreciable loss of its catalytic activity. The present investigation provides 1,4-DHPs in high yield within shorter reaction time and easier separation of products with acceptable purity. Hence this methodology is a green protocol with respect to reduce the use of organic solvents and consuming less microwave power.

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[34] *Microwave Promoted Synthesis of 1,4-Dihydropyridines in Aqueous Medium*. A mixture of 5 mmol of veratraldehyde, 11 mmol of ethyl acetoacetate, and 10 mmol of ammonium acetate was thoroughly mixed with 0.2 mmol of Zn[(L)proline]$_2$ complex in 20 mL of double distilled water and 5 mL of absolute ethanol (Scheme 1). The reaction mixture was taken in an open Erlenmeyer flask and irradiated using a household microwave oven (model: IFB 17PM 1S) with a power range of 200 W (≈75°C) and a pulse of 10 s. The progress of the reaction was monitored by TLC (silica gel precoated plate, eluent:*n*-hexane to ethyl acetate ratio = 80:20) up to disappearance of reactants. After completion of the reaction, the mixture was kept at 10–15°C for 24 h. The product slowly crystallized from aqueous phase and it was separated by simple filtration. The purification step was not required as the product was in pure form. The above-mentioned procedure was followed for all other reactions. The reaction time and yield for all the reactions are given in Table 1.

[35] *Catalyst Recycling Studies*. 2-Furfuraldehyde (5 mmol), acetylacetone (11 mmol), and ammonium acetate (10 mmol) were thoroughly mixed

with catalyst (0.2 mmol). The progress of reaction was monitored by TLC analysis. After completion of reaction, the reaction mixture was diluted with dichloromethane and recovered the catalyst by simple separation from aqueous phase and organic phase. The catalyst present in aqueous medium was used for the subsequent cycle. The same procedure was adopted for all recycling studies. The reaction time and yield for different cycles are presented in Table 2.