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L-Proline as an Efficient Organocatalyst for Synthesis of Pyridine Derivatives

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ABSTRACT

A simple protocol for the efficient preparation of pyridine derivatives has been achieved by refluxing 1, 3-dicarbonyl compound and substituted acetamide in presence of L-proline organo-catalyst. Particularly valuable features of this method include satisfactory yields of products and short reaction time.

Keyword: 1, 3-Dicarbonyl compound, cynoactamide, chloroacetamide, *L*-proline, pyridine.

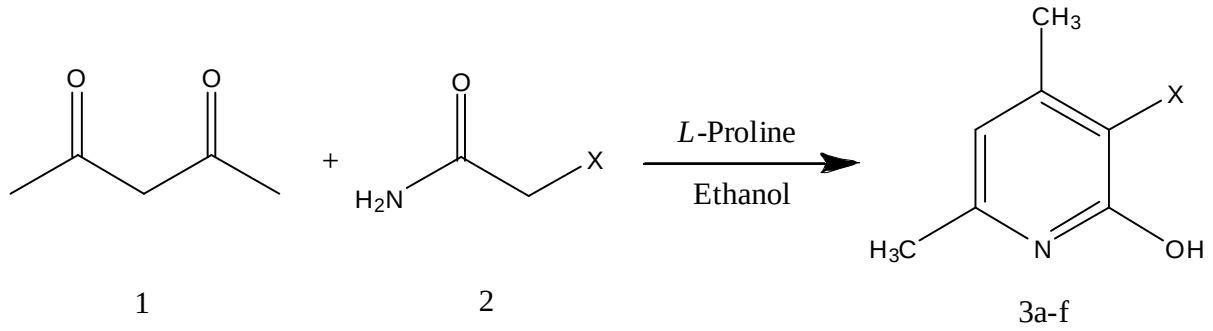
INTRODUCTION

Functionalized nitrogen-heterocycles play a predominant role in medicinal chemistry. The pyridine nucleus is prevalent in numerous natural products and is extremely important in chemistry of biological systems. It plays a key role catalyzing both biological and chemical systems. Many pyridine derivatives are of commercial interest find application in areas where bioactivity is important, as in medicinal drugs [1]. Some of them have been used as herbicides, fungicides, pesticides, medicines, and dyes [2-3].

Some of pyridine derivatives serve as high-potency agonists for the human adenosine receptors and act as potential therapeutic agents for the treatment of Parkinson's disease and Prion disease [4]. 2-Amino-3-cyanopyridines have been identified as IKK-β inhibitors [5]. Cyano-pyridines have played an important role in the heterocyclic chemistry [6]. 2-Pyridine radicals are incorporated into the structures of cardiotonic agents such as milrinone [7] and HIV-1 specific transcriptase inhibitors [8]. Besides, pyridine derivatives are important and useful intermediates in preparing variety of heterocyclic compounds. Therefore, the synthesis of pyridine derivatives continues to attract much interest in organic chemistry.

Thus, a number of methods have been developed to prepare these compounds using a variety of protocols. Extensive studies have been carried out on the synthesis of these valuable compounds. The Vilsmeier–Hack reaction [9] of conjugated oximes is a multi-step process and involves a Beckmann rearrangement of the starting oximes. Three-component condensations of aldehyde, malononitrile and thiol using various bases Et_3N, DABCO [10] and basic ionic liquid [bmIm]OH [11], and microwave irradiation of aldehyde [12], β-ketoester and ammonium nitrate using

bentonite clay [13]. In a very recent report, an enamino ester and alkynone were reacted via Michael addition–cyclodehydration, catalyzed by acetic acid/Lewis acid [14]. All these catalysts have their own merits and demerits. Few notable drawbacks of these routes are harsh reaction conditions, expensive of catalytic systems, commercial unavailability, longer reaction times and use of toxic solvents. Above discussed drawbacks of the reported methods prompted us to undertake the work for the development of highly efficient route for this cyclo-condensation. Above discussed drawbacks of the reported methods prompted us to undertake the work for the development of new route for synthesis of pyridine derivative.



1 2 3a-f

Scheme 1

MATERIALS AND METHODS

Melting points were determined in open capillary tube and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on Varian FTIR 640 spectrometer. ^{1}H NMR spectra were recorded on Burker 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard.

General procedure for synthesis of pyridine derivatives:

To the mixture of 1, 3-dicarbonyl compound (10 mmole) and substituted acetamide (12 mmole) in ethanol 20 mL, catalytic amount of *L*-proline (15 mol%) was added. The reaction mixture was stirred at 70 ºC for appropriate time (Table 3). Reaction was monitored by thin layer chromatography. After completion of reaction as indicated by TLC, reaction mixture was cooled to room temperature. Obtained precipitate was filtered and washed with water. Product was dried and crystallized with ethanol to give pure product. The compounds were identified from their spectral data.

Spectral data of representative compounds:

2-Hydroxy-4,6-dimethylpyridine-3-carbonitrile: **IR** (KBr): 3454, 3090, 2220, 1667, 698 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 6.8 (s, 1H), 5.2 (s, 1H), 2.67 (s, 3H), 2.35 (s, 3H),; **^{13}C-NMR** (300 MHz, $CDCl_3$): δ 167.12, 157.26, 155.45, 120.11, 108.17, 101.63, 30.14, 20.14; Anal. Calcd for $C_{13}H_9ClN_2$: C, 64.85; H, 5.44; N, 18.91; O, 10.80 Found: C, 64.81; H, 5.48; N, 18.88, O, 10.77.

3-Chloro-4,6-dimethylpyridin-2-ol: **IR** (KBr): 3487, 3100, 1667, 755, 652 cm^{-1}; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 7.12 (s, 1H), 4.96 (s, 1H), 2.8.2 (s, 3H), 2.20 (s, 3H),; **^{13}C-NMR** (300 MHz, $CDCl_3$): δ 161.26, 147.84, 140.42, 134.75, 110.24, 27.42, 17.19; Anal. Calcd for $C_{13}H_9ClN_2$: C, 53.35; H, 5.12; Cl, 22.50; N, 8.89; O, 10.15; Found: C, 53.31; H, 5.09; N, 8.83; O, 10.19.

RESULTS AND DISCUSSION

The present investigation deals with the synthesis of pyridine derivatives. The synthesis of pyridine derivatives was achieved by refluxing of 1, 3-dicarbonyl compound and cynoacetamide in presence of organocatalyst *L*-proline which is a Lewis acid. Results obtained are summarized in (Table 3).

To find the optimum conditions for reaction, the reaction was carried out at different temperature. At room temperature reaction did not proceed. As we increased temperature to 50 ºC there was formation of product but product obtained was in trace amount. There was increase in yield with increasing temperature but after 70º C percent yield dropped drastically (Table 1).

Table 1: Effect Of Temperature On Synthesis Of Pyridine Derivatives

Entry	Temperature (ºC)	Time (hrs)	Yield (%)[a]
1	RT	48	-
2	50	16	42
3	60	10	68
4	**70**	**6**	**84**
5	80	12	52
6	85	14	39

[a]*Isolated yield.*

The reaction was performed at this optimum temperature with other Lewis acid $ZnCl_2$, $AlCl_3$, Phenylboronic acid, molecular iodine and in absence of catalyst. With $ZnCl_2$ and $AlCl_3$ catalyst product obtained was good but unsatisfactory when compared to organocatalyst *L*-proline. Iodine and phenylboronic acid were no effective catalyst as yield obtained was very less, even less than in absence of catalyst (Table 2).

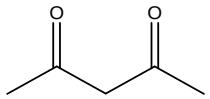
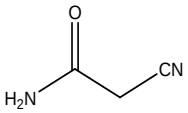
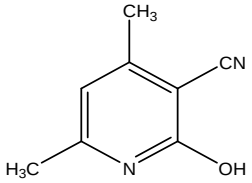
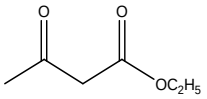
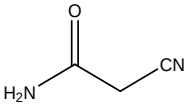
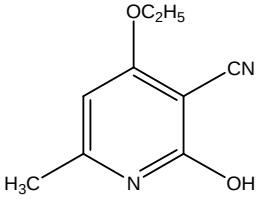
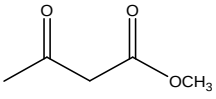
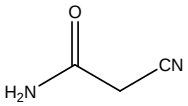
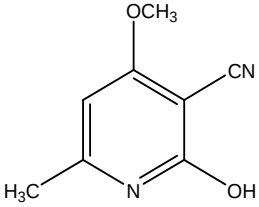
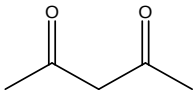
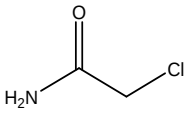
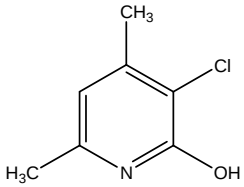
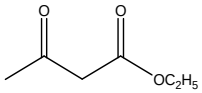
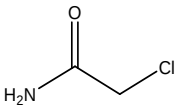
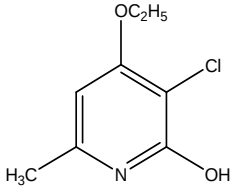
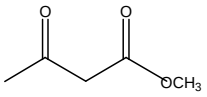
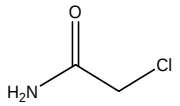
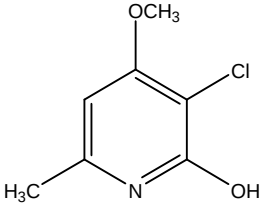
Table 2: Effect of catalyst on synthesis of pyridine derivatives

Entry	Catalyst (15 mole %)	Time (hrs)	Yield (%)[a]
1	No catalyst	48	25
2	$ZnCl_2$	14	56
3	$AlCl_3$	16	52
4	I_2	20	15
5	Phenylboronic acid	22	20
6	***L*-Proline**	**6**	**84**

[a]*Isolated yield.*

Result shows that *L*-proline is very effective catalyst for synthesis of pyridine derivatives. *L*-proline forms an imine with acetyl acetone, followed by cyclisation with cynoacetamide to form pyridine molecule. The method offers several advantages such as inexpensive catalyst, short reaction time and high yields.

Table 3: Synthesis of pyridine derivatives

Entry	Reactant **1**	Reactant **2**	Product **3**	Time (hrs)	M. P. (^oC)	Yield (%)
1				6.00	280	84
2				6.30	275	80
3				6.30	270	78
4				6.00	240	82
5				6.00	233	79
6				6.30	250	85

[a]*Isolated yield*

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