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L-proline-catalysed synthesis of functionalized unsymmetrical dihydro-1H-indeno[1,2-b]pyridines

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Abstract. Aromatic aldehydes have been employed in a one-pot four-component reaction with ethyl acetoacetate, 1,3-indandione and ammonium acetate in the presence of L-proline in water and under reflux condition to afford the corresponding dihydro-1H-indeno[1,2-b]pyridines in very good yields.

Keywords. Pyridines; biocatalyst; L-proline; synthesis; unsymmetrical.

1. Introduction

Multi-component reactions (MCRs) are a promising and vital field of chemistry both to academia and industry as they are rapid, efficient, time-saving and intrinsically atom-economical; and the synthesis of complicated molecules occurs without the isolation of any intermediate. It requires minimum effort, which minimizes the environmental load and is acceptable from a 'green chemistry' point of view. MCRs used for the synthesis of functionalized unsymmetrical dihydro-1H-indeno[1,2-b]pyridines have gained considerable attention in organic synthesis since dihydropyridines have a variety of biological activities and produce drugs such as nifedipine, nicardipine and amlodipine which are effective cardiovascular agents in the treatment of hypertension.[1] In particular, indenopyridines are one of the highly important medicinal scaffolds, which were developed initially as antihistamines,[2] are useful inhibitors of spermatogenesis in animals[3] and showed fungicidal activity.[4] Compounds with this motif show a wide range of pharmacological activities. Hydrogenated indenopyridines have valuable therapeutic uses.[5] They also have potential antidepressant activity.[6]

A proper synthesis of indeno[1,2-b]pyridines in the presence of acid or base catalysts, three-component at 70°C and four-component reaction under microwave irradiation, three-component reaction in the presence of sodium hydroxide under solvent-free condition and a green method for the synthesis of indeno[1,2-c]pyridines in ionic liquid catalysed by malononitrile, has been reported.[7] However, the use of high temperatures, expensive catalysts and longer reaction times limits the use of these methods. Therefore, the study for a better method for the synthesis of dihydroindenopyridines is of prime importance. Recently, L-proline has gained importance as a versatile catalyst for effecting various organic transformations such as the synthesis of coumarins in ionic liquid[8] and density functional study of the L-proline-catalysed α-aminoxylation of aldehydes.[9] In recent years, L-proline and L-proline derivatives were successfully used as organocatalysts in asymmetric Aldol and Michael addition reactions.[10] To the best of our knowledge, there was no attempt to use L-proline as a catalyst for the synthesis of dihydro-1H-indeno[1,2-b]pyridines. We, therefore, present an efficient and practical synthesis of dihydro-1H-indeno[1,2-b]pyridines from the corresponding aldehydes, ethyl acetoacetate, 1,3-indandione and ammonium acetate in water using catalytic amount of L-proline (scheme 1).

2. Experimental

2.1 *General procedure for synthesis of **4a***

In a typical reaction procedure, 1,3-indandione (1.0 mmol, 0.149 g), benzaldehyde (1.0 mmol, 0.107 g), L-proline (10 mol%, 0.0116 g), ethyl acetoacetate (1.0 mmol, 0.132 g) and ammonium acetate (2.5 mmol, 0.312 g) were thoroughly mixed in water under reflux condition till the completion of reaction (monitored by TLC; Ethyl acetate: n-hexane 1: 3). The resultant solid material was washed thoroughly with water to remove any unreacted ammonium acetate and was air-dried overnight, followed by crystallization using ethyl acetate and

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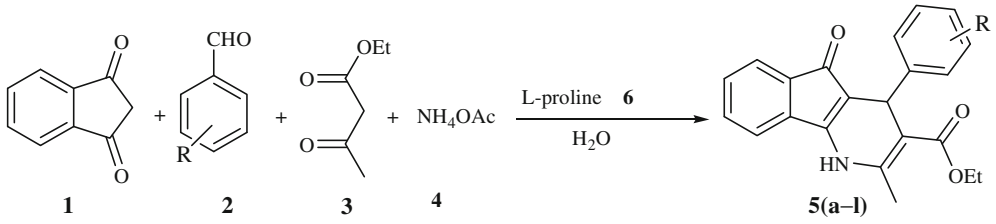


Scheme 1. Synthesis of dihydro-1H-indeno[1,2-b]pyridines using L-proline.

Table 1. Reusability of catalyst in synthesis of **4a**.

Runs	1st	2nd	3rd	4th
Yield%[a]	95	88	85	85

[a]Reaction condition: 1,3-indandione (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol), ethyl acetoacetate (1.0 mmol), L-proline (10 mol%) and water (5.0 mml) under reflux condition

Table 2. Synthesis of **4a** in the presence of L-proline.

Entry	Catalyst (mol %)	Time (h)	Yield (%)
1[a]	Free	4.00	0
2[a]	1	3:10	63
3[a]	2	2:35	71
4[a]	5	1:40	83
5[a]	10	1:00	95
6[b]	10	4.00	Trace
7[c]	10	4.00	20

Reaction condition: 1,3-indandione (1 mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol), L-proline and:
[a]in water (5 mml) under reflux condition
[b]solvent-free at room temperature
[c]in water (5.0 ml) at room temperature

n-hexane. The pure product was obtained as a yellow solid with 95% yield (0.327 g). IR (KBr, cm^{-1}) 3268, 2978, 1706, 1634, 1585, 1351. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.69–6.80 (m, 9H, Ar), 7.69 (s, 1H, NH), 5.00(s, 1H, CH), 4.03 (q, 2H, $J = 7.1$ Hz, CH_2), 2.48 (s, 1H, CH_3), 1.29 (t, $J = 7.06$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 300 MHz, δ ppm):192.5, 167.3, 150.7, 145.8, 142.2, 136.4, 134.5, 129.8, 128.6, 126.9, 125.8, 102.3, 61.8, 42.3. MS (m/e): 345[M^+].

2.2 *Reusability of catalyst*

After separation of the crude product, aqueous phase including catalyst was reused for further reaction. After three runs, catalytic activity of the catalyst was almost the same as that of freshly used catalyst (table 1).

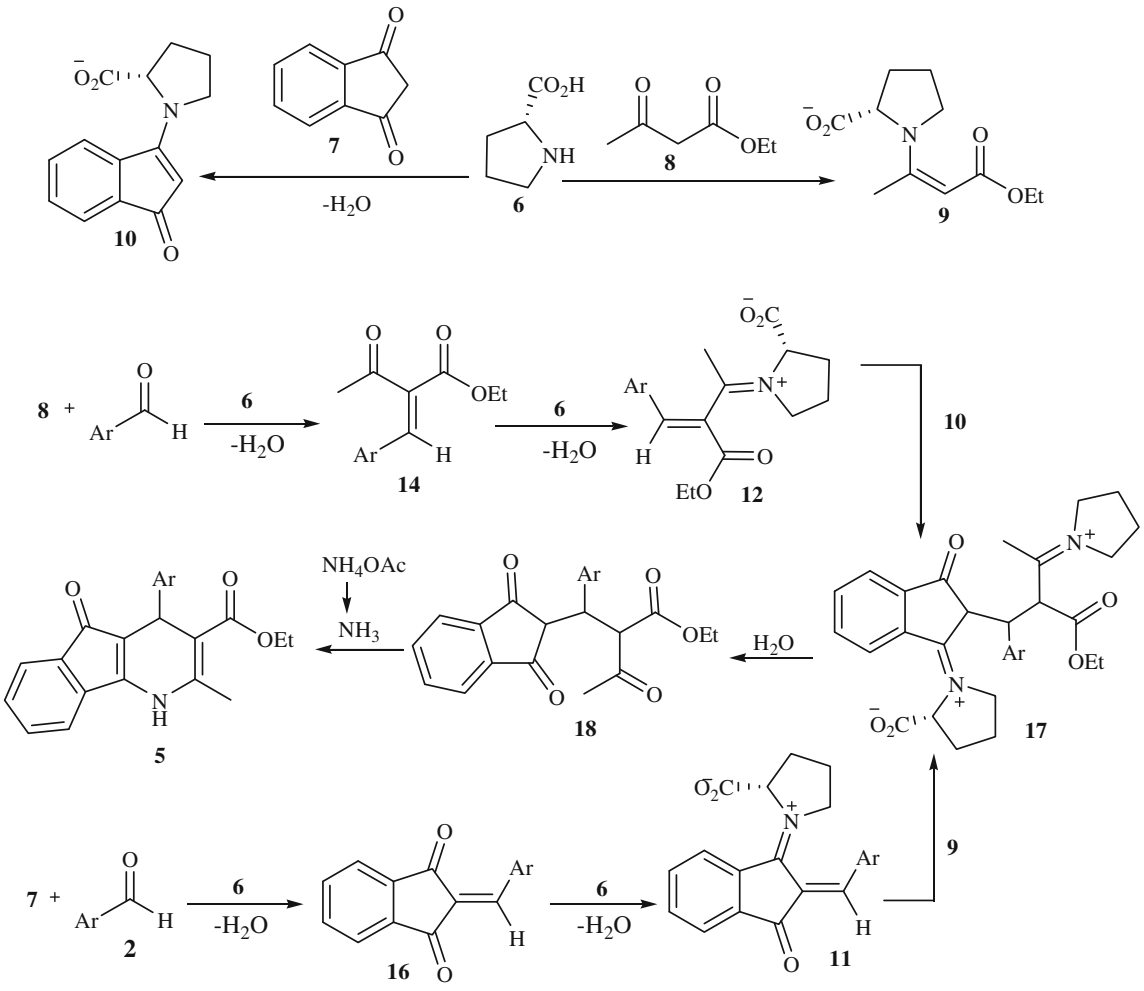
3. Results and discussion

Firstly, efforts were mainly focused on the evaluation of varying parameters such as solvent, and catalytic amount of the catalyst on rate and the yields of obtained 2-methyl-4-(phenyl)-5-oxo-4,5-dihydro-1H-indeno[1,2-b]dihydropyridine-3-carboxylic acid ethyl

Table 3. L-Proline-catalysed synthesis of dihydro-1H [1, 2-b] pyridines.

					M.p. (°C)	
Entry	R	Product	Time (h)	Yield (%)	Found	Reported [ref.]
1	H	**6a**	1:0	95	220	219–222 [7]
2	4-NO_2	**6b**	1:5	90	225	231–232 [13]
3	2-NO_2	**6c**	1:8	85	238	240–242 [12]
4	4-Cl	**6d**	1:2	87	211	210–213 [13]
5	2,4-DiCl	**6e**	1:3	80	180	181–185 [16]
6	4-Br	**6f**	1:25	91	240	243–246 [13]
7	2-OMe	**6g**	3:25	68	200	199–203 [15]
8	3-OMe	**6h**	3:2	78	200	195–197 [14]
9	3,4-DiMeO	**6i**	3:2	73	110	120–123 [16]
10	3-OH	**6j**	2:3	85	230	232–235 [15]
11	2-OH	**6k**	3:0	80	240	231–238 [16]
12	4-Me	**6l**	6:0	71	165	161–163 [14]

[a]Reaction condition: 1,3-indanedione (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol), ethyl acetoacetate (1.0 mmol), L-proline (10 mol%) and water (5.0 mml) under reflux condition



Scheme 2. Proposed mechanism for the synthesis of indeno[1,2-b]pyridines.

ester **4a** by reacting benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), 1,3-indandione (1.0 mmol), ammonium acetate (2.5 mmol) and L-proline (10 mol%). No product was obtained in water (5.0 ml), and solvent-free condition at room temperature. The results of these reactions in water (5.0 ml) under reflux condition is the best reaction condition (reaction time: 1 h, yield: 95%). Hence, water which is benign and a green solvent has been used in this study.

Also, it is suggested that L-proline certainly catalysed synthesis of **4a** (table 2). It is noteworthy to observe that the corresponding product was obtained in excellent yield, no intermediate was obtained.

To evaluate the scope of reaction, various aromatic aldehydes bearing electron-withdrawing and electron-donating groups and esters can be utilized in this protocol[11] (table 3). It has been observed that better yields are obtained from substrates possessing electron-withdrawing groups. In the case of ortho-substituted aldehydes, the yields are slightly lower (probably due to stearic hindrance) than para-substituted ones.

A probable mechanism for the synthesis may be postulated as shown in scheme 2. In the proposed mechanism, formation of alkylidene compounds **14** and **16** can arise from L-proline-catalysed aldol reaction followed by dehydration.[11] Again compounds **14** and **16** can form iminium ions **11** and **12** with L-proline to activate towards conjugate addition reaction of enamines **9** and **10** for the formation of intermediate **17**. Hydration of intermediate **17** to 1,5-dicarbonyl intermediate **18** occurs, which undergoes intramolecular cyclization with participation of the amino function to form dihydroindenopyridine **5**.

4. Conclusion

In conclusion, the present study describes a simple, efficient and novel green protocol for the preparation of dihydro-1H-indeno[1,2-b]pyridines using L-proline as a reusable catalyst. The salient features of this

procedure include: easy procedure; high product yield, avoidance of column chromatography, commercially viable, safe handling, no toxicity and reusability of the catalyst.

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