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L-Proline-catalyzed one-pot expeditious synthesis of highly substituted pyridines at room temperature

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ABSTRACT

Only 15 mol% of L-proline in ethanol proved to be a very efficient catalyst for the one-pot synthesis of a wide variety of highly substituted pyridines at room temperature. The methodology is mild, efficient, high yielding, and the products can be directly recrystallized from hot ethanol.

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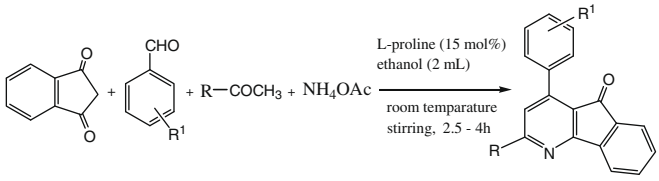
1. Introduction

Over the past few decades, multicomponent reactions (MCRs) have gained considerable interest in both academia and industry owing to exceptional synthetic efficiency, intrinsic atom-economy, high reactivity, and procedural simplicity.[1] MCRs have great contribution toward convergent synthesis of complex and important biologically active molecules from readily available starting materials, and have emerged as powerful tools for drug discovery.[2] The application of such MCRs toward the synthesis of polyarylpyridines constitutes an important and attractive subject in organic synthesis since these products find wide applications in preparative organic chemistry,[3] as therapeutic agents[4] in addition to substrates for the preparation of supramolecules.[5] These compounds have also instigated a rapidly growing interest in recent years as they are endowed with wide range of pharmaceutical activities such as antimalarial, vasodilator, anesthetic, anticonvulsant, antiepileptic, and agrochemicals such as fungicidal, pesticidal, and herbicidal.[6]

Since Kröhnke's original report on the synthesis of 2,4,6-triaryl pyridines,[7] there has been a plethora of research targeting the synthesis of both 2,4,6-triaryl and other polyaryl pyridine compounds.[8–17] Most of these synthetic methods suffer from one or more serious drawbacks such as laborious and complex work-up and purification, strong basic and acidic conditions, multistep reactions and occurence of side reactions, low yields, and the use of expensive reagents. In addition, most of the earlier-reported meth-



Scheme 1. Synthesis of highly substituted pyridines.

Table 1
Multicomponent reaction of 4-bromobenzaldehyde, indan-1,3-dione, 2-acetylthiophene, and ammonium acetate in the presence of different solvents and different catalyst (L-proline) concentrations

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) (isolated)
1	—	EtOH	48	6–7
2	—	MeOH	48	6–7
3	—	$CHCl_3$	48	Trace
4	—	CH_3CN	48	Trace
5	—	$C_6H_5CH_3$	48	Trace
6	—	CH_2Cl_2	48	Trace
7	—	H_2O	48	—
8	5	EtOH	8	50
9	10	EtOH	5	70
10	15	EtOH	3	90
11	20	EtOH	5	85
12	15	MeOH	12	75
13	15	$CHCl_3$	12	50
14	15	CH_2Cl_2	12	50
15	15	CH_3CN	12	65
16	15	$C_6H_5CH_3$	12	35
17	15	H_2O	24	—

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Table 2
Synthesis of highly substituted pyridines at room temperature using L-proline (15 mol%) as an organocatalyst

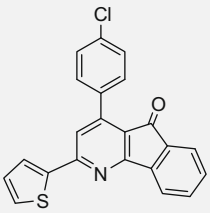
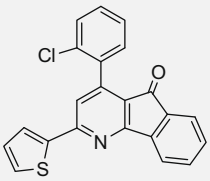
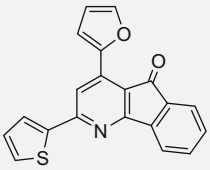
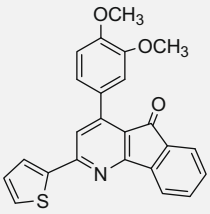
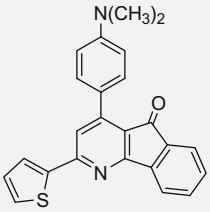
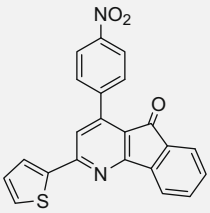
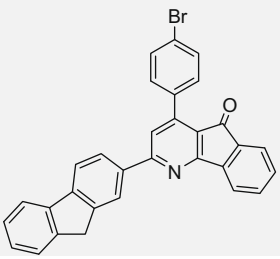
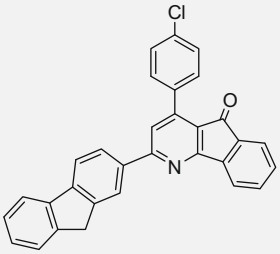
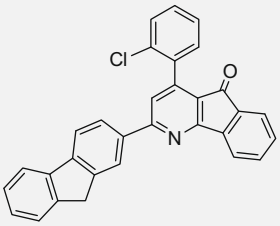
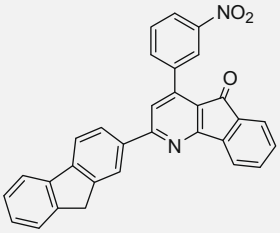
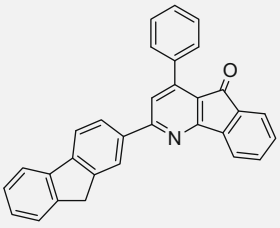
Entry	Products	Time (h)	Yield (%) (isolated)	Ref.
1		3	90	–
2		2.5	92	–
3		3	89	–
4		3.5	82	–
5		4	85	–
6		3	90	–
7		4	86	–
8		2.5	92	–

Table 2 (*continued*)

Entry	Products	Time (h)	Yield (%) (isolated)	Ref.
9		2.5	93	–
10		3	89	–
11		4	88	–
12		3	90	–

odologies require elevated temperature created by either microwave-oven irradiation[18–20] or heating the reaction mixture at high temperature.[21,22]

Therefore, the development of a new catalytic system to overcome these shortcomings and fulfill the criteria of a simple, facile, efficient, and environmentally benign protocol for the synthesis of highly substituted pyridines at ambient temperature is an important task for organic chemists.

In recent years, L-proline has attracted enormous interest in different organic reactions due to its experimental simplicity, ease of handling, cost effectiveness, and excellent solubility in water and in common organic solvents. L-proline has shown considerable catalytic efficiency in different transformations such as enamine-based direct catalytic asymmetric aldol condensation,[23] α-amination reaction,[24] Mannich reaction,[25] Diels–Alder reaction,[26a] Knoevenagel reaction,[26b] Michael condensation,[27] and as excellent promoter for the copper-catalyzed coupling reactions[28] as well as in solvent-free Biginelli reaction,[29] in unsymmetric Hantzsch reaction,[30] for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from wide range of substituted o-phenylenediamines and aldehydes.[31]

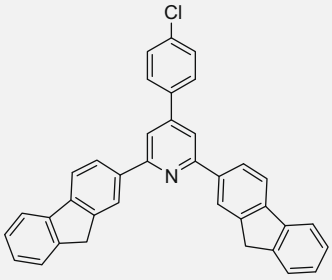
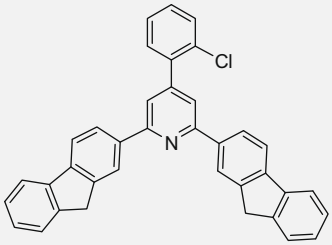
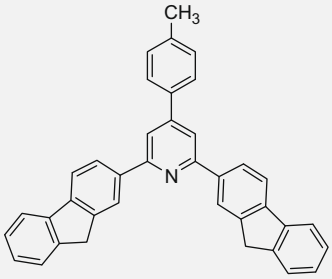
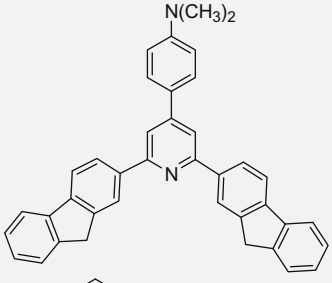
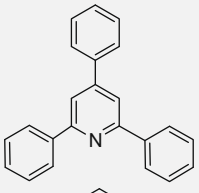
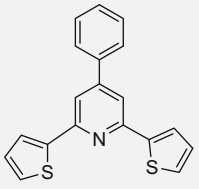
Besides catalyzing single reactions of C–O, C–N, and C–C bond formations, L-proline has also catalyzed varieties of multicomponent reactions. In one such report,[32] direct combinations of L-proline-catalyzed cascade Knoevenagel/hydrogenation and cascade Robinson annulation of CH acids (dimedone and 1,3-cyclohexane dione), aldehydes, Hantzsch ester, and methyl vinyl ketone furnished the highly functionalized Wieland–Miescher ketone analogues in good to high yields. Another very interesting example includes a practical organocatalytic process for the synthesis of optically active, highly substituted α-hydroxy ketones through L-proline-catalyzed[33] asymmetric desymmetrization (ADS) of prochiral ketones. Other amino acids or even amines have been used to catalyze[34] three-component hetero domino Knoevenagel/Diels Alder/epimerization reactions. Another practical and novel one-pot organocatalytic selective process for the amine-catalyzed cascade synthesis of highly substituted *ortho*-hydroxydiarylamines and *ortho*-pyrrolidin-1-yldiarylamines is also reported.[35]

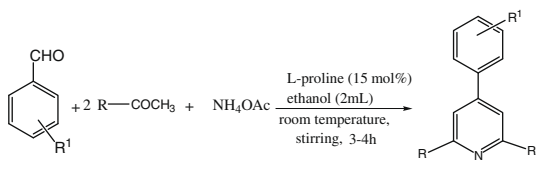
2. Results and discussion

In continuation of our synthesis toward biologically important heterocycles,[36] we report herein, for the first time, a simple, mild, and expeditious synthesis of highly substituted pyridines in excellent yields employing L-proline (15 mol%) as an organocatalyst at ambient temperature (Scheme 1).

In order to standardize the reaction, 4-bromobenzaldehyde (1 mmol), indan-1,3-dione (1 mmol), 2-acetylthiophene (1 mmol), and ammonium acetate (1.3 mmol) were dissolved in ethanol and stirred at room temperature for 48 h in the absence of the catalyst which led to very poor yields (only 6–7%, as obtained in crude ^{1}H NMR) of the substituted pyridine. We also tried different solvents under similar reaction conditions but no appreciable incre-

Table 3
Synthesis of 2,4,6-trisubstituted pyridines at room temperature using L-proline (15 mol%) as an organocatalyst

Entry	Products	Time (h)	Yield (%) (isolated)	Ref.
1		3	89	–
2		3.5	88	–
3		3	90	–
4		3	89	–
5		4	82	22
6		4	81	37



Scheme 2. Synthesis of 2,4,6-trisubstituted pyridines at room temperature.

ment in product yield was observed. Then it was thought worthwhile to study the reaction in the presence of organocatalyst like L-proline. Use of 15 mol% of the catalyst produced maximum yield (90%). A further increase of the catalyst concentration does not increase the yield. On the contrary, the reaction slows down on adding more than 15 mol% of catalyst. The standard reaction was also studied in the presence of glycine (15 mol%), when the desired product was obtained after 60 h in only 20% isolated yield. This

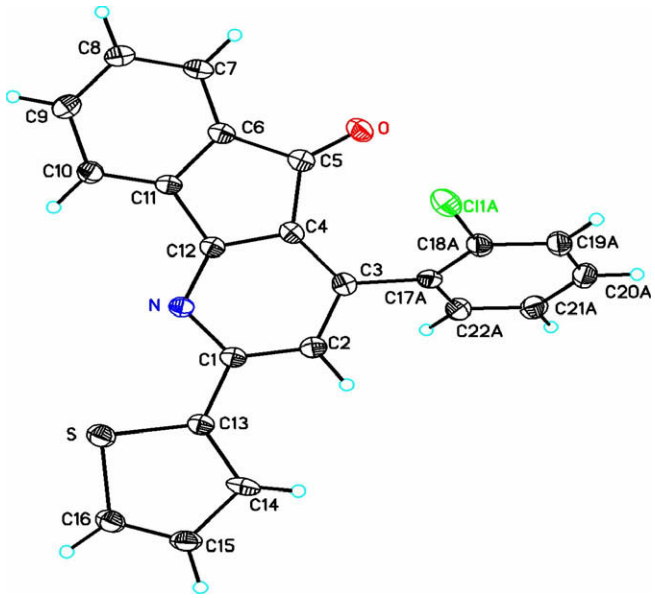


Figure 1. Ortep plot of a single crystal of 4-(2-chlorophenyl)-2-thiophen-2-yl-indeno[1,2-b]pyridin-5-one (entry 3, Table 2) showing the crystallographic numbering (CCDC 759008).

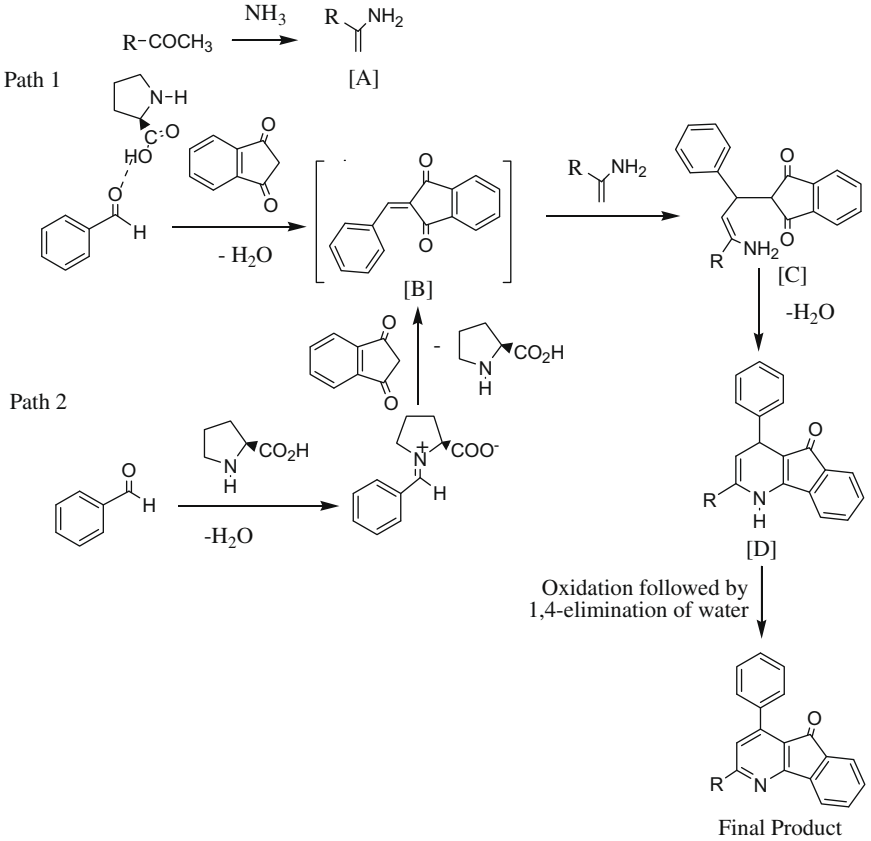
lower yield could be attributed firstly to the comparatively poor solubility of glycine in ethanol and secondly to the reaction passing via imine with lower reactivity rather than iminium ion with L-proline with much higher reactivity (vide mechanism). The detailed results of changing catalyst (L-proline) concentration and solvents are given in Table 1.

Encouraged by the above-mentioned results obtained for 4-bromobenzaldehyde, indan-1,3-dione, 2-acetylthiophene, and ammonium acetate, we investigated a number of other aromatic (possessing both electron-donating and electron-withdrawing groups) and heteroaromatic aldehydes as well as using 2-acetylfluorene in addition to 2-acetylthiophene to probe their behavior under the current catalytic conditions. As a result, a wide variety of highly substituted pyridines were obtained by stirring a mixture of aldehyde, indan-1,3-dione, 2-acetylthiophene or 2-acetylfluorene, and ammonium acetate in ethanol in the presence of L-proline (15 mol%) for 2.5–4 h in 82–93% isolated yields. The results are summarized below in Table 2.

In order to establish the scope of this catalytic transformation, the same reaction conditions were applied for the synthesis of 2,4,6-trisubstituted pyridines via one-pot three-component condensation of aromatic aldehydes (1 mmol), ammonium acetate (1.3 mmol), ketomethyl derivatives (2 mmol) as depicted in Scheme 2.

In all cases, the crude products obtained by extracting the reaction mixture with ethylacetate were purified by crystallization from hot ethanol. All the final products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses. The structure of one of the products (Table 2, entry 3) has been confirmed by X-ray crystal structure analysis of its single crystal and is shown below in Figure 1.

A probable mechanism for L-proline-catalyzed synthesis of highly substituted pyridines has been proposed (Scheme 3) in which the reaction proceeds through two different pathways (path-1 and path-2). Path-1 involves the activation of aldehydic carbonyl oxygen by the acid part of L-proline through intermolecular H-bonding and subsequent condensation with indan-1,3-dione to form the ene dione intermediate B. Path-2 gives the same



Scheme 3. Probable mechanism for L-proline-catalyzed highly substituted pyridines.

intermediate B via iminium catalysis which condenses with the condensation product of amine and ketones to form the intermediate C which on dehydration gives the dihydropyridines (D). Dihydropyridine on subsequent oxidation and 1,4-elimination of water produces the final product.

3. Conclusion

In conclusion, a novel, facile, one-pot, multicomponent methodology[38] for the synthesis of substituted pyridines catalyzed by 15 mol% of L-proline has been developed in high yield. Compared to the previously reported methods, most of which required elevated temperatures,[18–22] this methodology proceeds smoothly at room temperature and therefore is able to sustain a large number of functional groups. Mild reaction conditions, easy work-up, clean reaction profile, shorter reaction time, and wide range of substrate applicability are the key advantages of this methodology.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.106.

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38. *General experimental procedure for substituted pyridine formation*: In a 50 mL round-bottomed flask, aldehyde (1 mmol), indan-1,3-dione (1 mmol), 2-acetyl thiophene or 2-acetyl fluorene (1 mmol), and ammonium acetate (1.3 mmol) were stirred in the presence of 15 mol % of L-proline in ethanol (2 mL) at room temperature for the stipulated time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with ethylacetate (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and recrystallized from hot ethanol to afford the pure product. In the case of 2,4,6-triaryl pyridines (Scheme 2, Table 3), same procedure was followed except taking 2 mmol of either 2-acetyl thiophene or 2-acetyl fluorine or acetophenone. The IR, ^{1}H NMR, and ^{13}C NMR data of three representative compounds are given below: The spectral data for all the other new compounds are given in the Supplementary data.
4-(4-Bromophenyl)-2-thiophen-2-yl-indeno[1,2-b]pyridin-5-one (Table 2, entry 1): yellow solid, mp 232 °C (EtOH); IR (KBr): 3087, 2372, 1706, 1573, 1535, 1433, and 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J = 7.2 Hz, 1H), 7.77 (dd, J = 3.7 and 1.1 Hz, 1H), 7.68–7.50 (m, 7H), 7.44 (dt, J = 7.5 and 0.9 Hz, 1H), 7.39 (s, 1H), 7.17 (dd, J = 3.8 and 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.6, 166.7, 152.2, 148.2, 143.9, 142.5, 135.4, 134.8, 134.1, 131.5, 131.2, 130.6, 129.8, 128.4, 126.8, 124.2, 123.6, 122.1, 121.1, 118.6; Anal. Calcd for $C_{22}H_{12}BrNOS$: C, 63.17; H, 2.89; N, 3.35. Found: C, 63.05; H, 2.99; N, 3.37.
4-(4-Bromophenyl)-2-(9H-fluoren-2-yl)-indeno[1,2-b]pyridin-5-one (Table 2, entry 8): yellow solid, mp 250–252 °C (EtOH); IR (KBr): 3086, 2942, 1707, 1572, 1548, 1466, 745, and 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.84–7.51 (m, 8H), 7.46–7.33 (m, 3H), 4.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.0, 166.6, 161.5, 148.1, 144.1, 143.9, 143.0, 141.0, 137.2, 136.6, 135.5, 134.9, 134.4, 131.5, 131.1, 130.7, 127.5, 127.0, 126.4, 125.2, 124.1, 123.7, 122.3, 121.0, 120.5, 120.5, 120.2, 37.0; Anal. Calcd for $C_{31}H_{18}BrNO$: C, 74.41; H, 3.63; N, 2.80. Found: C, 74.30; H, 3.72; N, 2.82.
4-(4-Chlorophenyl)-2,6-bis-(9H-fluoren-2-yl)-pyridine (Table 3, entry 1): white solid, mp 248 °C (EtOH); IR (KBr): 3037, 2900, 2369, 1600, 1538, 1490, 1406, 1090, 828, and 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 2H), 8.21 (d, J = 7.9 Hz, 2H), 7.94–7.80 (m, 6H), 7.70 (d, J = 8.9 Hz, 2H), 7.59 (d, J = 7.1 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 7.1 Hz, 2H), 7.34 (t, J = 7.1 Hz, 2H), 4.02 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 148.9, 143.9, 143.8, 142.8, 141.3, 138.1, 137.6, 135.2, 129.3, 128.5, 127.0, 126.9, 126.0, 125.1, 123.8, 120.2, 120.0, 116.6, 37.1; Anal. Calcd for $C_{37}H_{24}ClN$: C, 85.78; H, 4.67; N, 2.70. Found: C, 85.61; H, 4.82; N, 2.72.