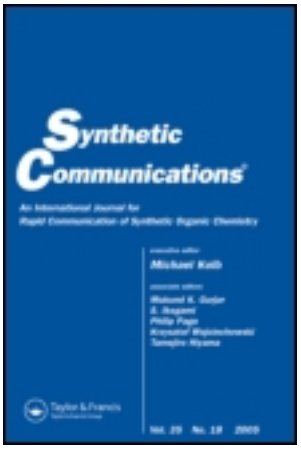

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Metal-Free, One-Pot, Rapid Synthesis of Tetrahydropyridines Using Acetic Acid as Solvent and Catalyst at Room Temperature

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METAL-FREE, ONE-POT, RAPID SYNTHESIS OF TETRAHYDROPYRIDINES USING ACETIC ACID AS SOLVENT AND CATALYST AT ROOM TEMPERATURE

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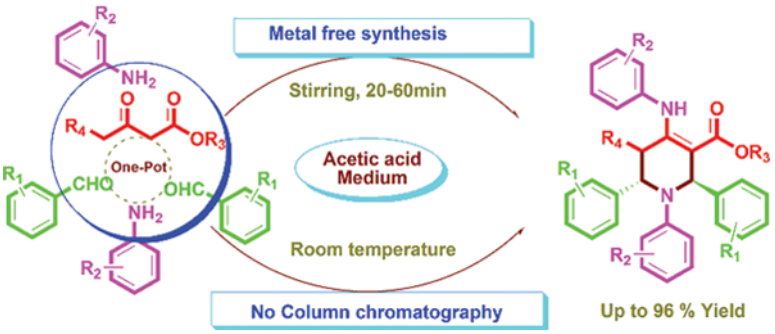
GRAPHICAL ABSTRACT



Abstract *Acetic acid–promoted, one-pot synthesis of tetrahydropyridines has been developed under metal-catalyst-free conditions via a tandem reaction. High atom economy, good yield, simple procedure, no expensive column chromatography, shorter reaction time, and metal-free and mild reaction conditions are some of the important features of this protocol. The current methodology provides an alternative approach for not only highly substituted tetrahydropyridines (THPs) but also fully substituted tetrahydropyridines (FTHPs) in moderate to good yields. The plausible mechanism for the formation of THPs was greatly promoted by the H^+ ion coming from acetic acid.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Acetic acid; acetoacetic esters; diastereoselectivity; intramolecular Mannich cyclization; tandem reaction; tetrahydropyridines

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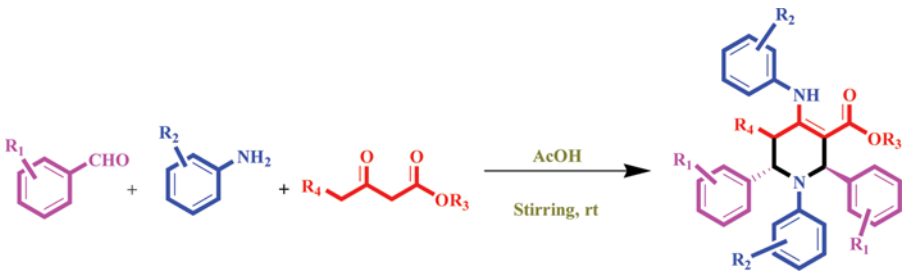
INTRODUCTION

Multicomponent reactions (MCRs) have received considerable attention because of the complexity of the molecules that can be easily achieved from readily available starting materials in one reaction sequence.[1] MCRs generally occur in one pot and exhibit high atom economy and product selectivity. In most of the cases, they yield a single product and thus MCRs are advantageous over linear stepwise synthesis because of operational simplicity, reduction in reaction time, ecological friendliness, saving of money and raw materials, inexpensive purification, and avoidance of protection and deprotection processes.[2] Green chemistry involves optimization of synthetic methodology without polluting the environment and reducing the cost. In this regard we have focused our attention on the synthesis of tetrahydropyridines at room temperature without using metal catalyst.

Tetrahydropyridines are widely distributed in naturally occurring alkaloids and synthetic drugs.[3] A variety of structural features are exhibited by synthetically prepared piperidines, including many exhibit significant biological properties. Many synthetic methods have been extensively studied for tetrahydropyridines because of their antihistamic,[4] anti-HIV,[5] anticancer,[6] antimicrobial,[7] antimalarial,[8] anti-inflammatory,[9] and anti-insecticidal activity.[10] A few of them are also potent inhibitors for many biological systems.[11] Considerable effort has been focused on synthetic methods and some of the synthetic routes have been recommended for the synthesis of highly substituted tetrahydropyridines.[12] Recently one-pot syntheses of these scaffolds have been achieved by employing $InCl_3$,[13] bromodimethylsulfonium bromide,[14] L-proline trifluoroacetic acid/TFA,[8] tetrabutyl ammonium tribromide,[15] molecular I_2,[16] ceric ammonium nitrate (CAN),[17] $ZrOCl_2 \cdot 8H_2O$,[18] picric acid,[19] BF_3-SiO_2[20], VCl_3,[21] thiourea dioxide (TUD),[22] $Bi(NO_3)_3 \cdot 5H_2O$,[23] and $LaCl_3 \cdot 7H_2O$[24] as efficient catalysts. These methods have some disadvantages, such as the use of expensive and excess amounts of catalysts. Therefore, the development of a simple, nontoxic, and effective synthetic strategy is needed for the synthesis of biologically active molecules.

Glacial acetic acid is an excellent polar protic solvent, and the hydrogen in the carboxylic group of acetic acid can easily be separated from the molecule by ionization, which gives an environment for the reaction to proceed faster. Na et al. developed a brand-new, bowl-shaped molecular architecture from the reaction of ninhydrin and phloroglucinol in acetic acid in excellent yields up to 95% via



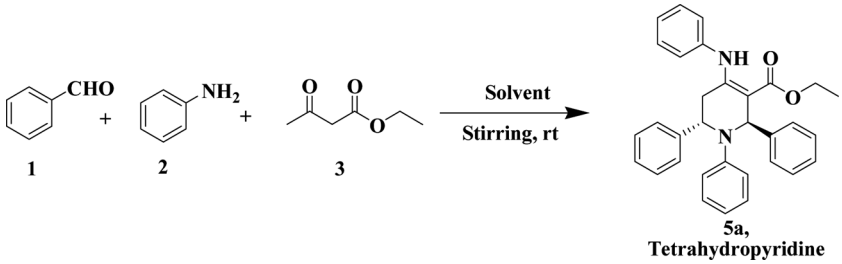
Scheme 1. Metal-free synthesis of highly substituted tetrahydropyridines using acetic acid. (Figure is provided in color online.)

MCR.[25] In the present report, we have explored acetic acid–promoted efficient synthesis and mechanistic investigations of the formation of THPs using an MCR (Scheme 1). Furthermore, the reaction is metal free; acetic acid is cheap, readily available, versatile, and efficient for promotion of many acid-catalyzed organic reactions.[26]

RESULTS AND DISCUSSION

Initially, the reaction of ethyl acetoacetate (EAA) (1 mmol), benzaldehyde (2 mmol), and aniline (2 mmol) in ethanol was examined in the presence of a catalytic amount of various Lewis acids ($AlCl_3$, $FeCl_3$, $LaCl_3$, $ZnCl_2$, $NiCl_2$, and $CuCl_2$), and other catalysts (SiO_2Cl, Al_2O_3, La_2O_3, triethyl amine, and Li_2CO_3 + L-proline) (SI Table 1). Interestingly, we ended up with THP **5a** in up to 80% yield in 4–16 h (SI Table1). When methanol was used as solvent, the catalysts $LaCl_3$ and SiO_2Cl offered THP **5a** in 80% and 78% yields, respectively. For the optimization and identification of the suitable solvent and effective reaction conditions, EAA, benzaldehyde, aniline, and 10 mol% of catalyst were selected as prototypes. Among the chosen solvents, MeOH was considered the best for the synthesis of tetrahydropyridines. Although acetonitrile, chloroform, ethanol, and dichloromethane allowed the reaction at a

Table 1. Screening of various solvents for the one-pot synthesis of tetrahydropyridine **5a**[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	None	MeOH	48	20
2	None	EtOH	48	15
3	None	i-PrOH	48	5
4	None	n-BuOH	48	1
5	None	CH_3CN	48	13
6	None	DCM	48	0
7	None	THF	48	0
8	None	Ethylacetate	48	2
9	None	Acetone	48	0
10	None	Toluene	40	0
11	None	Water	48	0
12	None	HCOOH	48	0
13	None	AcOH	0.5	94

[a]Conditions: Ethyl acetoacetate (0.5 mmol), benzaldehyde (1 mmol), and aniline (1 mmol) in solvent (3 ml), with stirring in room temperature.
[b]Isolated yields.

faster rate, the yield was less than the yield obtained using MeOH as solvent. THF and ethyl acetate gave poor yields, and no desired product was obtained with water. Interestingly, when we performed the reaction with acetic acid as solvent, we obtained 93% yield of the desired product THP **5a** within 30 min.

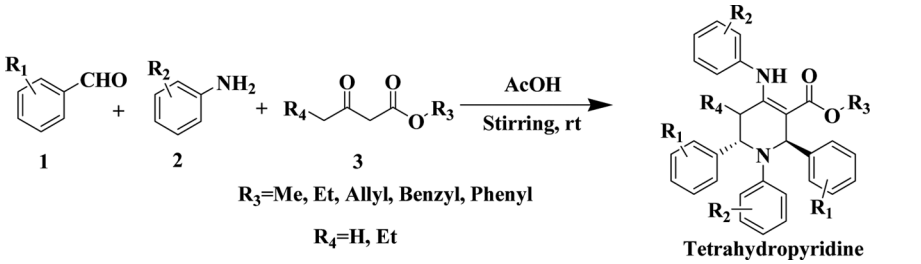
To examine the role of the catalyst, we performed the same reaction with different catalysts in acetic acid. We employed 10 mol% catalyst for the model reaction in acetic acid at room temperature but there was no significant change in the reaction time and yield. Then, it was of interest to know whether it was possible to synthesize a substituted tetrahydropyridine by this MCR in the absence of a catalyst. For this, aniline was treated with 1 equivalent of EAA in the solvent to form enamine in situ at room temperature. Similarly, 2 equivalents of aryl aldehyde and 1 equivalent of aniline were mixed separately in the solvent to form Schiff's base. Then these two were stirred along with 1 mol of benzaldehyde (benzaldehyde was added in excess during the formation of Schiff's base) for up to 48 h.

To study the effect of the solvent on the reaction, the reaction was carried out with various aprotic and protic solvents as shown in Table 1. In conclusion, we found that proton is not catalyzing the reaction but acetic acid is the specific catalyst. We got the desired THP in excellent yields with reaction time of 20 min using acetic acid as solvent at room temperature. There were no other side products, and predominantly antiselectivity was achieved. According to our knowledge there are only a few reports available in the literature for the synthesis of THPs that require less than 5h under reflux condition with moderate yields.[18] In the present protocol, we obtained excellent yields up to 96% and lowered the reaction time to 20 min without reflux conditions. As far as the temperatute effect is concerned, it does not have any significant effect on yield and the reaction time, because we are getting same yield at the same interval of time at all temperatures.

To further explore the scope and importance of this five-component reaction under optimized conditions, a variety of aromatic aldehydes containing electron-donating and electron-withdrawing substituents in the aromatic ring such as -F, -Cl, -Br, -NO_2, -CN, -Me, -OMe, and -Et were reacted with varying β-keto esters and a number of substituted amines. The reaction time and percentage yield for each of the product are shown in Table 2. To analyze the ester group effect on the yields of THPs, a mixture of benzaldehyde and p-chloroaniline was treated separately with methyl acetoacetate (MAA), ethyl acetoacetate (EAA), allyl acetoacetate (AAA), and benzyl acetoacetate (BAA) under the standard conditions. They yielded the corresponding THP scaffolds in 84%, 89%, 83%, and 80% yields, respectively (Table 2, entries 9, 22, 32, and 36). To study the substituent effect on aniline, a variety of anilines possessing electron-donating and electron-withdrawing substituents in the aromatic ring such as -Cl, -NO_2, and -Me were treated with a variety of aromatic aldehydes and EAA, and the results are summarized in Table 2 (entries 22–28).

Generally, for incorporating substitution at all the positions of the tetrahydropyridine ring, ethyl butyryl acetate (EBA), aniline, and substituted aryl aldehydes were allowed to react in acetic acid medium and we got fully substituted tetrahydropyridines (FTHPs) with good yields up to 89%, 87%, and 87% for **6a, 6b**, and **6c** respectively (Table 2, entries 29, 30, and 31). In the next attempt, for generating tetrahydropyridine moiety with alkyl substitution at 2 and 6 positions, we treated EAA and aniline with different aliphatic aldehydes including formaldehyde,

Table 2. Three-component, one-pot reaction leading to substituted tetrahydropyridines under acetic acid conditions[a]



Entry	R_1	R_2	R_3	R_4	Product (**4–9**)	Time (min)	Yield (%)[b]
1	H	H	Me	H	**4a**	27	90
2	2-OMe	H	Me	H	**4b**	45	86
3	3-NO_2	H	Me	H	**4c**	50	76
4	4-CN	H	Me	H	**4d**	35	94
5	4-Br	H	Me	H	**4e**	35	95
6	4-NO_2	H	Me	H	**4f**	47	78
7	4-Me	H	Me	H	**4g**	30	96
8	4-MeO	H	Me	H	**4h**	25	89
9	H	4-Cl	Me	H	**4i**	32	84
10	4-F	4-Cl	Me	H	**4j**	60	86
11	4-Me	4-Cl	Me	H	**4k**	30	92
12	H	H	Et	H	**5a**	25	93
13	2-F	H	Et	H	**5b**	42	81
14	3-F	H	Et	H	**5c**	40	86
15	3-Br	H	Et	H	**5d**	44	84
16	3-NO_2	H	Et	H	**5e**	55	71
17	3-Me	H	Et	H	**5f**	50	86
18	4-Me	H	Et	H	**5g**	25	94
19	4-Et	H	Et	H	**5h**	33	90
20	4-F	H	Et	H	**5i**	35	96
21	4-Cl	H	Et	H	**5j**	39	94
22	H	4-Cl	Et	H	**5k**	45	89
23	4-Me	4-Cl	Et	H	**5l**	30	91
24	4-Et	4-Cl	Et	H	**5m**	40	86
25	H	4-Me	Et	H	**5n**	20	94
26	4-Me	4-Me	Et	H	**5o**	30	91
27	4-Cl	4-Me	Et	H	**5p**	20	95
28	4-Me	4-NO2	Et	H	**5q**	60	79
29	4-F	H	Et	Et	**6a**	120	89
30	4-Cl	H	Et	Et	**6b**	90	87
31	4-CN	H	Et	Et	**6c**	75	87
32	H	4-Cl	Allyl	H	**7a**	50	83
33	3-NO_2	4-Cl	Allyl	H	**7b**	55	70
34	4-Me	4-Cl	Allyl	H	**7c**	45	88
35	H	H	Benzyl	H	**8a**	60	84
36	H	4-Cl	Benzyl	H	**8b**	75	80

[a]Conditions: 1,3-dicarbonyl compound (0.5 mmol), aromatic aldehyde (1 mmol), and aniline (1 mmol) in 2.5 ml of acetic acid with stirring at room temperature.

[b]Isolated yields.

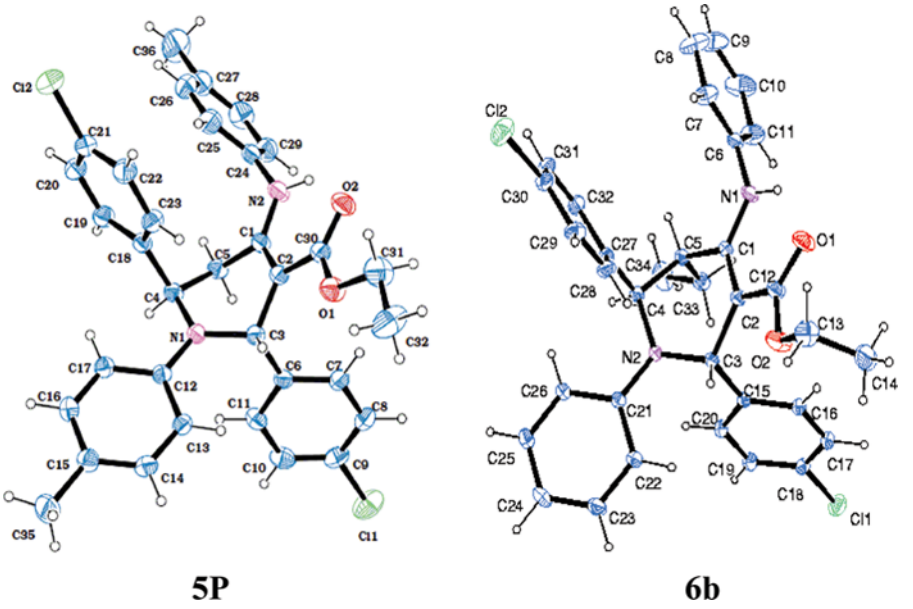
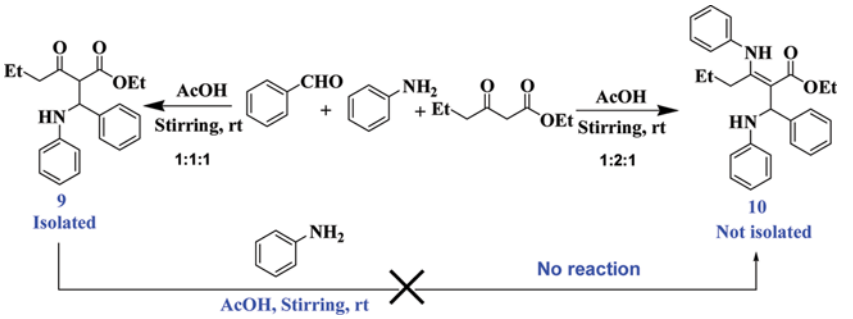


Figure 1. X-ray crystal structure (ORTEP diagrams) of **5p** and **6b**. (Figure is provided in color online.)

acetaldehyde, and propanaldehyde under the same reaction conditions. However, no desired compounds were formed in the reaction mass with up to 48 h of stirring. This is due to the difficulty in generating Schiff base from aliphatic aldehydes with aniline because of the electron-releasing nature of alkyl groups in aliphatic aldehydes. The dehydration from the aldol product is difficult and the in situ–formed product is highly unstable.

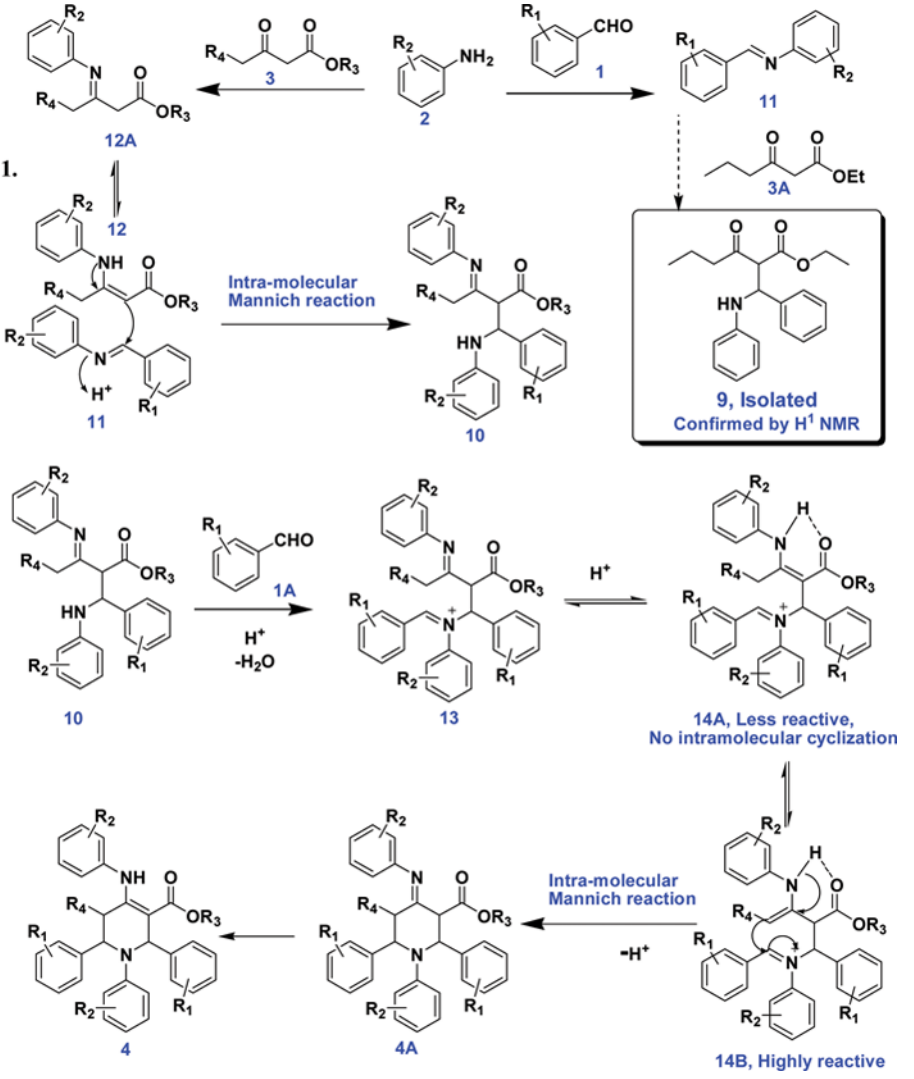
All the synthesized products were characterized by Fourier transform infrared (FTIR), ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectral (HRMS) analyses. The structures of **4a, 5a, 5p**, and **6b** were determined by single-crystal x-ray diffraction analysis and it can be concluded that the ring exists in *trans* form. The x-ray structures of **5p** and **6b** are shown in Fig. 1. The anticonformation was



Scheme 2. Synthesis of intermediate **9**, which is similar to key intermediate **10**. (Figure is provided in color online.)

confirmed by comparing the spectroscopic studies and the single-crystal x-ray diffraction analysis of **4a, 5a**, and **5p** with the literature, and it was concluded that the reaction was predominantly diastereoselective.

To find the exact mechanism of the reaction, we treated parent benzaldehyde and aniline with EBA under similar conditions in the molar ratio of 1:1:1. We had successfully isolated the intermediate **9**, which is very similar to **10**, and intermediate **10** could not be isolated. Because first aniline and ketone react, we do not get the product if we add 1 mol of aniline to intermediate **9** (Scheme 2). Earlier workers isolated a similar intermediate with diethylmalonate[16,20] and acetophenone[21] but failed to isolate an intermediate possessing both ester and alkyl moiety.



Scheme 3. Possible mechanism for the formation of THPs. (Figure is provided in color online.)

To understand the most predominant mechanism for the formation of functionalized tetrahydropyridines, the stepwise reaction was carried out. The plausible mechanism is outlined in Scheme 3. Initially, the reaction of aniline and EAA was carried out to give the β-enaminone (**12** and **12A**) which was confirmed by thin-layer chromatography (TLC). Similarly, the reaction of benzaldehyde and aniline was carried out to give the corresponding Schiff's base **11**. Further, this enamine **12** and Schiff's base **11** underwent intermolecular Mannich reaction in the presence of H^+ to afford intermediate **10**, which was confirmed by TLC. However, the intermediate **9**, which is similar to **10**, was successfully isolated from the reaction mass and confirmed by NMR studies. In the presence of H^+, the reaction of aldehyde with the intermediate **10** proceeded quickly to generate the intermediate **13** by the elimination of a H_2O molecule. The intermediate **13** underwent protonation to generate the intermediate **14A**, which is less reactive. Then **14A** underwent tautomerization to give more reactive intermediate **14B**, which furthermore underwent intramolecular cyclization to give functionalized piperidine derivatives **4A**. Thereafter, the piperidine derivative **4A** tautomerizes under acidic condition to provide the desired functionalized tetrahydropyridine derivatives.

In the next attempt, enamine **12** was added to formaldehyde and aniline, but the reaction did not occur among them. This confirms that there was no formation of Schiff's base **11A** from aliphatic aldehyde and aniline. The reaction was carried out by sequential addition of reactants as follows: 1 equivalent of 1,3-dicarbonyl compound and 2 equivalents of amine in acetic acid. This mixture was stirred for 5 min, followed by the addition of 2 equivalents of aldehyde, and the stirring continued for an appropriate time. The intermediate **10** was formed easily by intermolecular Mannich reaction of **11** and **12** in the presence of H^+, and also the reaction between **10** and remaining aldehyde in the reaction mass was significantly influenced by H^+ to the elimination of H_2O. Hence, we concluded that the THPs were efficiently synthesized via the intermediate **10** in the presence of H^+.

EXPERIMENTAL

All the solvents and chemicals were received commercially. Melting points were determined by using a Guna melting-point apparatus and are uncorrected. FTIR spectra were recorded using a Jasco-4100 spectrometer instrument. NMR spectra were taken with a Bruker AV III spectrometer at 500 MHz (^1H and ^{13}C) and at 400 MHz (^1H and ^{13}C) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as internal standard. HRMS analysis was obtained on a Jeol GC Mate.

General Procedure for the Preparation of Methyl 1,2,5,6-Tetrahydro-1,2,6-triphenyl-4-(phenylamino) Pyridine-3-carboxylate (4a)

A mixture of methyl acetoacetate (1 mmol), aniline (2 mmol), and 3 ml glacial acetic acid was stirred at room temperature for 5 min followed by the addition of benzaldehyde (2 mmol) and allowed to stir for an appropriate time (Table 1). Completion of the reaction was monitored by thin-layer chromatography (TLC) using a 1:9 ratio

of ethylacetate and hexane. The solid product formed in the reaction mixture was filtered, washed with methanol, and recrystallized using ethanol and THF (1:1 ratio).

Selected Data

White yellow solid; Melting point: 192–194 °C: IR (KBr): 3250, 3024, 2949, 2867, 1815, 1661, 1606, 1504, 1449, 1375, 1321, 1245, 1183, 1070, 978, 920, 748, 646 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) ppm: 2.78–2.74 (dd, $J = 32.0$, 4 Hz, 1H), 2.89–2.84 (dd, $J = 32.0$, 4.0 Hz, 1H), 3.93 (s, 3H), 5.14 (s, 1H), 6.28–6.26 (d, $J = 8.0$ Hz, 2H), 6.45 (s, 1H), 6.53–6.51 (d, $J = 8.0$ Hz, 2H), 6.61–6.57 (t, $J = 8.0$ Hz, Hz, 1H), 7.33–7.03 (m, 15H), 10.25 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 33.6, 51.0, 55.1, 58.2, 97.9, 112.9, 116.2, 125.8, 125.9, 126.4, 126.4, 126.6, 127.2, 128.3, 128.7, 128.9, 128.9, 137.8, 142.7, 143.9, 146.9, 156.3, 168.6.

CONCLUSION

In conclusion, an efficient, simple, and acetic acid–promoted protocol for the synthesis of highly functionalized tetrahydropyridines (THPs) by one-pot multicomponent reaction is developed using readily available starting materials under metal-free conditions. The advantageous features of this procedure are mild reaction conditions, high diastereoseletivity, high atom economy, good yields, operational simplicity, no tedious separation procedures, inexpensive starting materials, metal-free synthesis, environmentally benign reaction, and short reaction times when compared to the reaction catalyzed by the catalyst. The intermediate **9**, which was similar to the key intermediate for the formation of THP, was isolated by one-pot, three-component reaction of EBA, aniline, and aldehyde. From the mechanistic studies it is clearly known that the formation of THPs via intramolecular Mannich reaction was influenced by H^+.

SUPPLEMENTARY MATERIAL

General experimental details, characterization data of all the compounds, ^1H NMR and ^{13}C NMR spectra of all the compounds, and crystallographic data of **4a, 5a, 5p**, and **6b** can be found online.

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