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Green and sustainable one-pot synthesis of novel tetrahydropyridines using [Et3NH][HSO4] as an ionic liquid catalyst

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C H R O N I C L E

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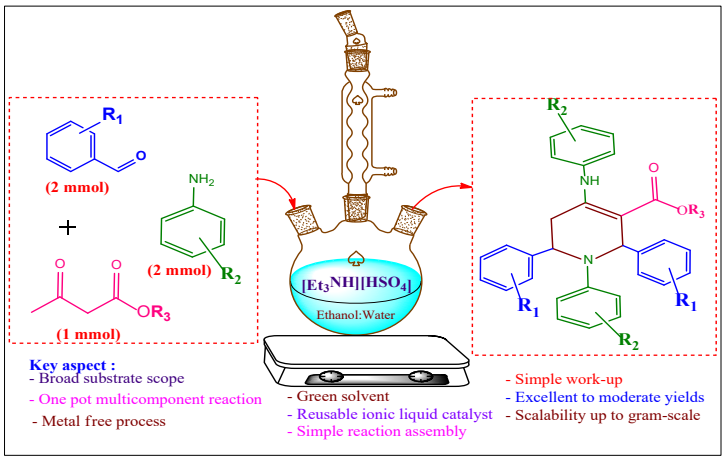
A B S T R A C T

Through the implementation of a simple, environment friendly one-pot multicomponent reaction with 1 mmol of methyl acetoacetate, 2 mmol of different substituted aromatic aldehydes, and 2 mmol of different substituted aromatic anilines in the presence of triethylammonium hydrogen sulfate [Et3NH][HSO4] bronsted acid as an ionic liquid catalyst and Ethanol: water as a green solvent at 60°C temperature. We have developed an affordable and dynamic procedure for the synthesis of novel, medicinally essential tetrahydropyridine derivatives. One-pot multicomponent synthesis is an energetic topic in heterocyclic chemistry due to its vital advantages of simple reaction process, high atom economy, low cost, less amount of waste generation, and simple workup procedures, which make this process economically productive for industrial applications. The final compounds were confirmed via FTIR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy and were in contrast with their reported methods.



Graphical Abstract

1. Introduction

Six-membered heterocyclic substances, particularly those that include one, two, five and six substitutes. Tetrahydropyridines constitute an important class of organic compounds, and because of their wide spectrum of biological and therapeutic applications, they have attracted a great deal of attention. They exhibit numerous pharmacological characteristics. For example, Loracarbef is an antibiotic. It is a carbacephem, but it is sometimes grouped together with the second-generation cephalosporin antibiotic. As an anti-microbial activity, Also it has shown a wide range of effectiveness

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against gram-positive as well as gram-negative bacteria, including those that cause infections of the skin, kidneys, sinuses, tonsils, respiration system, and urinary tract.[1] In humans and other primates, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydroxpyridine is toxic and can induce symptoms comparable to Parkinson's syndrome.[2] A class of aryltetrahydropyridine derivatives with glycine-derived compounds as cancer drug medicines was proposed by Gwaltney et al. as Farnesyl transferase inhibitors (FTIs).[3] Although it is a recognized antagonism of the M5 receptors, xanomeline is an orthostaric muscarinic acetylcholine channel with intermediary selective of the M1 and M4 subtypes (M1/M4 channel agonists).[4] Misra et al. used a multicomponent procedure to synthesize fluoro-functionalized aryltetrahydropyridine. These substances have shown significant antiplasmodial action against infection with malaria caused by Plasmodium falciparum.[5] GTS-21 (also known as DMBX-A), is a novel, small-molecule, orally active and selective alpha-7 nicotinic acetylcholine (nACh) receptor agonist that has demonstrated memory and cognition enhancement activity in human clinical trials.[6] **Fig. 1** illustrates some examples of both synthetic and also naturally occurring bioactive molecules that have the tetrahydropyridines structure.

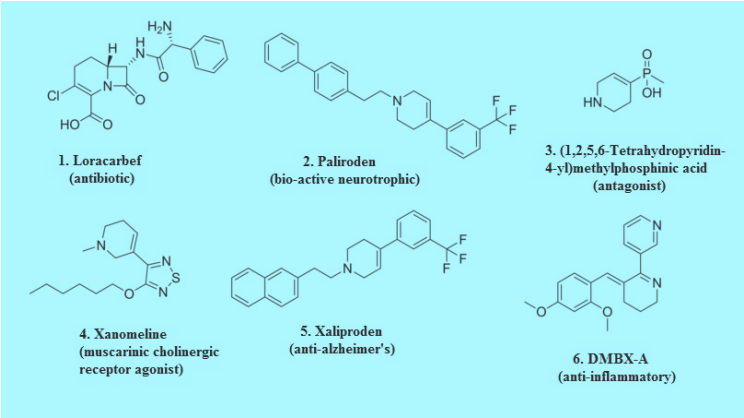


Fig. 1. Naturally occurring as well as synthetic bioactive compounds containing the tetrahydropyridines skeleton.

There are several known procedures to create 1, 2, 5, 6-tetrahydropyridines. By partially reducing matching 1-methyl pyridinium salt with borohydride, they have been created.[7] Tetrahydropyridines are generated by a modified Ireland-Claisen synthesis that involves the intermediates silyl enol and the ethers of ester or carboxylic acids.[8] Tetrabutyl ammonium tribromide (TBATB),[9] bromodimethyl sulfonium bromide (BDMS),[10] cerium ammonium nitrate (CAN),[11] Ni (Salen) complexes, and other catalytic methods have been reported for the preparation of tetrahydropyridine. The typical method for the preparation of tetrahydropyridine derivative products is through the one-pot multicomponent reaction of methyl acetoacetate, various substituted aromatic aldehydes, and various substituted aromatic anilines.[12] The following substances can be used as catalysts: l-proline/TFA;[13] indium(III) chloride (InCl3),[14] iodine (I2),[15] iron(III) chloride (FeCl3),[16]. picric acid,[17] oxalic acid,[18] bismuth(III) nitrate (Bi(NO3)3•5H2O),[19] silica-supported boron trifluoride (BF3•SiO2),[20] and zirconium(IV) oxychloride octahydrate (ZrOCl2•8H2O).[21] Making substituted tetrahydropyridine is typically challenging, particularly with molecules with a N-aryl function.[22] On the other hand, various previously documented synthesis processes have been created. The synthesis of Morita-Baylis-Hillman acetate with 1,3-azadienes via annulations is one of them.[23] Other instances of these include Wittig rearrangements,[24] intermolecular in allyl silane-nitrone cycloaddition reaction caused by phosphine,[25] proline-assisted cascade Mannich type both intramolecular cyclization,[26] acid-catalyzed cyclization of ene,[27] and the use of derivatives. Diels-Alder reaction,[28] enyne cross-metathesis,[29] and reaction of dihydropyran with anilines are some of these.[30] Radomir Jasiński et.al studied that the mechanistic aspects of cycloaddition reactions involving conjugated nitroalkenes.[31] Also Agnieszka Kąckaa and Radomir Jasińskia et.al showed that in the presence of ethylammonium cation, a nitroethyl benzoates decomposition process is expected to take place much faster than under “conventional” (non-catalyzed) conditions.[32]

But most methods have certain limits in terms of their application and reaction circumstances; these include handling hazardous and toxic compounds, estimating the cost of commercial processes, having longer reaction times, having challenging workup processes, and producing yields that are not up to par. consequently, the development of a catalytic process that overcomes these limitations and is simultaneously more effective and profitable.

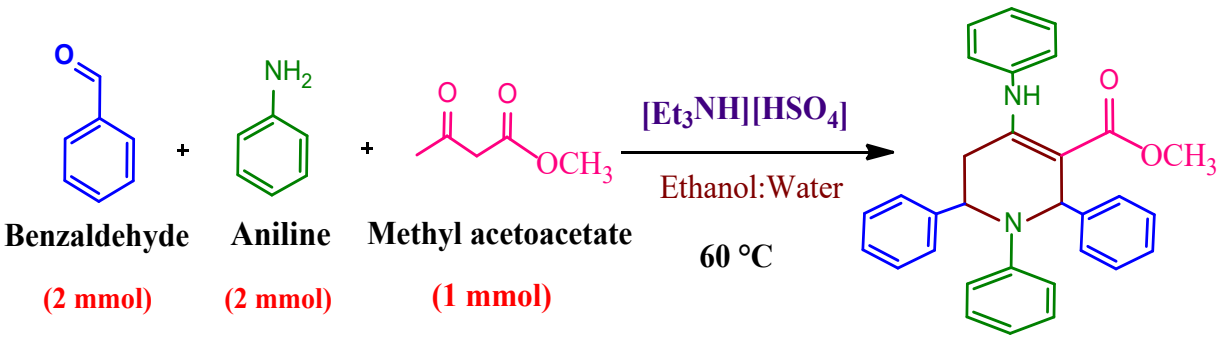
Here, we provide the unique synthesis methods for 1, 2, 5, and 6-substituted tetrahydropyridine derivatives that are catalyzed by $[Et_3NH][HSO_4]$ ionic liquid and are carried out in a one-pot multicomponent green solvent medium. applicability of ionic-liquid as a green and inexpensive catalyst with good recyclability and compatibility with a broad range of functional group having heteroatom, electron-withdrawing, and electron-releasing groups manifested the sustainability, eco-friendliness, and efficiency of the present methodology. These days, there is a desire for rate increases and cleaner

reactions with the goal of green chemistry and environmentally friendly technologies. Reusable catalysts are used in organic synthesis to maximize efficiencies and reduce hazardous waste.

2. Results and discussion

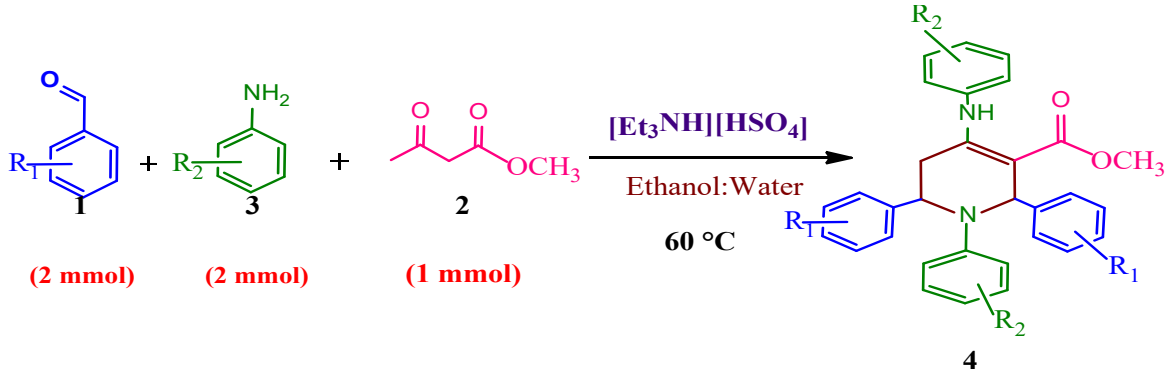
Using inexpensive ingredients N,N Diethylethanamine (Et3N) and sulfur dioxide (H2SO4), as well as a neutralization procedure, it was first possible to quickly synthesize triethylammonium hydrogen sulfates [Et3NH][HSO4] ionic liquid in this study without the need for a solvent. The low price is a result of the use of mild, non-volatile compounds, non-corrosive acidic ionic liquids, and affordable amine and acid.

Subsequently, a model reacts consisting of benzaldehydes and the methyl acetoacetate reacted with aniline compounds in the presence of triethylammonium hydrogen sulfates [Et3NH][HSO4] ionic liquid as a catalyst was carried out under various conditions in order to find a systematic and environmentally friendly procedure to synthesize 1, 2, 5, 6-substituted tetrahydropyridine derivatives **(Scheme 1).**



Scheme 1. Schematic representation of triethylammonium hydrogen sulfate [Et_3NH][HSO_4] ionic liquid catalyzed the synthesis of methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate.

First, we worked on screening a number of solvents, such as water, acetonitrile (CH3CN), dichloromethane (CH2Cl2), ethanol (EtOH), acetone (CH3COCH3), methanol (MeOH), chloroform (CHCl3), and dichloromethane (CH2Cl2) (**Table 1**, entries 1–10 and 13-17). solvent free condition in (**Table 1**, entries 11–12) and in the presence of an azeotropic mixture (ethanol: water) (**Table 1**, entries 14–17). As indicated in (**Table 1**, entry 16), these data show that a satisfactory yield was attained under azeotropic combination (ethanol: water) circumstances; it is due to azeotropic mixture enhancing solubility or promoting better interaction between the catalyst and reactants. Another key variable in this reaction was the reaction temperature; at higher temperatures, the compounds undergo chemical degradation and that was observed on TLC analysis. As a result, we made an effort to maximize the model reaction's reaction temperature and demonstrated that at 60°C, the maximum yield in the quickest response time was attained. A closer look has also been given to the impact of catalyst in the amount (**Table 1**, entries 16). Note that even though 10 mol% of catalyst had the ability for catalyzing a reaction, Thus, it's possible that condensation would not have happened in the absence of the catalysts (**Table 1**, entries 1-3). After obtaining these intriguing results, we looked into the applicability of the current method using a variety of aromatic aldehydes **1** and methylacetoacetate **2**, along with aromatic amines **3** that had both electron-withdrawing and electron-releasing compounds on the aromatic ring. As indicated in (**Scheme 2)** 1, 2, 5, 6-substituted tetrahydropyridine derivatives 4a–o were synthesized with the help of (-Cl,-F,-Br,-Ome,-Me,-CF3) as well as aromatic heteroamines.



Scheme 2. Schematic representation of triethylammonium hydrogen sulfate [Et_3NH][HSO_4] ionic liquid catalyzed the synthesis of 1, 2, 5, 6-substituted tetrahydropyridines derivatives.

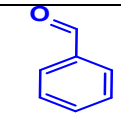
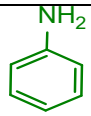
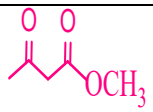
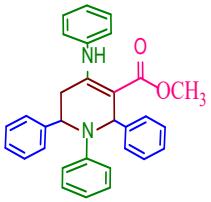
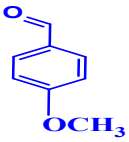
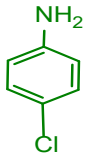
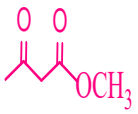
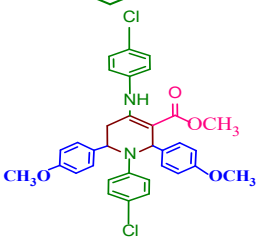
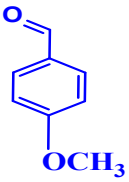
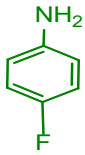
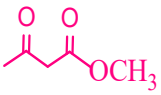
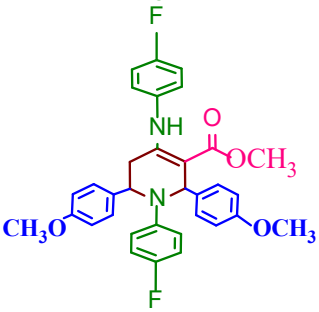
Table 1. Exploring optimal reaction parameters for the synthesis of methyl 1, 2, 6-triphenyl-4-(phenyl amino)-1, 2, 5, 6 tetrahydropyridines 3-carboxylate.

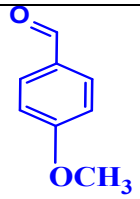
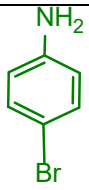
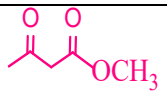
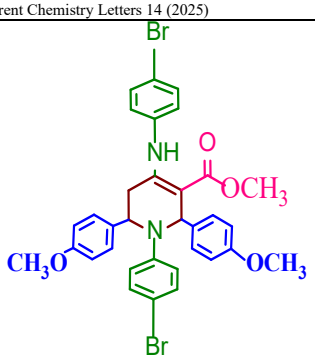
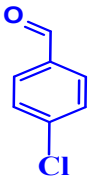
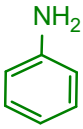
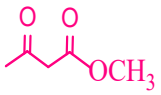
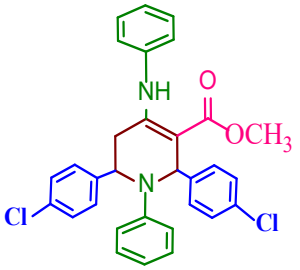
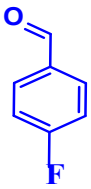
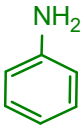
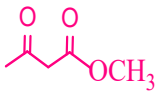
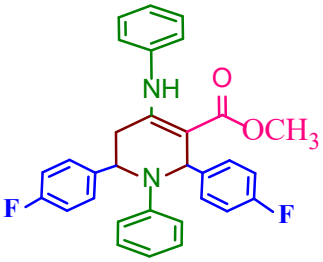
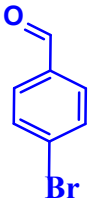
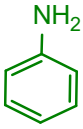
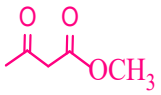
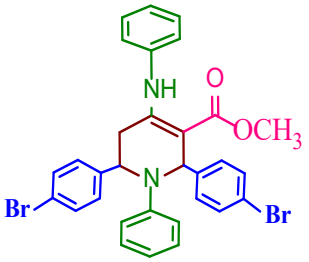
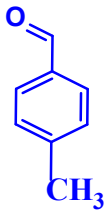
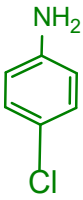
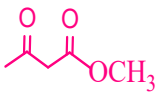
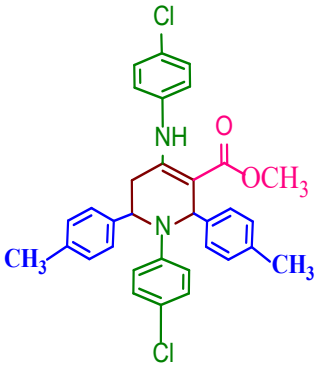
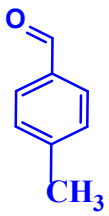
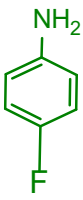
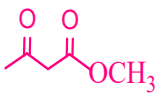
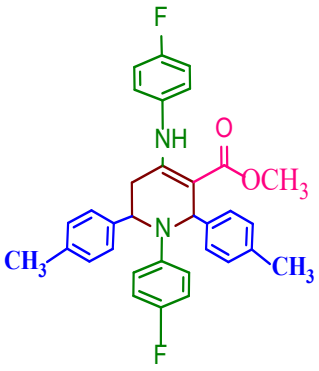
Entry	Catalyst, solvent and temperature [a]	Time	Yield (%)
1	Catalyst-free, CH_3CN, 85°C	24 h	Trace
2	Catalyst-free, EtOH, 80°C	24 h	Trace
3	Catalyst-free, Water, 100°C	24 h	Reaction not proceeds
4	[Et3NH][HSO_4] (2.5 mol%), EtOH, 80°C	8 h	45
5	[Et3NH][HSO_4] (2.5 mol%), CH_3CN, 85°C	8 h	40
6	[Et3NH][HSO_4] (2.5 mol%), MeOH, 65°C	8 h	42
7	[Et3NH][HSO_4] (2.5 mol%), $CHCl_3$, 65°C	8 h	34
8	[Et3NH][HSO_4] (2.5 mol%), CH_2Cl_2, 45°C	8 h	26
9	[Et3NH][HSO_4] (2.5 mol%), THF, 70°C	8 h	38
10	[Et3NH][HSO_4] (2.5 mol%),CH_3COCH_3,60°C	8 h	38
11	[Et3NH][HSO_4] (2.5 mol%), Solvent-free, RT	5 h	55
12	[Et3NH][HSO_4] (5 mol%), Solvent-free, 60°C	3 h	62
13	[Et3NH][HSO_4] (5 mol%), EtOH, 80°C	3 h	68
14	[Et3NH][HSO_4] (5 mol%), EtOH: water 80°C	3 h	78
15	[Et3NH][HSO_4] (5 mol%), EtOH: water, 60°C	2 h	85
16	[Et3NH][HSO_4] (10 mol%), EtOH: water, 60°C	1 h	94
17	[Et3NH][HSO_4] (10 mol%), EtOH: water, RT	8 h	68

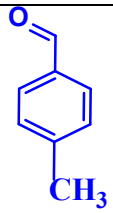
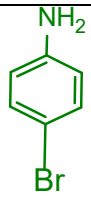
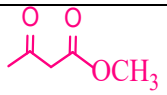
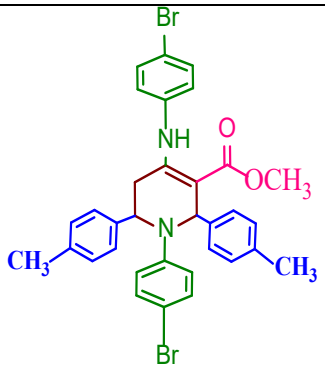
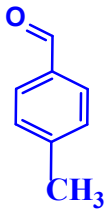
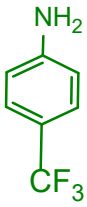
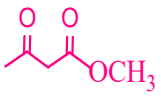
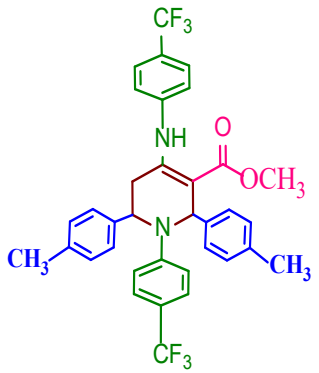
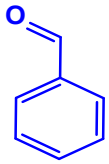
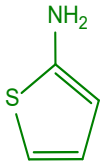
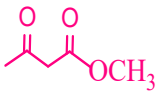
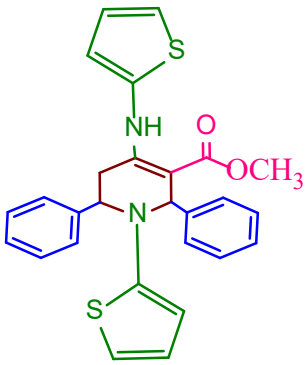
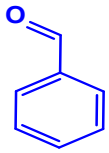
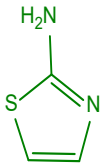
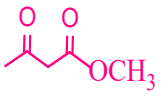
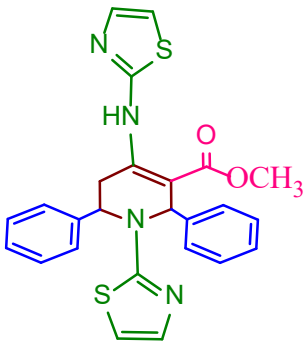
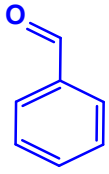
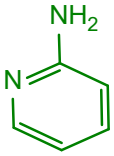
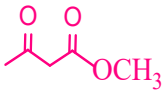
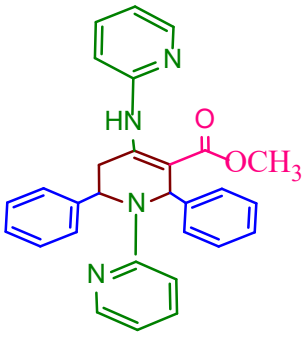
[a] Benzaldehyde (2 mmol), Methyl acetoacetate (1 mmol), Aniline (2 mmol).

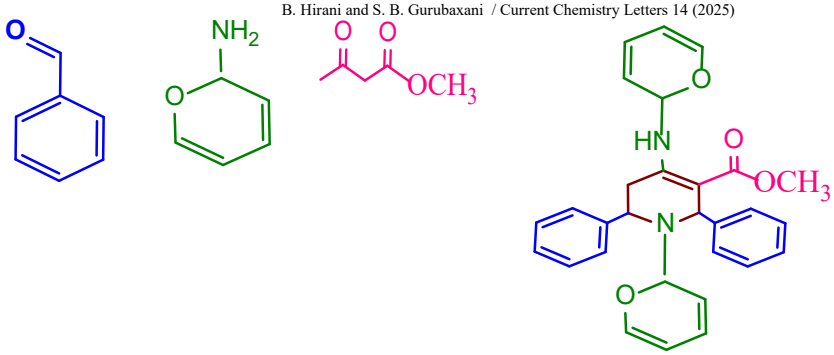
Results of this study are summarized in **Table 2**. relationships between the synthetic ring's substituents and ones like CF3 group (**Table 2**, entry 11). Because CF3 is a bulkier group and this group is electronegative and withdraws electrons, which slows down reactions and the product yield was only modest. However, our study found that heteroatom-containing amines provided medium to good yield (**Table 2**, entry 12–15) because heterocyclic amines have basic nitrogen atoms and are less reactive to electrophilic substitution than benzene rings. All the compounds were characterized using ^{1}H-NMR, ^{13}C-NMR, FTIR, and M.P. By comparing the physical and spectroscopic attributes of the known compounds with those found in the literature, the relative anti-configuration of the end product was verified[32, 33, 34].

Table 2. Synthesis of 1, 2, 5, 6-substituted tetrahydropyridine derivatives **4a-o**.

Entry	Aldehydes	Amines	MAA[b]	Product [a]	Structures	Yield in %
1					**4a**	**94**
2					**4b**	**91**
3					**4c**	**94**

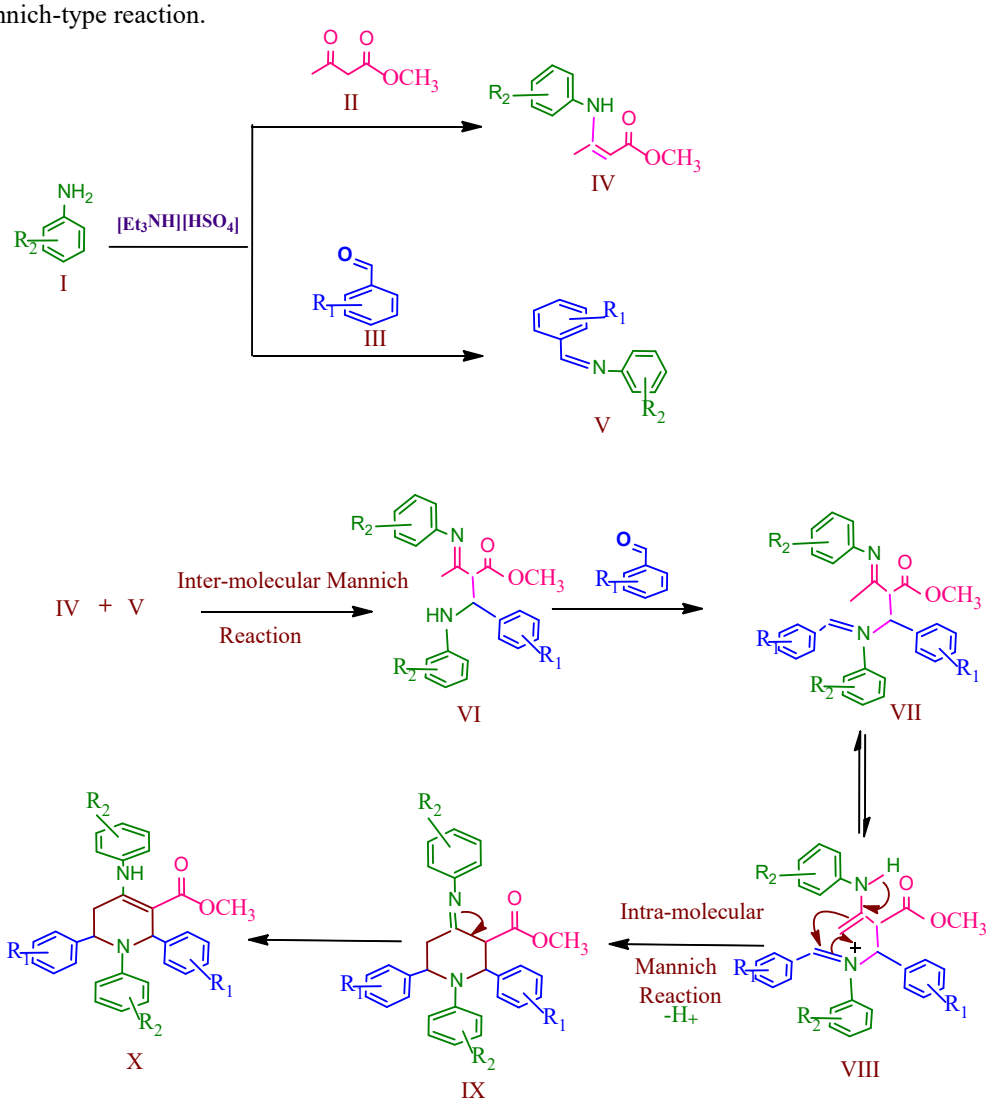
4					**4d**	**89**
5					**4e**	**96**
6					**4f**	**96**
7					**4g**	**94**
8					**4h**	**93**
9					**4i**	**91**

10					**4j**	**90**
11					**4k**	**84**
12					**4l**	**86**
13					**4m**	**83**
14					**4n**	**89**

15				4o	85

[a] Reagents and conditions : Aldehydes (2mmol) and [b] Methyl acetoacetate (1 mmol) with Amines (2 mmol), Ethanol: water (1:1) 10 ml, [Et3NH][HSO4] (10 mol%), at 60°C in 1 hr.

Scheme 3 shows a probable biochemical approach of this five-component reaction that is equivalent to the started mechanism described in the literature[35, 36, 37]. According to the mechanism explained, aniline (I), β-ketoester (II), and the aromatic aldehyde (III) condensed to create enamine (IV) and imine (V), with a catalytic quantity of 10 mol% [Et3NH][HSO4] starting the process. After that, enamine (IV) and imine (V) undergo an intermolecular Mannich-type reaction that produces intermediate (VI). The intermediate (VI) is produced when the intermediate (VII) and the second aromatic aldehyde molecule undergo a process known as condensation. After tautomerization, the intermediate (VII) yields intermediate (VIII), which follows a conversion into the required functionalized tetrahydropyridine derivatives (X) by an intramolecular Mannich-type reaction.



Scheme 3. Plausible mechanism for the formation of 1, 2, 5, 6-substituted tetrahydropyridines derivatives.

The literature method for the synthesis of 1, 2, 5, 6-substituted tetrahydropyridine derivatives is summarized in **(Table 3)** It was observed that previous methods require higher temperatures, longer reaction times, and tedious

procedures for the preparation of the catalyst. The present method offers shorter reaction times, operational simplicity, and good to excellent yields and shows extensive substrate ranges with high functional group tolerance. [Et_3NH][HSO_4] was found to be an inexpensive, safer, and eco-friendly catalyst as well as a reaction medium.

Table 3. Comparative Study with a reported method for the synthesis of 1, 2, 5, 6-substituted tetrahydropyridine derivatives

Entry	catalyst and solvent	temperature	time (min)	Yield (%)	References
1	[Bmim]Br, solvent-free	80 °C	4–5 h	72–90	33
2	[Et_3NH][HSO_4], Ethanol: water (1:1)	60 °C	1 h	85–96	this work

Using aniline, methyl acetate, and benzaldehydes as model substrates, the reusability of the catalyst is investigated from a perspective of green chemistry. Thin layer chromatography (TLC) was used to monitor the reaction; once it finished, the solid result was filtered and given an ethanol wash. The catalyst was retrieved by evaporating the filtrate. After being dried and cleansed with methanol, the recovered catalyst was employed again in the same reaction under ideal circumstances. The catalyst's recyclability was investigated for three consecutive cycles with yields that cover 96% to 84%. It was decreased, due to more hydrated catalyst during reaction and reaction taking longer with each cycle. **(Fig. 2).**

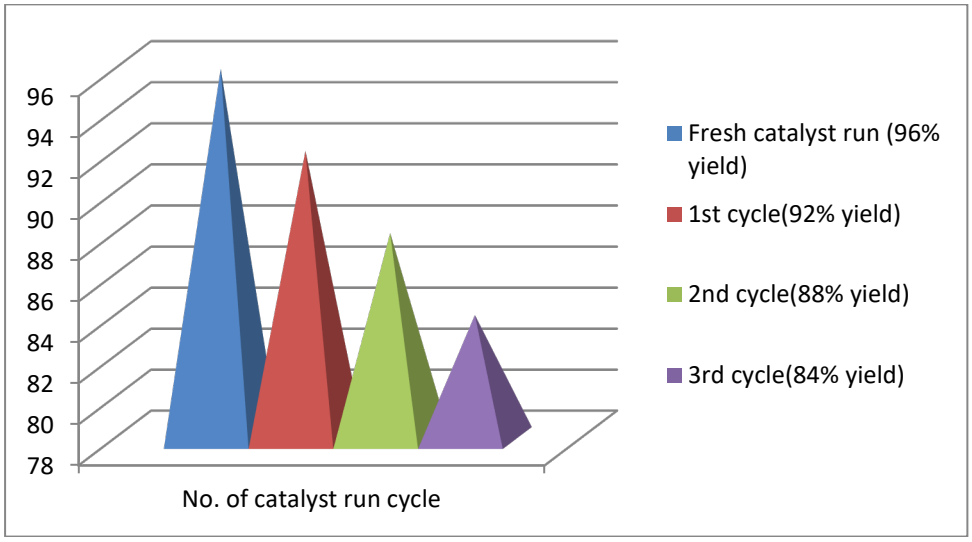


Fig. 2. Reusability of catalyst.

3. Experimental

General

Using DMSO-d6 and CDCl3 as solvents and TMS as the internal standard substance, IR spectra were recorded on a Bruker Alpha II FTIR-spectrometer, while 1H and 13C NMR were recorded on a Bruker AC 400 spectrometer operating at 400 MHz for 1H and 100 MHz for 13C. The uncorrected melting points (°C) achieved from the Labtronics digital melting point of the device had been measured in open glass capillaries.

The general procedure to prepare the ionic liquid triethylammonium hydrogen sulfate [Et3NH][HSO4]

After an hour at 0–5 °C, 19.6 g, 0.2 mol of sulfuric acid (98%), was added to the 20.2 g, 0.2 mol of triethylamine. That follows the addition, and the reaction mixture became agitated for another one hour at 70°C to make sure the reaction was complete. After that, the residue was heated to 80°C under strong vacuum until the residue's weight did not alter in order to eradicate the water particles. 39.6 g of [Et3NH][HSO4] yielded 99%. The synthesized [Et3NH][HSO4] IL is Brownish orange solid was characterized by melting point is 82.5-83.5ºC , FT-IR,^{1}H and ^{13}C NMR spectrum and its acidity was determined by pH is 4.1 of its 0.1 mM solution in H2O.

General procedure for the synthesis of derivatives of 1, 2, 5, 6-tetrahydropiridines 4a–o

A mixture of various aromatic compounds (2 mmol), different aromatic aldehydes (1 mmol), methyl acetoacetate (3 mmol), in ethanol: water (1:1) 10 ml was prepared as followed by [Et3NH][HSO4] (10 mol%) ionic liquid as an catalyst. Stirred for the one-hour reaction time at 60°C, was included in (**Table 2**, entry 1-15). The solid product was collected by filtration after the reaction finished, which was monitored by TLC (n-hexane/acetone, 10:1). Cool methylene dichloride (5 mL) was added after the ethanol disappeared and the catalyst was recovered; the mixture was then washed with ethanol and purified by recrystallization from ethanol: ethyl acetate (2:1). to obtain the most ultimate derivatives of 1, 2, 5, and 6-tetrahydropiridines 4a-o.

Methyl-1-(4-chlorophenyl) 4-(amino (4-chlorophenyl)) -2, 6-bis (4-methoxyphenyl) -1, 2, 5, 6 Tetrahydropyridine-3-carboxylate (4b).

This solid white appearance. M.P.: 242-244 °C, Yield=91%, FTIR (KBr) v, cm-1: 3020 (NH), 1656 (C=O), 1H NMR (400 MHz, CDCl3): δ 2.68-2.71 (m, 1H), 2.81-2.84 (m, 1H), 3.78 (s, 6H), 3.92 (s, 3H), 5.03 (br s, 1H), 6.20-6.38 (m, 5H), 6.80-6.81 (m, 3H), 7.12-7.26 (m, 9H), 10.20 (s, 1H), 13C NMR (100 MHz, CDCl3), 25°C): δH=13.4(OCH3), 33.6(C5), 55.1(C6), 58.2(C2), 98.2(C3), 113.0,116.1,126.7,126.4,126.6, 128.9, 142.8, 144.1, 147.0, 156.1 (C4, C-Ar), 168.2(CO).

4. Conclusion

In summary, an easily understood, reliable protocol has been constructed for the one-pot multicomponent synthesis to produce a highly tailored novel tetrahydropyridine framework that has therapeutic value. This can be produced throughout a five-component tandem reaction that involves aromatic aldehydes, methylacetoacetate, and aromatic amines at 60 °C, together with the help of triethylammonium hydrogen sulfate [Et3NH][HSO4] Bronsted acid ionic liquid as a catalyst. This protocol's key advantages are affordable starting materials, catalysts that are harmless for the environment, steer clear reaction profiles, mild reaction conditions, good to better yield, operational simplicity, and a clever work-up strategy.

Author Contributions

Bhavesh Hirani: Concepts, assumptions, methods, literature background, as well as structure. Dr. Sevak B Gurubaxani**:** Edition and review

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