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Design of ionic liquid sulfonic acid pyridinium hydrogen sulfate as an efficient, eco-friendly, and reusable catalyst for one-pot synthesis of highly functionalized tetrahydropyridines

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Abstract Novel ionic liquid sulfonic acid pyridinium hydrogen sulfate ([Pyridine-SO_3H]HSO_4) is synthesized and characterized by various techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, TG, DTG, as well as mass spectra. This ionic liquid is used as an efficient, homogeneous, and recyclable catalyst for one-pot synthesis of highly functionalized tetrahydropyridines from the three-component condensation of aromatic aldehydes, ethyl acetoacetate, and substituted anilines under solvent-free conditions. The main advantages of this protocol are the short reaction time, high yields, mild and clean conditions, and several reuse times without noticeably decreasing the catalytic activity.

Keywords One-pot · Sulfonic acid pyridinium hydrogen sulfate · Tetrahydropyridines · Solvent-free conditions · Multicomponent reaction

Introduction

Multicomponent reactions (MCRs) provide a variety of complex molecules through one-step condensation of three or more starting materials. They reduce chemical waste, are ease of separation and operation time, while being atom economic [1–3]. Among the different multicomponent reactions, the condensation of an aldehyde (2 mmol), an amine (2 mmol), and a β-keto ester (1 mmol) is one of the best examples, where tetrahydropyridines are produced as the main products. Tetrahydropyridine derivatives are found in a wide spectrum of natural products (e.g., alkaloids), pharmaceuticals, biologically active, and synthetic compounds [4–6]. They have been shown to have a wide range of biological activities, such as anti-

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hypertensive [7], anti-bacterial [8], anti-convulsant, anti-inflammatory activities [9] and antimalarial activities [10].

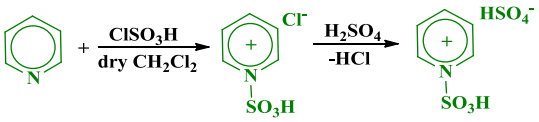
In recent years, various methods have been developed for the synthesis of functionalized piperidines in the presence of catalysts such as $InCl_3$ [11], L-proline/TFA [10], tetrabutylammonium tribromide (TBATB) [5], 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]) [12], $ZrOCl_2.8H_2O$ [13], $Bi(NO_3)_3.5H_2O$ [14], trityl chloride (Ph_3CCl) [15], cerium ammonium nitrate (CAN) [16], $Ni(ClO_4)_2.6H_2O$ [17], $BF_3.SiO_2$ [18], $Al(H_2PO_4)_3$ [19], molecular iodine (I_2) [20], $Ce(OTf)_4$ [21] and $FeCl_3/SiO_2$NPs [22]. However, most of these methods suffer from various disadvantages such as long reaction times, use of toxic metals or of volatile organic solvents, un-recyclable catalysts, low yields, tedious work-up procedure, and harsh reaction conditions. Therefore, to overcome these limitations, the development of a process without a solvent, efficient, mild and green is needed for the synthesis of these valuable compounds. Recently, the use of ionic liquids (ILs) as eco-friendly solvents, catalysts, and reagents in organic reactions has attracted much attention from researchers due to their unique advantages such as high thermal and chemical stability, low vapor pressure, lack of flammability, ability to dissolve a wide range of materials, insolubility in nonpolar solvents, and ease of recyclability [23–28].

In continuation of our interest in developing green protocols for the synthesis of tetrahydropyridines [29, 30], we report herein from three-component coupling reaction of aromatic aldehydes, aromatic amines, and ethyl acetoacetate by using novel ionic liquid sulfonic acid pyridinium hydrogen sulfate ([Pyridine–SO_3-H]HSO_4) as an eco-friendly solvent and as a reusable, efficient, and homogeneous catalyst for the synthesis of highly tetrahydropyridines at 100 °C under solvent-free conditions (Scheme 1 and 2).

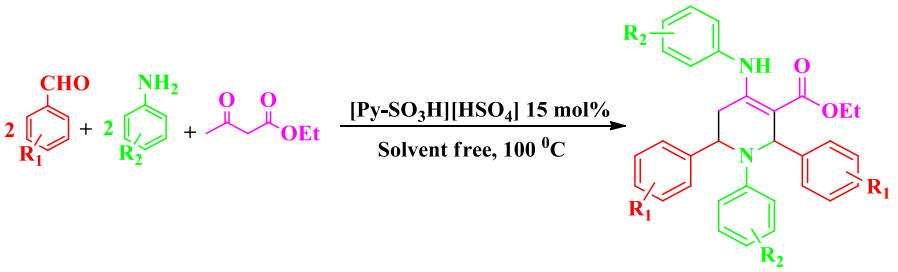
Experimental

General

All reagents were purchased from Merck and Aldrich companies, and used without further purification. All yields refer to isolated products. Progress of the reactions was monitored by thin-layer chromatography (TLC) using silica gel SIL G/UV 254 plates. Melting points were recorded on an Electrothermal type 9100 apparatus without correction. Fourier transform infrared (FT-IR) spectra were recorded on an Avatar 370 FT-IR Thermo-Nicolet spectrometer using pressed KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at



Scheme 1 The synthetic scheme of sulfonic acid pyridinium hydrogen sulfate preparation



Scheme 2 The three-component reaction of functionalized piperidines synthesis

400 and 100 MHz, respectively, and the chemical shifts are expressed in δ parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. The abbreviations used are: singlet (s), doublet (d), triplet (t), and multiplet (m). Thermal gravimetry (TG) and differential thermal gravimetric (DTG) of the ionic liquid was studied at the range of 25–600 °C, with a temperature increase rate of 10 °C min^{-1} in a argon atmosphere on a Bahr STA 503 apparatus. Mass spectra were obtained on a Varian Mat CH-7 at 70 eV. The element analyses (C, H, N) were obtained from a Thermo Finnigan Flash EA microanalyser.

Preparation of the ionic liquid

Chlorosulfonic acid (0.70 g, 6.0 mmol) was added dropwise to a stirred solution of pyridine (0.474 g, 6.0 mmol in dry CH_2Cl_2 (20 ml) over a period of 5 min in an ice bath. After the addition was completed, the reaction mixture was stirred for 60 min, and then sulfuric acid (0.588 g, 98 %, 6.0 mmol) was added dropwise over a period of 3 min at room temperature, followed by stirring for three more hours under nitrogen to remove the produced HCl, and subsequent heating for 1 h at 50 °C, and CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3 × 20 ml) [31], and dried under vacuum to give sulfonic acid pyridinium hydrogen sulfate as a viscous pale yellow oil (1.98 g, 97 % yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (t, $J = 7.45$ Hz, 2H), 8.64 (t, $J = 7.81$ Hz, 1H), 8.93 (d, $J = 5.76$ Hz, 2H), 11.61 (s, 1H), 13.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.79, 142.98, 148.21; IR (Nujol): 576, 886, 1,003, 1,069, 1,174, 1,329, 1,530, 1,631, 2,496–3,420 cm^{-1}; MS (EI, 70 eV): $m/z = 258$ (M^++1); 257 (M^+); 160 (M^+-SO_4H), 176 (M^+-SO_3H), and 79 (M^+-SO_3H and SO_4H) as well.

General procedure for the preparation of functionalized piperidines (4a–r)

In a 10-ml round-bottom flask equipped with a condenser, a mixture of the aromatic amine (2 mmol), ethyl acetoacetate (1 mmol), and [Pyridinium-SO_3H]HSO_4 (0.0,385 g, 15 mol %) was stirred at 100 °C for 10 min. Afterwards, the aromatic aldehyde (2 mmol) was added, and the resulting mixture was kept under stirring for the specified time in Table 3, the progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was cooled to room

temperature, extracted by the warm EtOAc (10 ml) to separate the catalyst. EtOAc was removed and the crude product was recrystallized from aqueous ethanol (96 %) to afford the pure product, which required no further purification. The recovered catalyst was washed with EtOAc (2 × 10 ml), dried, and reused, without considerable catalytic activity decrease.

Spectral data of the selected products

Ethyl-(3-bromophenyl)-4-(3-bromophenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6 tetrahydropyridine-3-carboxylate (4n)

White solid; m.p: 183–185 °C; IR (KBr): 3,237, 3,056, 2,966, 2,855,1,647, 1,604, 1,451, 1,372, 1,252, 1,071 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.50 (3H, t, $J = 7.5$ Hz, CH_3), 2.71 (1H, dd, $J = 14.6$, 2.7 Hz, C_5–H′), 2.79 (1H, dd, $J = 14.6$, 5.4 Hz, C_5–H″), 4.32–4.37 (1H, m), 4.44–4.50 (1H, m), 5.09 (1H, m, C_6–H), 6.30 (1H, s), 6.37–6.43 (4H, m), 6.61 (1H, s, C_2–H), 6.78 (2H, d, $J = 7.6$ Hz), 6.90–7.30 (9H, m), 10.30 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.97, 34.58, 55.89, 58.59, 61.36, 99.61, 112.8, 116.75, 120.98, 123.64, 124.51, 125.42, 128.68, 128.99, 128.18, 129.46, 129.95, 130.31, 131.25, 131.79, 133.64, 134.51, 140.1, 142.22, 142.53, 148.88, 156.05, 168.4; MS (EI, 70 eV): $m/z = 700$ [M^+]; Elemental analysis for: $C_{32}H_{26}Br_2Cl_2N_2O_2$: C, 54.81; H, 3.74; N, 3.99. Found: C, 54.65; H, 4.15; N, 4.05 %.

Ethyl-(4-bromophenyl)-4-(4-bromophenylamino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3carboxylate (4o)

White solid; m.p: 185 °C; IR (KBr): 3,239, 3,064, 2,979, 2,834, 1,647, 1,603, 1,462, 1,370, 1,248, 1,068 cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (3H, t, $J = 8.0$ Hz, CH_3), 2.70 (1H, dd, $J = 15.4$, 2.7 Hz, C_5–H′), 2.83 (1H, dd, $J = 15.4$, 5.6 Hz, C_5–H″), 3.79 (6H, s, OCH_3), 4.27–4.35 (1H, m, O–CH_2), 4.42–4.49 (1H, m, O–CH_2), 5.04 (1H, s, C_6–H), 6.20 (2H, d, $J = 6.0$, ArH), 6.29 (1H, s, C_2–H), 6.39 (2H, d, $J = 6.80$ Hz, ArH), 6.76–6.88 (5H, m, ArH), 7.04–7.24 (7H, m, ArH), 10.26 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.93, 34.73, 55.83, 56.4, 56.5, 58.8, 61.1, 100.2, 109.5, 114.9, 115.3, 115.8, 120.3, 128.3, 128.5, 128.7, 132.7, 133.1, 135.1, 136.2, 138.2, 147.1, 156.4, 159.4, 160.1, 169.3; MS (EI, 70 eV): $m/z = 692$ [M^+]; Elemental analysis for: $C_{34}H_{32}Br_2N_2O_4$: C, 58.97; H, 4.66; N, 4.05. Found: C, 59.16; H, 4.43; N, 3.89 %.

Ethyl-(3-iodophenyl)-4-(3-iodophenylamino)-2,6-bis(phenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4p)

White solid; m.p: 171–173 °C; IR (KBr): 3,252, 3,051, 2,986, 2,872, 1,652, 1,592, 1,448, 1,373, 1,253, 1,070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (3H, t, $J = 7.2$ Hz, CH_3), 2.72 (1H, dd, $J = 14.4$, 2.2 Hz, C_5–H′), 2.84 (1H, dd, $J = 14.4$, 5.4 Hz, C_5–H″), 4.30–4.33 (1H, m, O–CH_2), 4.40–4.48 (1H, m, O–CH_2), 5.08–5.18 (1H, m, C_6–H), 6.26–6.33 (1H, m, ArH), 6.37 (1H, s, C_2–H), 6.49 (1H, m, ArH),

6.63 (2H, t, $J = 7.0$ Hz, ArH), 6.76 (1H, t, $J = 7.5$ Hz, ArH), 6.85 (2H, d, $J = 7.2$ Hz, ArH), 6.94 (1H, d, $J = 6.0$ Hz, ArH), 7.15–7.29 (9H, m, ArH), 7.43 (1H, d, $J = 6.8$ Hz, ArH), 10.29 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 34.5, 56.2, 59.2, 61.1, 95.1, 96.5, 99.8, 113.5, 122.7, 126.3, 126.5, 127.3, 127.3, 127.6, 127.8, 128.7, 129.6, 130.2, 131.5, 135.5, 136.1, 140.2, 142.9, 144.2, 149.3, 156.4, 169.2; MS (EI, 70 eV): $m/z = 726$ [M^+]; Elemental analysis for: $C_{32}H_{28}I_2N_2O_2$: C, 52.91; H, 3.89; N, 3.86. Found: C, 52.78; H, 3.65; N, 3.85 %.

Ethyl-(3-iodophenyl)-4-(3-iodophenylamino)-2,6-di(4-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)

White solid; m.p: 208–209 °C; IR (KBr): 3,239, 3,080, 2,978, 2,859, 1,647, 1,603, 1,454, 1,371, 1,255, 1,068 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.52 (3H, t, $J = 7.6$ Hz, CH_3), 2.28 (3H, s, CH_3 at phenyl), 2.37 (3H, s, CH_3 at phenyl), 2.68 (1H, dd, $J = 15.5$, 2.2 Hz, C_5–H′), 2.81 (1H, dd, $J = 15.5$, 5.6 Hz, C_5–H″), 4.34 (1H, m, O–CH_2), 4.47 (1H, m, O–CH_2), 5.05 (1H, d, $J = 2.5$, C_6–H), 6.23-6.83 (2H, m, ArH), 6.4 (1H, s, C_2–H), 6.47–6.51 (2H, m, ArH), 6.75–6.93 (4H, m, ArH), 7.03–7.44 (8H, m, ArH), 10.28 (1H, s, NH); Elemental analysis for: $C_{34}H_{32}I_2N_2O_2$: C, 54.13; H, 4.28; N, 3.71; Found: C, 54.19; H, 4.35; N, 3.52 %.

Ethyl-(3-iodophenyl)-4-(3-iodophenylamino)-2,6-bis(4-nitrophneyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4r)

Light yellow solid; m.p: 137–140 °C; IR (KBr): 3,246, 3,058, 2,979, 2,872, 1,652, 1,593, 1,448, 1,372, 1,253, 1,070 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.54 (3H, t, $J = 7.5$ Hz, CH_3), 2.8 (2H, d, $J = 15.2$ Hz, C_5–H′, H″), 4.34–4.47 (2H, m, O–CH_2), 5.25 (1H, m, C_6–H), 6.42–6.5 (2H, m, C_6–H, ArH), 6.75–6.8 (1H, m, ArH), 7.17(2H, m, ArH), 7.19 (2H, m, ArH), 7.48–7.63 (4H, m, ArH), 8.07–8.35 (10H, m, ArH), 8.52 (2H, d, $J = 8.5$, ArH), 10.28 (1H, s, NH); Elemental analysis for: $C_{32}H_{26}I_2N_4O_6$: C, 47.08; H, 3.21; N, 6.86; Found: C, 47.24; H, 3.35; N, 6.52 %.

Ethyl-(3-iodophenyl)-4-(3-iodophenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s)

White solid; m.p: 189–190 °C; IR (KBr): 3,234, 3,069, 2,956, 2,875,1,657, 1,604, 1,459, 1,375, 1,249, 1,075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (3H, t, $J = 7.5$ Hz, CH_3), 2.69 (1H, dd, $J = 14.6$, 2.7 Hz, C_5–H′), 2.82 (1H, dd, $J = 14.6$, 5.4 Hz, C_5–H″), 4.32–4.37(1H, m, O–CH_2), 4.44–4.50 (1H, m, O–CH_2), 5.06 (1H, m, C_6–H), 6.26 (1H, s, C_2–H), 6.37–6.46 (4H, m, ArH), 6.55 (1H, s, ArH), 6.74 (2H, d, $J = 7.6$ Hz, ArH), 6.93–7.24 (9H, m, ArH), 10.29 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 33.9, 55.4, 59.1, 61.9, 99.2, 113.4, 117.4, 121.7, 123.8, 124.2, 125.4, 128.4, 128.8, 129.2, 129.6, 129.9, 130.2, 131.4, 131.7, 133.9, 134.7, 141.4, 142.5, 142.8, 147.9, 155.8, 168.9; MS (EI, 70 eV): $m/z = 793$ [M^+]; Elemental analysis for: $C_{32}H_{26}Cl_2I_2N_2O_2$: C, 48.33; H, 3.30; N, 3.52. Found: C, 48.39; H, 3.21; N, 3.69 %.

Results and discussion

Characterization of the catalyst

After the preparation of sulfonic acid pyridinium hydrogen sulfate ionic liquid, [Pyridine–SO_3H]HSO_4 via the reaction of [Pyridine–SO_3H]Cl with sulfuric acid (Scheme 2), its structure was identified by FT-IR, ^{1}H NMR, ^{13}C NMR as well as mass spectra. The FT-IR vibrations at 1,329, 1,174, and 576 cm^{-1} are assigned to the asymmetric stretching, symmetric stretching, and bending of S–O modes of sulfonic acid and sulfate groups, respectively [28, 31]. The N–S stretching vibration was also appeared at 886 cm^{-1}. This specific infrared peak indicates the sulfonic group-pyridine connection. In addition, the presence of the sulfur–nitrogen bond in the ionic liquid increased the number of vibrational modes and changed the overall shape of the IR spectrum in comparison with the pure pyridine and sulfuric acid. The strong bands at 1,631 and 1,530 cm^{-1} arising from the pyridinium ring were also present. By comparison with SOH bending frequencies in sulfuric acid and other sulfonic acids, the bands at 1,003 and 1,069 cm^{-1} were assigned to SOH bending modes [32]. The Broad and strong bands at 2,496 to 3,420 cm^{-1} can be arisen by stretching the hydroxyl groups in the [Pyridine–SO_3H]HSO_4 ionic liquid (Fig. 1).

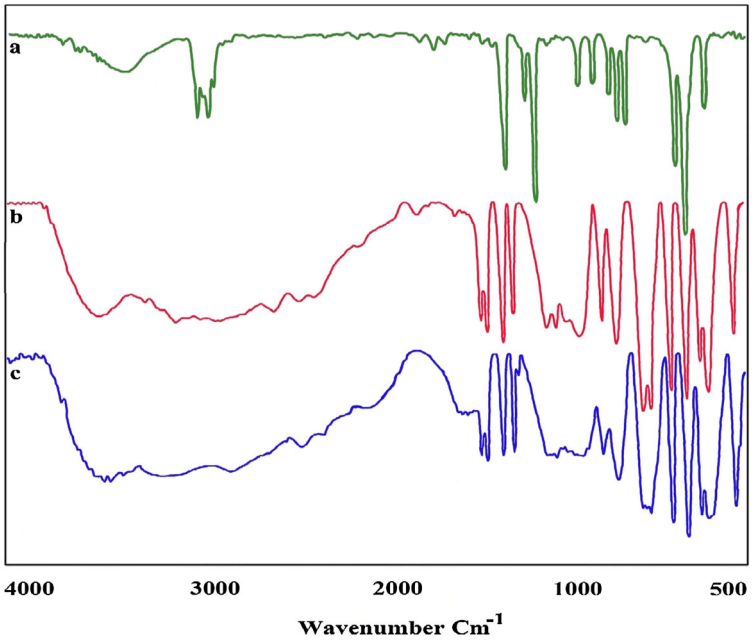


Fig. 1 FT-IR spectra of pyridine (*a*), sulfonic acid pyridinium chloride ([Pyridine–SO_3H]Cl) (*b*) and sulfonic acid pyridinium hydrogen sulfate ([Pyridine–SO_3H]HSO_4) (*c*)

The ^{1}H NMR and ^{13}C NMR spectra of the ionic liquid obtained in DMSO-d_6 are displayed in Figs. 2 and 3, respectively. The peaks at 13.86 and 11.61 ppm, are assigned to $–SO_3H$ and SO_4H^- protons, respectively. The assignment is based on the comparison with ^{1}H NMR spectra of, [Pyridine–SO_3H]Cl, $ClSO_3H$, H_2SO_4 and pyridinium chloride in DMSO-d_6 available in the literature [28]. The chemical shifts of the acidic hydrogens of H_2SO_4, [Pyridine–SO_3H]Cl, $ClSO_3H$ and pyridinium chloride are at 14.32, 13.67, 13.45, and 11.37 ppm, respectively. The ^{1}H NMR data of the ionic liquid are different from those in pyridine, $ClSO_3H$, H_2SO_4 and the intermediate [Pyridine–SO_3H]Cl. Moreover, while pyridine and $ClSO_3H$ are readily soluble in CH_2Cl_2, [Pyridine–SO_3H]Cl and [Pyridine–SO_3H]HSO_4 ILs are insoluble in CH_2Cl_2.

The mass spectrum of the [Pyridine–SO_3H]HSO_4 ionic liquid showed the correct molecular ion peak at 257. Other ion peaks are also observed at 258 (M^++1), 160 (M^+-SO_4H), 176 (M^+-SO_3H), and 79 (M^+-SO_3H and SO_4H) as well.

In order to obtain information on the thermal stability, thermogravimetry (TG) and differential thermogravimetry analysis (DTA) of the ionic liquid is investigated in 25–600 °C range, with a temperature increase rate of 10 °C min^{-1}, under the inert atmosphere of argon. The corresponding diagrams are depicted in Fig. 4. The first strong loss weight was observed after 135 °C and the second strong weight loss appears after 320 °C. Therefore, the molecular decomposition occurred for this catalyst after 135 °C.

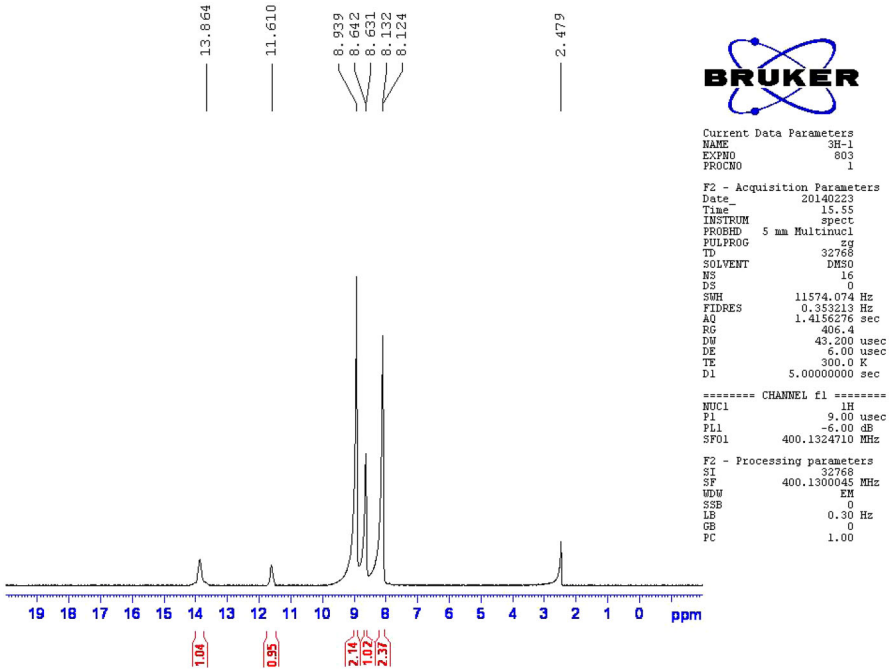


Fig. 2 The ^{1}H NMR spectrum of sulfonic acid pyridinium hydrogen sulfate

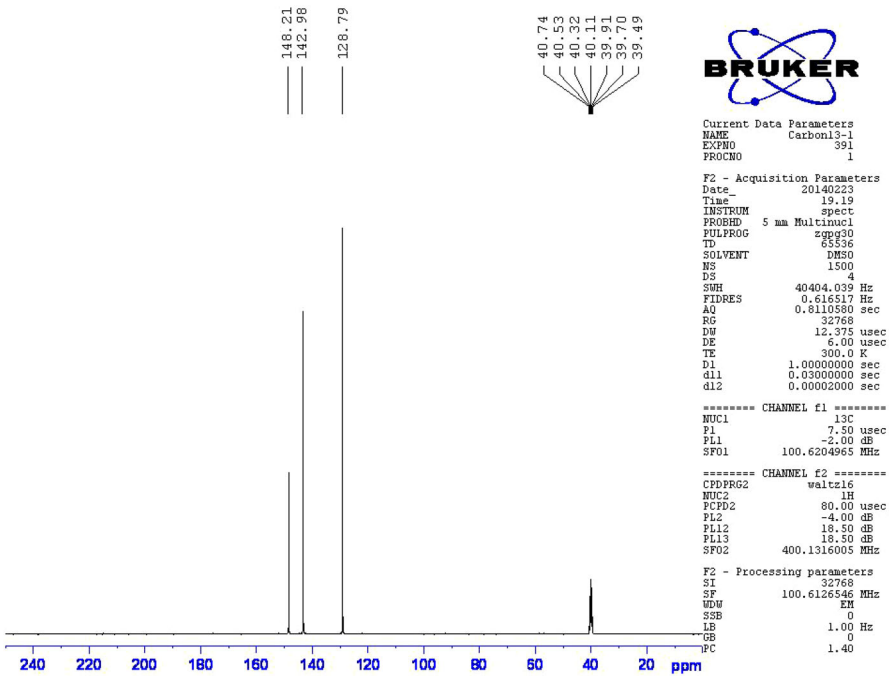


Fig. 3 The ^{13}C NMR spectrum of sulfonic acid pyridinium hydrogen sulfate

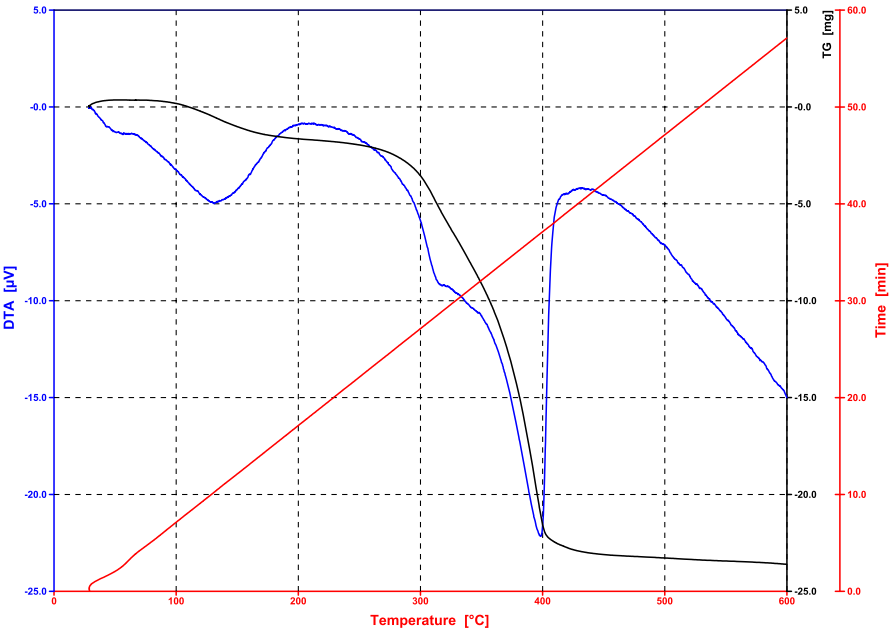


Fig. 4 The TG/DTG diagrams of [Pyridine–SO_3H]HSO_4

Application of [Pyridine–SO_3H]HSO_4 in the tetrahydropyridines synthesis

After characterization of the ionic liquid, we examined its efficacy to catalyze the synthesis of tetrahydropyridines. To optimize the reaction conditions, the condensation of 4-methyl benzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol) was studied in the presence of different amounts of [Pyridine–SO_3H]HSO_4 and [Pyridine–SO_3H]Cl at different temperatures ranging from 70–110 °C, under solvent-free conditions. The results are summarized in Table 1. The best results were obtained using 15 mol % of [Pyridine–SO_3H]HSO_4 at 100 °C (Table 1, entry 4). Increasing the amount of the catalyst, reaction time and temperature did not improve the results (Table 1, entries 5, 6, and 10). A control experiment was also done at 100 °C in the absence of our catalyst, which did not lead to noticeable product even after a long reaction time (Table 1, entry 1).

To investigate the effect of varying the solvent, the same reaction was carried out in different solvents, including EtOH, CH_3CN, THF, $CHCl_3$, CH_2Cl_2, and H_2O. As shown in Table 2, it was found that the reaction in ethanol lead to the highest yield compared to the other solvents. The non-occurrence of the reaction in other solvents may be due to the poor solubility of the ionic liquid. In the case of H_2O solvent, [Pyridine-SO_3H]HSO_4 was soluble in water, but the starting materials were not. Moreover, the catalyst hydrolyzes in the aqueous media.

After optimization of the reaction conditions, synthesis of a variety of functionalized piperidines was performed to explore the efficiency and the scope of the protocol. The corresponding results are depicted in Table 3. Various aromatic aldehydes containing either electron-withdrawing or electron-donating substituents successfully react with various anilines and ethyl acetoacetate to afford high to excellent yields of products and short reaction times.

Table 1 The effect of different amounts of catalysts and temperature on the synthesis of 4b[a]

Entry	Catalyst amount (mol %)	Temp. (°C)	[Pyridine–SO3H]HSO4		[PyridineSO3H]Cl	
			Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	–	100	480	Trace	480	Trace
2	5	100	36	36	54	25
3	10	100	36	71	54	53
4	15	100	36	93	54	80
5	20	100	36	93	54	79
6	25	100	36	91	54	77
7	15	70	36	62	54	45
8	15	80	36	75	54	63
9	15	90	36	80	54	70
10	15	110	36	79	54	71

[a] Reaction conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and ethyl acetoacetate (1 mmol)

[b] Isolation yield

Table 2 Synthesis of compound 4b[a] in the presence of [pyridine–SO_3H]HSO_4 (15 mol %) in different solvents

Entry	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)
1	EtOH	78	180	78
2	CH3CN	82	260	60
3	THF	66	480	25
4	CHCl3	62	420	Trace
5	CH2Cl2	40	460	Trace
6	H2O	100	600	–
7	Solvent-free	100	36	93

[a] Reaction conditions: 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), ethyl acetoacetate (1 mmol), [pyridine-SO_3H]HSO_4 (15 mol %)

[b] Isolation yield

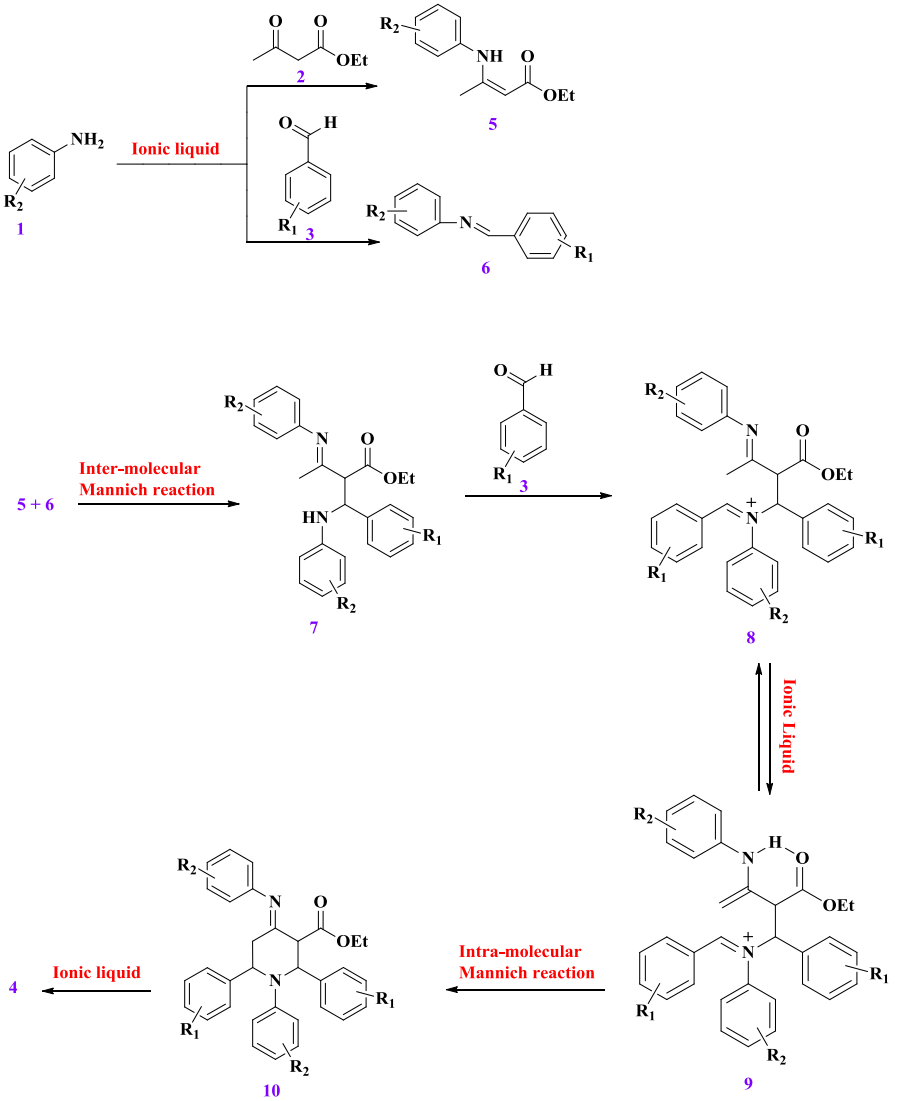
Table 3 Three-component reaction of various aldehyde, amines, and ethyl acetoacetate catalyzed by [Pyridine-SO_3H]HSO_4 for one-pot synthesis of highly functionalized tetrahydropyridine

Entry	R1	R2	Product	Time (min)	Yield[a] (%)	Mp (°C)	Lit. Mp (°C) [ref]
1	4-Cl	4-Me	4a	39	92	231–232	227–229 [14]
2	4-Me	H	4b	36	93	230–232	230–231 [16]
3	4-Me	4-OMe	4c	43	94	226–227	221–224 [16]
4	4-OMe	4-Cl	4d	35	90	176–177	180–181 [14]
5	4-Me	4-Cl	4e	39	86	219–220	218–220 [15]
6	4-NO2	H	4f	46	88	249–251	247–250 [16]
7	H	4-Br	4g	34	91	194–195	193–196 [15]
8	H	H	4h	41	84	178–179	175–176 [16]
9	4-Me	4-Br	4i	36	89	237–239	234–236 [15]
10	H	4-Me	4j	38	92	198–199	193–196 [15]
11	3-Me	H	4k	41	88	159–160	155–157 [15]
12	H	4-Cl	4l	36	93	199–201	201–202 [16]
13	H	4-OMe	4m	35	92	169–171	172–173 [16]
14	4-Cl	3-Br	4n	49	89	183–185	183–185 [30]
15	4-OMe	4-Br	4o	42	94	185	184–186 [29]
16	H	3-I	4p	46	87	171–173	170–172 [30]
17	4-Me	3-I	4q	42	90	208–209	205–207 [29]
18	4-NO2	3-I	4r	45	89	137–140	142–140 [29]
19	4-Cl	3-I	4s	41	87	189–190	.....

[a] Isolation yield

The structures of products (4a-r) were identified by comparison of their spectroscopic data and melting points with those of literature reports. Also, the structure of products (4n-s) was confirmed by elemental analysis and spectral data (FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy).

Our proposal for the condensation is shown in Scheme 3 [5, 12, 16]. Initially, the dehydration arylamine (1) and ethyl acetoacetate (2) gives the β-enaminone (5) in the presence of sulfonic acid pyridinium hydrogen sulfate, which also happens between aryl-aldehyde (3) and arylamine (1) to form imine (6). Next, the reaction between β-enaminone (5) and activated imine (6) in the presence of sulfonic acid pyridinium hydrogen sulfate as a Lewis acid via intermolecular Mannich reaction affords the intermediate (7). The reaction of the intermediate (7) with the second aryl-aldehyde produces another intermediate (8) by the loss of water. Intermediate



Scheme 3 Possible reaction mechanism for the piperidines condensation 4

Table 4 Comparison of the results of the condensation of benzaldehyde, ethyl acetoacetate and 4-chloroaniline in the presence of [Pyridine–SO_3H][HSO_4] with those obtained using other catalysts

Entry	Catalyst	Conditions	Time (h)	Yield[a] (%)	TOF[b] (h^{-1})	Ref
1	CAN	CH3CN, r.t	23	78	0.129	[16]
2	[Hpyro][HSO4]	EtOH, reflux	8	80	0.666	[12]
3	I2	MeOH, r.t	8	78	0.975	[20]
4	Al(H2PO4)3	EtOH, r.t	10	85	0.425	[19]
5	Ph3CCl	MeOH, 50 °C	5.5	80	0.666	[15]
6	TBATB	EtOH, r.t	9	70	0.777	[5]
7	BF3.SiO2	MeOH, 65 °C	8	71	0.591	[18]
8	Bi(NO3)3·5H2O	EtOH, r.t	12	80	0.666	[14]
9	Ni(ClO4)2.6H2O	EtOH, r.t	18	81	0.450	[17]
10	[Py–SO3H]HSO4	Solvent-free, 100 °C	36 min	93	10.333	–[c]

[a] Isolated yield

[b] Turn-over frequency

[c] This work

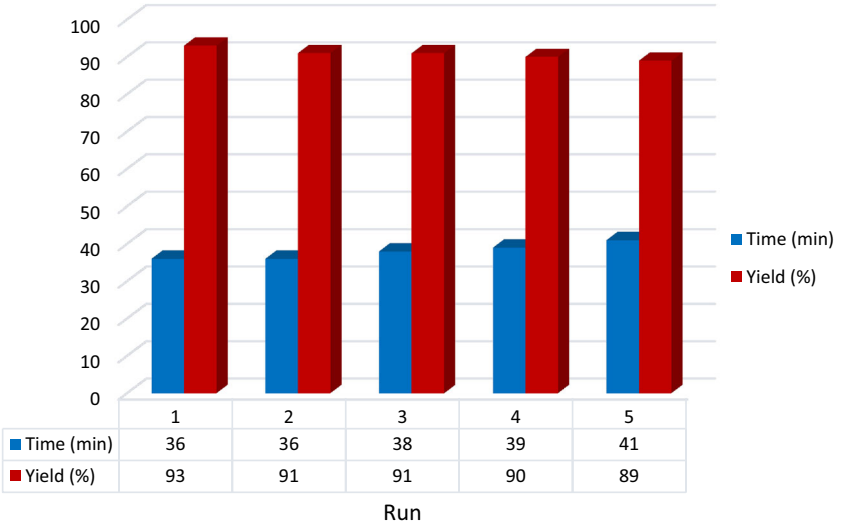


Fig. 5 The condensation of 4-methylbenzaldehyde with aniline and ethyl acetoacetate in the presence of reused [pyridine-SO_3H]HSO_4 (15 mol %) under solvent-free conditions at 100 °C

(8) tautomerizes to (9), which is stabilized by intramolecular hydrogen bonding. Then, intramolecular Mannich-type reaction forms the intermediate (10). Finally, due to conjugation with the ester group, the intermediate (10) tautomerizes to afford the final product (4).

To show the merit of the present work, we compared the results of our catalyst with some reported catalysts for the synthesis of functionalized tetrahydropyridine

derivatives. The results of these catalysts, which perform the one-pot multicomponent condensation of 4-methylbenzaldehyde, ethyl acetoacetate, and aniline have been tabulated in Table 4. As is shown, our catalyst has remarkably improved this in different aspects, for example reaction conditions, time, yield, and turn-over frequency (TOF). The present catalyst exhibited higher yields of products in shorter times, not requiring the use of organic solvents, and the TOFs were higher compared to the other reported system. Additionally, the present catalyst is more beneficial from economical and accessibility points of view and is stable both in air and water.

Reusability is one of the important properties of this catalyst. The recyclability of [Py–SO_3H][HSO_4] was investigated for the reaction upon the condensation of 4-methyl benzaldehyde, ethyl acetoacetate, and anilines. After completion of the reaction, the reaction mixture was extracted by the warm EtOAc and separated from the catalyst. We observed that the catalyst could be reused for the next cycle without any appreciable loss of its activity (Fig. 5).

Conclusions

In summary, we have developed a simple, inexpensive methodology comprising ionic liquid [Pyridine–SO_3H]HSO_4, as a green, highly efficient and homogeneous catalyst for the one-pot multicomponent condensation of aromatic aldehydes, aromatic amines, and ethyl acetoacetate for the synthesis of functionalized piperidines. The present methodology offers several advantages, including short reaction time, high yields, easy work-up procedures, mild reaction conditions, avoiding hazardous organic solvents, as well as being reusable several times without noticeably decreasing the catalytic activity.

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