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Design, preparation and characterization of new ionic liquid 1,3-disulfonic acid benzimidazolium chloride as an efficient and recyclable catalyst for the synthesis of tetrahydropyridine under solvent-free conditions

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In the present work, 1,3-disulfonic acid benzimidazolium chloride as a new ionic liquid, is synthesized, characterized by studying its FT-IR, ^{1}H NMR, ^{13}C NMR as well as mass spectra. This ionic liquid is used as an efficient, homogeneous and recyclable catalyst for synthesis of highly functionalized tetrahydropyridine via one-pot multi-component condensation of aromatic aldehydes, ethyl acetoacetate, and anilines under solvent-free conditions. The present synthetic route is a green protocol offering several advantages, such as high yield of products, shorter reaction time, mild reaction conditions, minimizing chemical waste and easy work-up procedures. Further, the catalyst could be reused and recovered at least four times without appreciable loss of activity.

Introduction

Over the past decade academia and industry have been working together in order to develop new greener alternative solvents.[1] The main aim is to reduce significantly the important drawbacks and hazards associated with traditional solvents, replacing them with safer and more efficient alternatives. In this regard, ionic liquids have attracted significant research interest in the context of green synthesis due to their adjustable physical and chemical properties.[2] They have been introduced as an alternative green reaction medium due to their exceptional features such as high thermal and chemical stability, low vapor pressure, non-flammability, non-volatile, large electrochemical window, potential recyclability and the ability to dissolve many organic and inorganic materials.[3,4] Ionic liquids also have various applications such as sensors, fuel cells, batteries, capacitors, thermal fluids, plasticizers, lubricants, extractants, extractants, and solvents in analysis, synthesis, catalysis, and separation.[5]

Multi-component reactions (MCRs), are excellent tools in modern organic synthesis and medicinal chemistry due to the product diversity, great efficiency, simple procedures, convergence, reduction in reaction steps and time savings.[6-8] One of the most representative examples of multi-component reactions is preparation of tetrahydropyridines. Tetrahydropyridine derivatives are among the most important classes of nitrogen-containing heterocycles, they are found in many natural products, pharmaceutical agents, and functionalized materials.[9-11] Tetrahydropyridines and compounds based on these core templates exhibit a wide range of biological activities such as anti-hypertensive,[12] neurotoxic activity,[13] anti-bacterial,[14] anti-convulsant, anti-inflammatory activities,[15] and antimalarial.[16] Although numerous methodologies have been for the synthesis of functionalized tetrahydropyridines by using $LaCl_3.7H_2O$,[17] L-proline/TFA ,[16] 1-methyl-2-oxopyrrolidinium hydrogen sulfate ([Hpyro][HSO_4]),[18] molecular iodine (I_2),[11] $ZrOCl_2.8H_2O$,[19] $Bi(NO_3)_3.5H_2O$,[20] SPINOL-phosphoric acids,[21] $BF_3.SiO_2$,[22] trityl chloride (Ph_3CCl),[23] nano-sphere silica sulfuric acid (NS-SSA),[24] cerium ammonium nitrate (CAN),[25] silica sulfuric acid (SSA),[26] citric acid,[27] L-proline nitrate,[28] and acetic acid.[29] Unfortunately, most of the reported methods suffer from one or more of the following drawbacks, such as longer reaction time, low product yields, use hazardous solvents or non-recyclable catalysts, harsh reaction conditions such as strong acids or elevated temperature and poor compliance with the green chemistry protocols. Due to these disadvantages of the existing methods, there have been increasing demands for more efficient, reusability and environmentally-benign methodologies for the synthesis of these high-value compounds. In continuation of our research on the development of eco‐friendly and sustainable methodologies via MCRs for the synthesis of tetrahydropyridines,[30-33] we report here synthesis of a new ionic liquid, 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl) as a highly efficient and green catalyst for the preparation of tetrahydropyridines via the one-pot three-components (in situ five components) reaction of anilines, ethyl acetoacetate and aromatic aldehydes under solvent-

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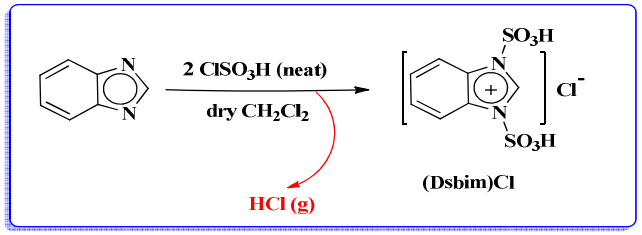
free conditions (Scheme 1). To the best of our knowledge, there seems to be no report on the synthesis of tetrahydropyridine derivatives by using ([Dsbim]Cl) ionic liquid as an eco-friendly catalyst. The homogeneous catalyst could be recovered easily and reused five times without significant loss of its catalytic activity.



Scheme 1. General formulation for the preparation of 1,3-disulfonic acid benzimidazolium chloride [Dsbim]Cl) and using it for the synthesis of functionalized tetrahydropyridines.

Results and discussion

Characterization of the catalyst

The structure of ionic liquid 1,3-disulfonic acid benzimidazolium chloride [Dsbim]Cl, was identified by FT-IR, ^{1}H NMR, ^{13}C NMR, as well as mass spectra. The corresponding FT-IR spectral data of benzimidazole and 1,3-disulfonic acid benzimidazolium chloride [Dsbim]Cl ionic liquid are presented in Fig. 1. The FT-IR spectrum of [Dsbim]Cl showed a broad and strong bands at 2536 to 3432 cm^{-1} related to the OH of the SO_3H groups.[34,35] Moreover, the two peaks observed at 1189 cm^{-1} and 1263 cm^{-1} correspond to the O–SO_2 symmetric and asymmetric stretching, respectively and other band at 1063 cm^{-1} is assigned to N–SO_2 stretching.[35] The symmetric N–S stretching vibration also appeared at 886 cm^{-1}.[36]

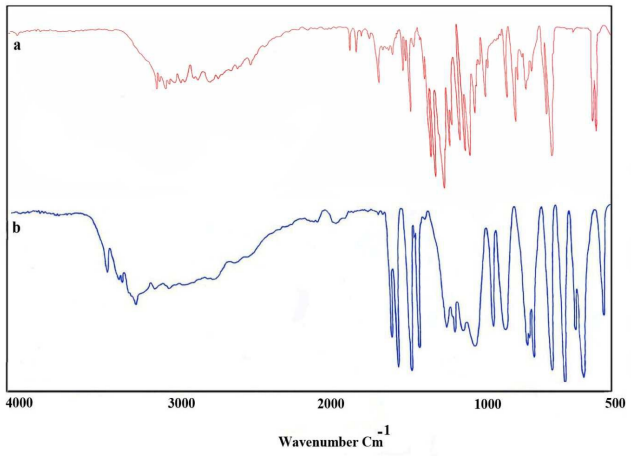


Fig.1. FT-IR spectra of benzimidazole (a) and 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl) (b).

The ^{1}H NMR and ^{13}C NMR spectra of the ionic liquid obtained in DMSO-d_6 are displayed in **Fig. 2** and **3**. Here, we study ^{1}H NMR data of the catalyst. The important peak of ^{1}H NMR spectrum of ionic liquid were related to the acidic hydrogens (SO_3H) which observed in 13.64 ppm. To confirm that this peak (13.64 ppm) is correctly related to the hydrogen of SO_3H in the compound, not hydrogen of $ClSO_3H$ (its unreacted starting material) in DMSO-d_6, we ran the ^{1}H NMR spectra of chlorosulfonic acid in DMSO-d_6 presented in literature [4]. In these spectra, the peaks of the acidic hydrogens of [Dsbim]Cl and $ClSO_3H$ were observed in 13.64 and 13.45 ppm, respectively. The difference between the peaks of the acidic hydrogens in ([Dsbim]Cl) and its starting materials confirmed that the peak observed in 13.67 ppm of the ^{1}H NMR spectra of [Dsbim]Cl is correctly related to the SO_3H group of this compound. Moreover, while benzimidazole and $ClSO_3H$ are readily soluble in CH_2Cl_2, ([Dsbim]Cl) ionic liquid is insoluble in CH_2Cl_2.

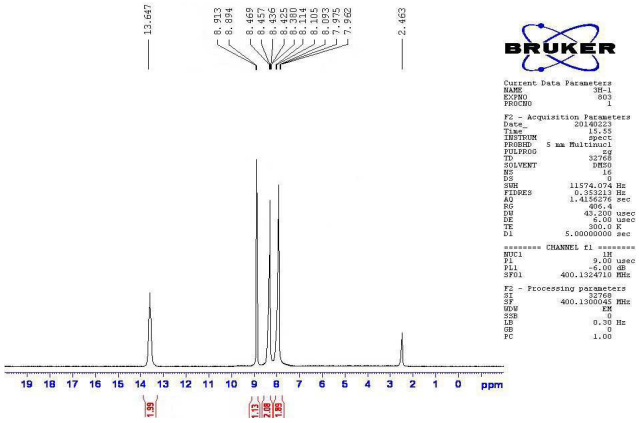


Fig. 2. ^{1}H NMR spectrum of 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl).

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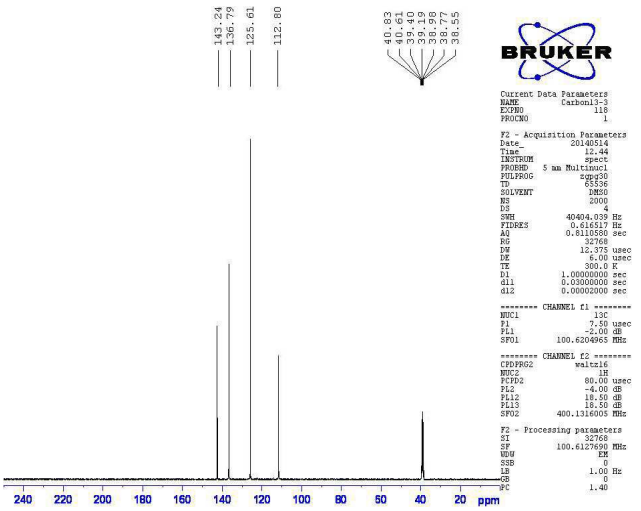

Fig. 3. The ^{13}C NMR spectrum of 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl).

The mass spectrum of the 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl) ionic liquid is shown in Fig. 4. In this spectrum the correct molecular ion peak appears at 314. Other ion peaks are also observed at 279 (M^+-Cl), 198 (M^+-SO_3H and Cl), 162 ($2SO_3H$), 154 (M^+-$2SO_3H$), 118 (M^+-$2SO_3H$ and Cl) and 81 (SO_3H) as well.

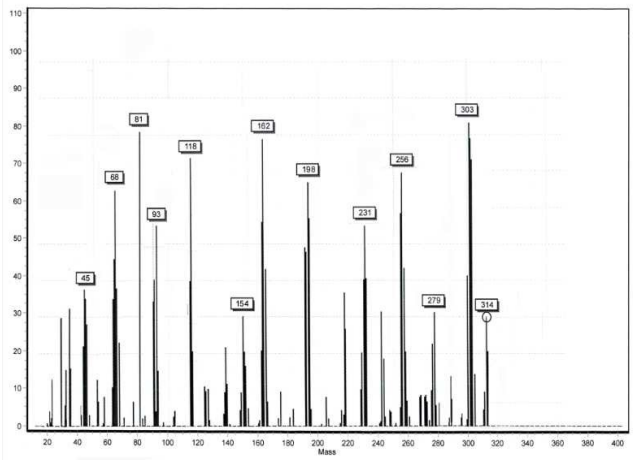

Fig. 4. Mass spectra of 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl).

3.2. Synthesis of tetrahydropyridines catalyzed by [Dsbim]Cl

The condensation of 4-chloroaniline (2 mmol), ethyl acetoacetate (1 mmol) and benzaldehyde (2 mmol) was chosen as a model reaction for the optimization of parameters such as the amount of catalyst, solvents and temperature of reaction. The results are summarized in Table 1. Initially, the reaction was examined in the absence of the catalyst at 80 °C; no desired product was obtained under solvent-free conditions even after 2.5 h. Therefore, the model reaction was repeated in the presence of 5, 7.5, 10 and 15 mol% of 1,3-disulfonic acid benzimidazolium chloride ([Dsbim]Cl). Using 10 mol% of the catalyst, the best results regarding reaction time and yield was obtained (Table 1, entry 4). Using lower amount of catalyst resulted in lower yield, while higher amount did not affect the reaction time and yield. To evaluate the influence of temperature, the model reaction was performed in the range of 70–100 °C. It was found that 80 °C was the optimal temperature and the reaction was incomplete at lower temperature.

Table 1. Effect of different amounts of catalysts and temperature on the condensation of benzaldehyde (2 mmol), 4-chloroaniline (2 mmol) and ethyl acetoacetate (1 mmol).

Entry	Catalyst (mol %)	temp. (°C)	Time (min)	Yield (%) [a]
1	-	80	150	-
2	5	80	70	56
3	7.5	80	32	81
4	10	80	32	95
5	15	80	32	95
6	10	90	35	88
7	10	100	35	90
8	10	70	55	71

[a] Isolated yield.

In order to evaluate the effect of solvent, we investigated different solvents, including $CHCl_3$, H_2O, THF, EtOAC, CH_3CN and EtOH under refluxing conditions using 10 mol% of the catalyst. The results of these experiments revealed that the use of a solvent led to a significant reduction in the yield of the desired product 4l in all cases compared with the yield obtained under solvent-free conditions (Table 2, entries 1–7).

Table 2. Synthesis of compound 4l in the presence of [Dsbim]Cl (10 mol%) in different solvents.

Entry	Solvent	Temperature(°C)	Time (min)	Yield (%)[b]
1	$CHCl_3$	Reflux	360	trace
2	H_2O	Reflux	360	-
3	THF	Reflux	360	trace
4	EtOAC	Reflux	300	32
5	CH_3CN	Reflux	230	60
6	EtOH	Reflux	100	78
7	Solvent-free	80	32	95

Reaction conditions: benzaldehyde (2 mmol), 4-chloroaniline (2 mmol), ethyl acetoacetate (1 mmol), [Dsbim]Cl (10 mol %), [b] Isolated yield.

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After optimization of the reaction conditions, synthesis of a variety of functionalized tetrahydropyridines was performed to explore the efficiency and the scope of the protocol. The corresponding results are depicted in Table 3. Various aromatic aldehydes containing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic ring were utilized successfully react with various anilines and ethyl acetoacetate to afford high to excellent yields of products and in short reaction times under solvent free.

The structures of products (4a–p), were identified by comparison of their spectroscopic data and melting points with those of literature reports. Also, the structures of products (4q–v), were confirmed by elemental analysis and spectral data (FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy). For example, the FT-IR spectrum of 4u, as a representative example, contained broad peaks at 3234 cm^{-1}, which were attributed to the stretching vibrations of amine protons (NH groups). Furthermore, the bands at 3069, 2956 and 2875 cm^{-1} were attributed to the stretching vibrations of the CH, CH_2, and CH_3 groups in the molecules, whereas the strong bands at 1657 cm^{-1} were attributed the stretching vibrations of carbonyl groups (C=O stretching). The FT-IR spectrum of 4u also contained strong bands at 1375 cm^{-1}, which indicated the presence of C–N stretching. The band at 1604 and 1459 cm^{-1} in the FT-IR spectrum of 4u was characteristic of a C=C stretching vibration, and the strong band at 1249 and 1075 cm^{-1} confirmed the presence of C-O bond stretching. The ^{1}H NMR spectrum of 4u exhibited a triplet at δ= 1.47 ppm for the methyl protons of the carbethoxy group. The methylene protons of the carbethoxy group, were observed as two doublets of quartets at δ= 4.32-4.37 and 4.44-4.50 ppm. A doublet of doublets appeared at δ= 2.69 and 2.82 for the methylene protons of the tetrahydropiperidines ring (H′-5, H″-5). One of the methine protons of the tetrahydropiperidines ring (H-6) was observed as a multiplets at δ= 5.06 ppm, and another methine proton (H-2) appeared as a singlet at δ= 6.26 ppm. The aromatic proton signals were a mixture of doublets and multiplets at δ = 6.37–7.24 ppm. The secondary amino group (NH) signal shows their chemical shift in the higher frequency region at 10.29 ppm. The higher chemical shift is due to strong intramolecular hydrogen bonding with ester carbonyl carbon. Furthermore, ^{13}C NMR analysis of 4u revealed the presence of 28 distinct carbons, which was in agreement with the proposed structure. The mass spectrum of 4u showed a molecular ion signal at m/z 793 corresponding to the molecular formula $C_{32}H_{26}Cl_2I_2N_2O_2$.

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Table 3. Synthesis of tetrahydropyridines catalyzed by [Dsbim]Cl.

Entry	R^1	R^2	Product	Time (min)	Yield [b] (%)	Mp (°C)	Lit. Mp (°C) [ref]
1	4-Me	4-Me	4a	38	86	156-158	169-171 [23]
2	4-Me	H	4b	34	89	229-230	230-231 [25]
3	4-Me	4-NO_2	4c	25	94	215-216	213-215 [30]
4	4-Me	4-OMe	4d	30	93	224-226	221-224 [25]
5	4-OMe	4-Cl	4e	29	94	180-182	179-181 [28]
6	H	4-Br	4f	30	96	197-198	194-196 [30]
7	4-Me	4-Cl	4g	35	93	219-220	218-220 [23]
8	4-Cl	4-OMe	4h	29	95	189-191	186-188 [30]
9	4-OMe	H	4i	30	90	166-168	165-167 [28]
10	4-NO_2	H	4j	25	92	246-248	247-250 [25]
11	H	4-OMe	4k	28	94	173-174	172-173 [25]
12	H	H	4l	37	89	170-172	171-172 [28]
13	4-Cl	H	4m	31	96	228-230	228-229 [30]
14	4-Me	4-Br	4n	27	91	233-235	234-236 [23]
15	H	4-Me	4o	33	90	198-199	193-196 [23]
16	H	4-Cl	4p	32	95	203-205	204-206 [28]
17	H	3-I	4q	34	91	172-171	171-173 [31]
18	4-OMe	4-Br	4r	29	92	182-184	184-186 [30]
19	4-NO_2	3-I	4s	27	90	139-141	137-140 [31]
20	4-Me	3-I	4t	30	89	209-207	208-209 [31]
21	4-Cl	3-I	4u	33	90	189-187	189-190 [32]
22	3-Me	4-Me	4v	38	90	182-180	181-182 [32]

Reaction conditions: benzaldehyde (2 mmol), 4-chloroaniline (2 mmol), ethyl acetoacetate (1 mmol), [Dsbim]Cl (10 mol %), [b] Isolated yield.

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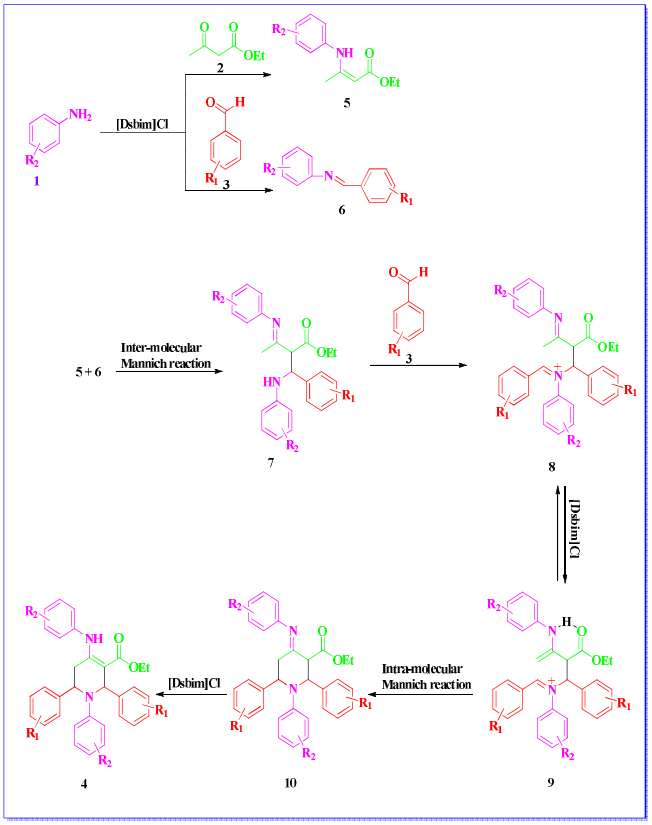
A plausible mechanism for the formation of tetrahydropyridines is proposed in Scheme 2 [11, 20, 25]. It was expected that arylamine (1) reacts with ethyl acetoacetate (2) to give enamine (5) in the presence of 1,3-disulfonic acid benzimidazolium chloride, which also reacts with arylaldehyde (5) to provide imine (6) with elimination of water. Next, the reaction between enaminone (5) and activated imine (6) in the presence of [Dsbim]Cl as a Bronsted acid via intermolecular Mannich-type reaction affords the intermediate (7). The reaction of the intermediate (7) with the second arylaldehyde produces another intermediate (8) by the loss of water. Intermediate (8) tautomerizes to (9), which is stabilized by intramolecular hydrogen bonding. Then, intramolecular Mannich-type reaction forms the intermediate (10). Deprotonation and tautomerization of the intermediate (10) afford the desired tetrahydropyridine derivatives (4).



Scheme 2. Possible reaction mechanism for the tetrahydropyridines condensation 4.

To show the merit of the present work, we compared the results of our catalyst with some reported catalysts for the synthesis of similar functionalized tetrahydropyridine derivatives. The results of these catalysts, which perform the one-pot multi-component condensation of benzaldehyde, ethyl acetoacetate and 4-chloroaniline have tabulated in Table 4. As it is shown, our catalyst has remarkably improved this in different terms {reaction time, yield, turn-over number (TON) and turn-over frequency (TOF)}.

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Table 4. Comparison of the results of the condensation of benzaldehyde, ethyl acetoacetate and 4-chloroaniline in the presence of [Dsbim]Cl with those obtained using other catalysts.

Catalyst/ Conditions	Catalyst loading	Time (h)	Yield [a] (%)	TON [b]	(h^{-1}) TOF [c]	Ref
$LaCl_3.7H_2O$/ MeOH, r.t	10 mol%	4	80	8	2	[17]
[Hpyro][HSO_4]/ EtOH, reflux	15 mol%	8	77	5.13	0.641	[18]
$Bi(NO_3)_3{\cdot}5H_2O$/ EtOH, r.t	10 mol%	14	76	7.6	0.543	[20]
Ph_3CCl/ MeOH, 50 °C	15 mol%	5	84	5.6	1.12	[23]
CAN/ CH_3CN, r.t	15 mol%	35	68	4.53	0.13	[25]
SSA/ MeOH, 85 °C	20 mol%	14	73	3.65	0.26	[26]
citric acid/ MeOH, r.t	20 mol%	6	70	3.5	0.583	[27]
$RuCl_3{\cdot}2H_2O$ / EtOH, r.t	15 mol%	4	93	6.2	1.55	[32]
[Dsbim]Cl/ Solvent-free, 80 °C	10 mol%	32 min	95	9.5	17.81	-[d]

[a] Isolated yield, [b] Turn-over number, [c] Turn-over frequency, [d] This work.

Recycling of the catalyst is one of the most significant criteria of green chemistry, hence the recovery and reuse of the IL catalyst was examined. The recyclability of [Dsbim]Cl was investigated for the reaction upon the condensation of benzaldehdye, ethyl acetoacetate and 4-chloroanilines. After completion of the reaction had been confirmed by TLC, the reaction mixture was extracted by warm EtOAc, and separated from the catalyst. Afterward the reused catalyst was employed for another reaction. We observed that the catalyst could be reused for the next cycle without any appreciable loss of its activity (Fig 5).

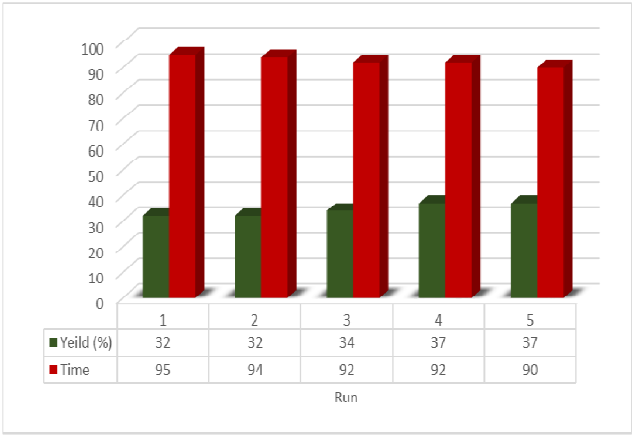

Fig. 5. The condensation of benzaldehyde with 4-chloroaniline, and ethyl acetoacetate, in the presence of reused [Dsbim]Cl (10 mol%) under solvent-free conditions at 80 °C.

Experimental

General

All reagents were purchased from Merck and Aldrich companies, and used without further purification. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. 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. FT-IR spectra were recorded using KBr pellets on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. NMR spectra were collected on a Bruker Avance-400 MHz spectrometer (δ in ppm). Mass spectra were obtained on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser.

Preparation of the ionic liquid

To a round-bottomed flask (50 mL) containing benzimidazole (0.708 g, 6.0 mmol) in dry CH_2Cl_2 (15 mL), was added chlorosulfonic acid (1.40 g, 12 mmol) dropwise over a period of 5 min at room temperature. After the addition was completed, the reaction mixture was stirred for 3 h under pressure of nitrogen (to remove the produced HCl), stand for 5 min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3 × 50 mL) and dried under vacuum to give [Dsbim]Cl as a viscous pale yellow oil in (1.97 g, 98% yield).

Spectral data: IR (Nujol): υ 574, 679, 750, 886, 1063, 1189, 1331, 1530, 1631, 2536-3432 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.09 (t, J = 7.45 Hz, 2H), 8.43 (t, J = 7.81 Hz, 1H), 8.90 (d, J = 5.76 Hz, 2H), 13.64 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ

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112.80, 125.61, 136.79, 143.24; MS: m/z= 315 (M^++1), 314 (M^+), 279 (M^+-Cl), 232 (M^+-SO_3H), 198 (M^+-SO_3H and Cl), 162 ($2SO_3H$), 154 (M^+-$2SO_3H$), 118 (M^+-$2SO_3H$ and Cl) and 81 (SO_3H).

General procedure for the preparation of functionalized tetrahydropyridines (4a-v)

In a 10 mL round bottom flask equipped with a condenser, a mixture of the aromatic amine (2 mmol), ethyl acetoacetate (1 mmol), and [Dsbim]Cl (0.0312 g, 10 mol%) was stirred at 80 °C for 10 min. After that, 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.

2.3.1. Spectral data of the selected products

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

White solid; m.p: 170-172 °C; IR (KBr): 3252, 3051, 2986, 2872, 1652, 1592, 1448, 1373, 1253, 1070 cm^{-1}; ^1H 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, 5.4Hz, 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 (m/z): 726; 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-(4-bromophenyl)-4-(4-bromophenylamino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3carboxylate (4r).

White solid; m.p: 184-186 °C; IR (KBr): 3239, 3064, 2979, 2834, 1647, 1603, 1462, 1370, 1248, 1068 cm^{-1}: ^1H 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, 5.6Hz, 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 (m/z): 692; 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(4-nitrophneyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s).

Light yellow solid; m.p: 139-142 °C; IR (KBr): 3246, 3058, 2979, 2872, 1652, 1593, 1448, 1372, 1253, 1070 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ 1.54 (3H, t, J = 7.5 Hz, CH_3), 2.8 (2H, d, J = 15.2Hz, 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-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4t).

White solid; m.p: 203-204 °C; IR (KBr): 3239, 3080, 2978, 2859, 1647, 1603, 1454, 1371, 1255, 1068 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, 5.6Hz, C_5-H″), 4.34 (1H, dq, J = 10.8, 7.2 Hz, O-CH_2), 4.47 (1H, dq, J = 10.8, 7.0 Hz, 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-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4u).

White solid; m.p: 189-190 °C; IR (KBr): 3234, 3069, 2956, 2875,1657, 1604, 1459, 1375, 1249, 1075 cm^{-1}; ^1H 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, 5.4Hz, C_5-H″), 4.32-

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4.37 (1H, dq, J = 10.5, 7.2 Hz, O-CH_2), 4.44-4.50 (1H, dq, J = 10.5, 6.8 Hz, 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.

Ethyl 4-(p-tolylamino)-1,2,5,6-tetrahydro-1,2,6-trip-tolylpyridine-3-carboxylate (4v).

White solid; m.p: 181-182 °C; IR (KBr): 3249, 3068, 2956, 2869, 1649, 1585, 1452, 1372, 1249, 1075 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (3H, t, J = 7.2 Hz, CH_3), 2.17 (3H, s, CH_3, at phenyl), 2.27 (3H, s, CH_3, at phenyl), 2.31-2.33 (6H, m, J = 8.5, CH_3, at phenyl), 2.70 (1H, dd, J = 15.2, 2.2 Hz, C_5-H′), 2.83 (1H, dd, J = 15.2, 5.4 Hz, C_5-H″), 4.33 (1H, dq, J = 10.8, 7.2 Hz, O-CH_2), 4.47 (1H, dq, J = 10.8, 7.0 Hz, O-CH_2), 5.08 (1H, m, C_6-H), 6.15 (2H, m, ArH), 6.37 (1H, s, C_2-H), 6.45 (2H, m, ArH), 6.89 (3H, d, 10.5 Hz), 6.95 (2H, d, 7.6 Hz), 7.03-7.26 (7H, m, ArH), 10.19 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 20.5, 21.2, 21.7, 34.4, 56.2, 58.2, 60.1, 95.1, 113.5, 125.2, 125.5, 127.3, 127.6, 127.8, 128.7, 126.5, 127.2, 128.8, 129.3, 130.1, 135.2, 138.9, 139.4, 146.3, 154.4, 169.6; MS (m/z): 726; Elemental analysis for: $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.40; H, 7.43; N, 5.34.

Conclusion

In summary, we have introduced an efficient, recyclable and homogeneous Bronsted acidic ionic liquid, [Dsbim]Cl as a catalyst and used it in the one-pot multi-component condensation of aromatic aldehydes, anilines and ethyl acetoacetate for the synthesis of tetrahydropyridines in excellent yields. Owing to its operational simplicity, high yields, short reaction time, easy work up, mild reaction condition as well as non-corrosive and non-pollution aspects, this method will be better than many other existing ones.

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Design, preparation and characterization of ionic liquid 1,3-disulfonic acid benzimidazolium chloride as an efficient and recyclable catalyst for the synthesis of tetrahydropyridine under solvent-free conditions

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Abstract

In the present work, 1,3-disulfonic acid benzimidazolium chloride as a new ionic liquid, is synthesized, characterized by studying its FT-IR, ^{1}H NMR, ^{13}C NMR as well as mass spectra. This ionic liquid is used as an efficient, homogeneous and recyclable catalyst for synthesis of highly functionalized tetrahydropyridine via one-pot multi-component condensation of aromatic aldehydes, ethyl acetoacetate, and anilines under solvent-free conditions. The present synthetic route is a green protocol offering several advantages, such as high yield of products, shorter reaction time, mild reaction conditions, minimizing chemical waste and easy work-up procedures. Further, the catalyst could be reused and recovered at least four times without appreciable loss of activity.