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One-pot multi-component synthesis of 1,2,4,5-tetrasubstituted imidazoles using sulfonic acid-functionalized pyridinium chloride as an efficient and recyclable catalyst

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KEYWORDS
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Ionic liquid;
Solvent-free;
Benzyl;
Primary amine;
Aldehyde.

Abstract. Sulfonic acid-functionalized pyridinium chloride ionic liquid {[Pyridine-SO_3H]Cl} can effectively promote the one-pot multi-component condensation reaction between benzil, aldehydes, primary amines, and ammonium acetate under solvent-free conditions at 100°C to give the desired 1,2,4,5-tetrasubstituted imidazoles in high yields and short reaction times.

1. Introduction

In the last decades, Ionic Liquids (ILs) have been introduced as useful solvents, catalysts, and reagents for organic transformations [1,2]. The unique properties of these organic compounds include high thermal and chemical stability, wide liquid-state temperature range, non-volatility, non-flammability, and large electrochemical window [1,2]. ILs have been also utilized in spectroscopy, electrochemistry [3], extraction, as well as separation processes [1], and as solvent, catalyst, and reagent for organic transformations [1,2,4-7]. Among the various kinds of ILs, BrØnsted acidic ones have been especially applied as efficient, green, recyclable, and selective catalysts to promote a wide range of organic reactions [8-11].

Imidazole derivatives are one of the most significant groups of five-membered nitrogen-containing heterocycles. For example, they are an essential component of various biological and pharmaceutical molecules such as histidine, histamine, biotin, losartan, olmesartan, eprosartan, and trifenagrel [12,13]. Furthermore, imidazolium salts (as ionic liquids) have been used as green solvents as well as catalysts in organic transformations [14], and as N-heterocyclic carbenes in organometallic chemistry [15,16]. 1,2,4,5-

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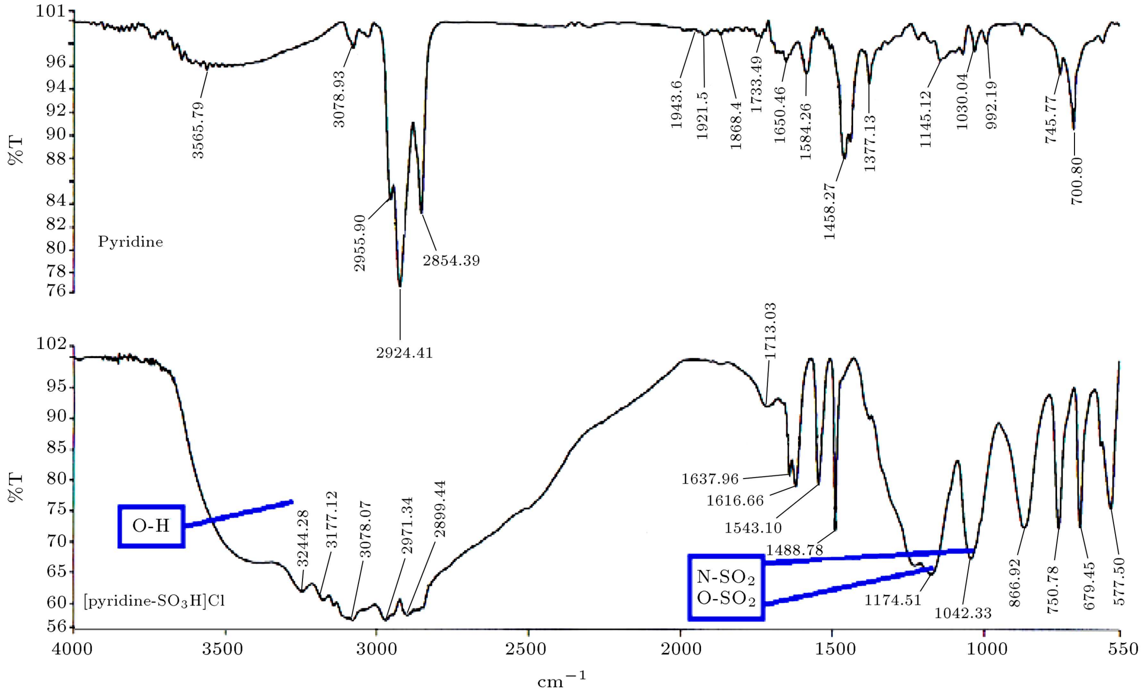


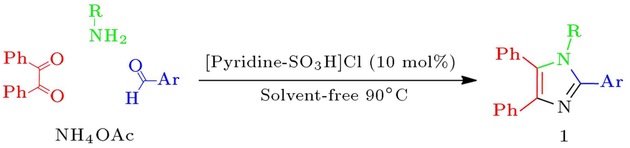
Figure 1. IR spectrum of sulfonic acid functionalized pyridinium chloride [Pyridine-SO_3H]Cl in comparison with pyridine.

tetrasubstituted imidazoles are an important class of imidazoles which are prepared via the one-pot multi-component condensation of benzil with aldehydes, primary amines, and ammonium acetate using several catalysts [16-26]. Nevertheless, most of the previous procedures suffer from different disadvantages, including strongly acidic conditions which cause performance of side reactions, difficult workup and purification, producing waste materials, the use of expensive catalysts, moderate yields, and long reaction times.

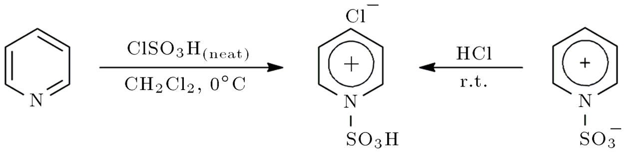
In continuation of our previous studies on the preparation and application of sulfonic acid-functionalized ionic liquids as catalysts in organic transformations [10,11], we report here the use of sulfonic acid-functionalized pyridinium chloride {[Pyridine-SO_3H]Cl} as an efficient, green, and reusable catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles from benzil, aldehydes, primary amines, and ammonium acetate (Scheme 1).

2. Results and discussion

First, [Pyridine-SO_3H]Cl ionic liquid was synthesized via the reaction between pyridine (1 equiv.) and $ClSO_3H$ (1 equiv.) in dry CH_2Cl_2 at 0°C (Scheme 2) [27-29]. Alternatively, the IL was prepared by the reaction of sulfur trioxide-pyridine complex with an excess amount of gaseous HCl at room temperature (Scheme 2) [27-29]. [Pyridine-SO_3H]Cl was characterized by IR, ^1H NMR, ^{13}C NMR, Thermal Gravimetry (TG), and Differential Thermal Gravimetric (DTG) analysis (Figures 1-4).



Scheme 1. Preparation of 1,2,4,5-tetrasubstituted imidazoles.



Scheme 2. Preparation of [Pyridine-SO_3H]Cl.

Thermal Gravimetric (TG) and Derivative Thermal Gravimetric (DTG) analyses of [Pyridine-SO_3H]Cl were studied at the range of 25 to 600°C with a temperature increase rate of 10°C.min^{-1} in a nitrogen atmosphere. In TG pattern (Figure 4), we observed multi-stage decomposition pattern in [Pyridine-SO_3H]Cl. Some weight losses were observed about 18%, 40%, and 14% which can be related to loss of HCl, SO_3, and $CH_2{=}CH_2$, respectively. Therefore, [Pyridine-SO_3H]Cl could be applied as catalyst below 200°C, and decomposed after 200°C [24].

To obtain the optimal reaction conditions, the solvent-free reaction of benzil (1 mmol) with *p*-chlorobenzaldehyde (1 mmol), aniline (1 mmol), and ammonium acetate (1 mmol) was chosen as a model reaction and examined in the presence of different molar ratios of [Pyridine-SO_3H]Cl at the range of 80-

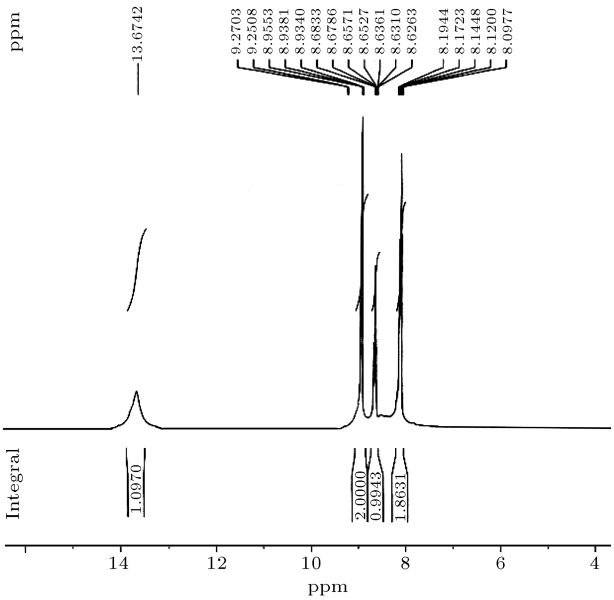


Figure 2. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of sulfonic acid functionalized pyridinium chloride [Pyridine-SO_3H]Cl.

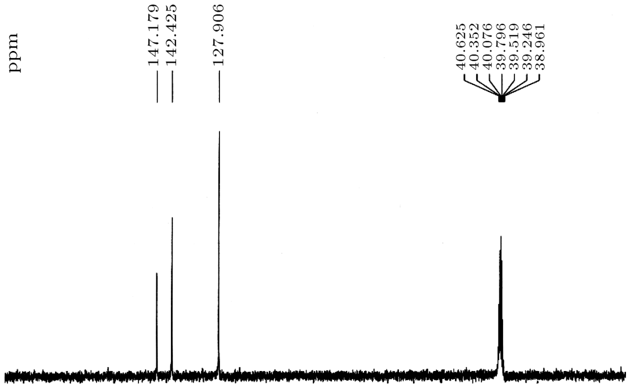


Figure 3. ^{13}C NMR (300 MHz, DMSO-d_6) spectrum of sulfonic acid functionalized pyridinium chloride [Pyridine-SO_3H]Cl.

110°C; the respective results are displayed in Table 1. As Table 1 indicates, the best results were observed when the reaction was performed using 10 mol% of the ionic liquid at 100°C.

Afterward, the efficacy and scope of [Pyridine-SO_3H]Cl on the synthesis of 1,2,4,5-tetrasubstituted imidazoles were assessed under the optimized conditions. Thus, various arylaldehydes (aromatic aldehydes bearing electron-donating substituents, electron-withdrawing substituents and a halogen atom on their aromatic rings, and heteroaromatic aldehydes) and amines (aliphatic or aromatic) were reacted with benzil and ammonium acetate (Scheme 1); the corresponding results are summarized in Table 2. As shown in Table 2, all reactions were completed effectively to furnish the desired products in high yields and short reaction times.

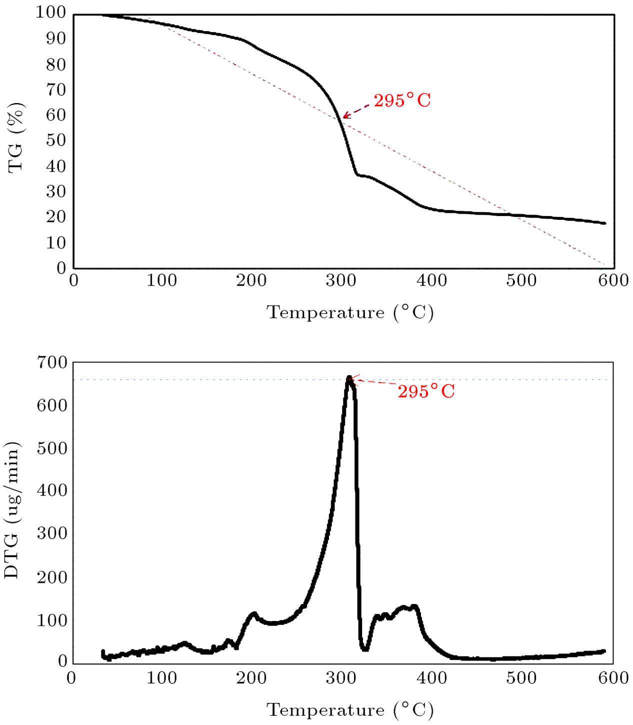


Figure 4. TG/DTG diagrams of sulfonic acid functionalized pyridinium chloride [Pyridine-SO_3H]Cl.

Table 1. Effect of the catalyst amount and temperature on the reaction of benzil with *p*-chlorobenzaldehyde, aniline, and ammonium acetate.

Catalyst	Mol% of catalyst	Temp. (°C)	Time (min)	Yield[a] (%)
-	-	100	60	20
[Pyridine-SO_3H]Cl	7	100	20	73
[Pyridine-SO_3H]Cl	10	100	20	91
[Pyridine-SO_3H]Cl	10	80	20	78
[Pyridine-SO_3H]Cl	10	110	20	91

[a] Isolated yield.

We proposed a mechanism for the reaction (Scheme 3) which was supported by the literature [16,17]. In fact, hydrogen bond formation between SO_3H group of [Pyridine-SO_3H]Cl and the functional groups of the substrates activates them for the reaction (Scheme 3).

In another study, recyclability of the catalyst was examined on the reaction of benzil (1 mmol) with *p*-chlorobenzaldehyde (1 mmol), aniline (1 mmol), and ammonium acetate (1 mmol). After completion of the condensation, the reaction mixture was extracted by warm ethanol (absolute) or warm ethyl acetate to separate the catalyst (the product was soluble in these solvents, but [Pyridine-SO_3H]Cl wasn't soluble). Afterward, the recycled catalyst was used for the next run. We observed that the catalytic activity

Table 2. The synthesis of 1,2,4,5-tetrasubstituted imidazoles using [Pyridine-SO_3H]Cl (10 mol %) under solvent-free conditions at 100°C.

Entry	**Ar**	**R**	**Time (min)/ yield^a (%)**	**M.p. (°C) found/reported [Ref.]**
1a	C_6H_5	C_6H_5	20/89	218-220/218-221 [17]
1b	C_6H_5	$C_6H_5CH_2$	15/90	155-157/156-159 [17]
1c	4-CH_3-C_6H_4	C_6H_5	25/89	189-190/190-192 [17]
1d	4-CH_3-C_6H_4	$C_6H_5CH_2$	17/90	164-166/165-168 [17]
1e	4-Cl-C_6H_4	4-Cl-C_6H_4	20/87	188-189/189-191 [16]
1f	3-NO_2-C_6H_4	4-CH_3-C_6H_4	15/92	146-150/145-147 [16]
1g	4-NO_2-C_6H_4	4-CH_3-C_6H_4	17/93	216-218/215-217 [16]
1h	4-Cl-C_6H_4	$C_6H_5CH_2$	17/89	157-160/161-163 [16]
1i	4-Cl-C_6H_4	4-F-C_6H_4	20/88	195-200/198-201 [16]
1j	4-CH_3-C_6H_4	4-CH_3-C_6H_4	20/86	190-194/194-196 [16]
1k	3-OCH_3-C_6H_4	$C_6H_5CH_2$	30/82	130-132/130-132 [17]
1l	4-Cl-C_6H_4	C_6H_5	20/91	147-150(148-151 [17]
1m	4-OH-C_6H_4	$C_6H_5CH_2$	15/93	133-136/135-138 [17]
1n	4-OCH_3-C_6H_4	$C_6H_5CH_2$	15/83	157-160/158-161 [17]
1o	4-OH-C_6H_4	C_6H_5	15/92	279-281/282-284 [17]
1p	4-CN-C_6H_4	4-CH_3-C_6H_4	15/93	197-200/198-201 [16]
1q	4-OH-C_6H_4	4-CH_3-C_6H_4	17/93	231-234/233-235 [16]
1r	2-thienyl	4-CH_3-C_6H_4	35/84	198-200/199-202 [16]
1s	2-thienyl	4-OH-C_6H_4	25/86	199-201/198-201 [16]

[a] Yield of purified product.

Table 3. The reaction between benzil, *p*-chlorobenzaldehyde, aniline, and ammonium acetate using recycled [Pyridine-SO_3H]Cl under solvent-free conditions at 100°C.

Entry	**Cycle**	**Time (min)**	**Yield^a (%)**
1	1st run	20	91
2	2nd run	20	89
3	3rd run	25	86
4	4th run	30	85

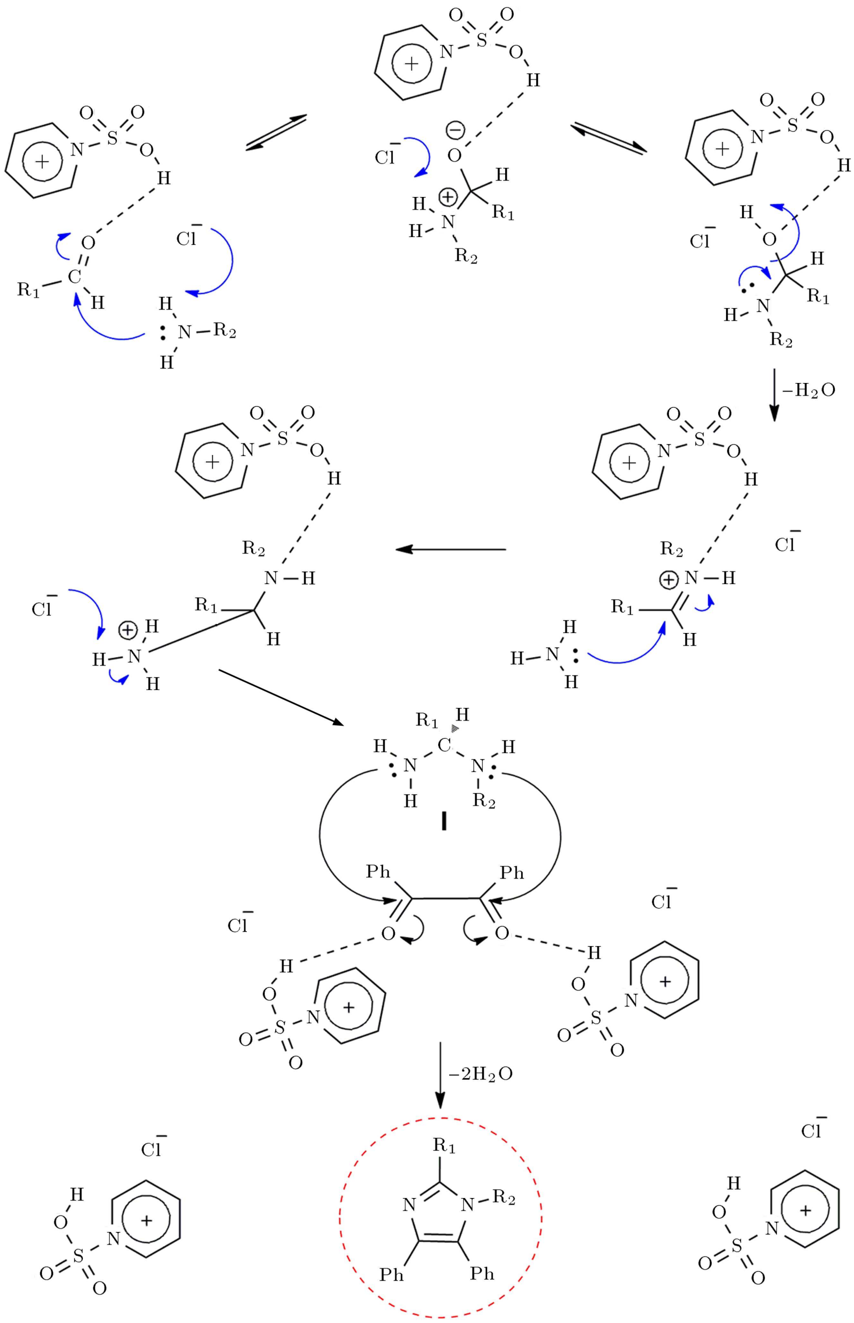
[a] Isolated yield.

of [Pyridine-SO_3H]Cl was restored within the limits of experimental errors for four successive runs (Table 3).

To compare the efficiency of our catalyst with the reported catalysts for the preparation of 1,2,4,5-tetrasubstituted imidazoles, we have depicted the results of these catalysts to perform the condensation of benzil with benzaldehyde, aniline, and ammonium acetate in Table 4. As Table 4 indicates, [Pyridine-SO_3H]Cl has remarkably improved the synthesis of 1,2,4,5-tetrasubstituted imidazoles; the reaction time was shorter and the yield was higher when our catalyst was utilized. Preparation of the 1,2,4,5-tetrasubstituted imidazoles has been previously achieved using 1,3-disulfonic acid imidazolium hydrogen sulfate {[Dsim]HSO_4} [17]. [Pyridine-SO_3H]Cl, in comparison to [Dsim]HSO_4, afforded the different products in slightly longer reaction times; nevertheless, the synthesis of [Pyridine-SO_3H]Cl was extremely easier (the reaction times for the preparation of our presented catalyst and [Dsim]HSO_4 were 0.5 h and 24 h, respectively. Moreover, [Pyridine-SO_3H]Cl has been synthesized in one step; however, [Dsim]HSO_4 has been prepared in two steps. Thus, considering different factors, [Pyridine-SO_3H]Cl was better than [Dsim]HSO_4 for the reaction.

3. Conclusion

In summary, we have used [Pyridine-SO_3H]Cl as a green, reusable, and efficient catalyst for the one-pot four-component reaction of aldehydes with amines (aliphatic or aromatic), benzil, and ammonium acetate at 100°C in solvent-free conditions to afford 1,2,4,5-tetrasubstituted imidazoles. The promising points for the presented work include generality, simplicity, efficiency, high yields, short reaction times, easy preparation and recyclability of the catalyst, cleaner reaction profile, and good compliance with the green chemistry protocols.



Scheme 3. The proposed mechanism for the synthesis of 1,2,4,5-tetrasubstituted imidazoles using [Pyridine-SO_3H]Cl.

Table 4. Comparison between the results of the synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by [Pyridine-SO_3H]Cl and the reported catalysts.[a]

Catalyst, conditions	Catalyst loading	Time (min)	Yield[b] (%)	TOF[c] (min^{-1})	Ref.
[Bmim]Br, solvent-free, 140°C	228 mol%	150	91	0.002	16
[Dsim]HSO_4, solvent-free, 90°C	1 mol%	15	84	5.6	17
TrCl, solvent-free, 110°C	10 mol%	30	79	0.263	27
$InCl_3.3H_2O$, methanol, r.t.	10 mol%	531	83	0.015	28
$FeCl_3$, ethanol, r.t.	5 mol%	90	80	0.177	29
[Pyridine-SO_3H]Cl, solvent-free, 100°C	10 mol%	20	89	0.445	-[d]

[a] The reactions were carried out by condensation of benzil with benzaldehyde, aniline, and ammonium acetate;

[b] Isolated yield; [c] Turn-over frequency; [d] Our work.

4. Experimental

4.1. Materials and methods

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison to their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Thermal Gravimetry (TG) and Differential Thermal Gravimetry (DTG) were analyzed by a Perkin Elmer (Model: Pyris 1). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

4.2. The procedure for the preparation of [Pyridine-SO$_3$H]Cl ionic liquid

"A solution of pyridine (0.395 g, 5 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise to a stirring solution of chlorosulfonic acid (0.58 g, 5 mmol) in dry CH_2Cl_2 (40 mL) over a period of 10 min at 0°C. After the addition was completed, the reaction mixture was stirred for 20 min, stand for 5 min, and the CH_2Cl_2 was decanted. Afterwards, the liquid residue was triturated with CH_2Cl_2 (3×10 mL) and dried under powerful vacuum at 90°C to give [Pyridine-SO$_3$H]Cl as a viscous colorless oil in 95% yield (0.929 g)" [24-26]. Viscous colorless oil; IR (Nujol): 750, 866, 1042, 1174, 1488, 2650-3550 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ (ppm) 8.11 (t, J 7.45 Hz, 2H), 8.65 (t, J 7.81 Hz, 1H), 8.94 (d, J 5.76 Hz, 2H), 13.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ (ppm) 127.9, 142.4, 147.1; MS: m/z = 196 (M$^+$+1), 195 (M$^+$).

4.3. General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles

A mixture of benzil (1 mmol), aldehyde (1 mmol), primary amine (1 mmol), ammonium acetate (1 mmol) and [Pyridine-SO$_3$H]Cl (10 mol%) in a 10 mL round-bottom flask, connected to a reflux condenser, was stirred in an oil-bath (100°C). After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature and extracted by warm ethanol or ethyl acetate (10 mL). The product was soluble in these solvents; but, [Pyridine-SO$_3$H]Cl was not soluble; thus, the catalyst remained in the flask which was washed by ethyl acetate (5 mL) and dried under reduced pressure to afford pure [Pyridine-SO$_3$H]Cl in 97% yield. To obtain the 1,2,4,5-tetrasubstituted imidazole, after extraction of the product from the reaction mixture, the solvent of the filtrate was evaporated and the resulted solid (crude product) was purified by recrystallization in ethanol or ethyl acetate.

5. Selected spectral data of the products

1,2-Bis(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (1e). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 7.17-7.19 (m, 1H), 7.23-7.25 (m, 4H), 7.29-7.32 (m, 5H), 7.38-7.42 (m, 6H), 7.50 (d, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 127.2, 127.4, 129.0, 129.2, 129.44, 129.49, 129.9, 130.1, 130.8, 130.9, 131.3, 132.0, 132.3, 134.1, 134.3, 135.0, 136.2, 145.8.

1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole(1h). ^{1}HNMR (500 MHz, DMSO-d$_6$) δ: 5.16 (s, 2H), 6.75 (d, J = 7.0 Hz, 2H), 7.12-7.22 (m, 6H), 7.29-7.30 (m, 2H), 7.40-7.41 (m, 3H), 7.45-7.50 (m, 4H), 7.68 (d, J = 8.0 Hz, 2H). ^{13}CNMR (125 MHz, DMSO-d$_6$) δ: 48.6, 126.5, 127.0, 127.2, 128.1, 128.9, 129.4, 129.5, 129.8, 130.5, 131.0, 131.3, 131.4, 131.6, 134.4, 135.2, 137.9, 146.7.

1-Benzyl-2-(3-methoxyphenyl)-4,5-diphenyl-1H-imidazole (1k). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 3.68 (s, 3H), 5.16 (s, 2H), 6.79 (d, J = 7.5 Hz, 2H), 6.98-7.00 (m, 1H), 7.13-7.16 (m, 3H), 7.17-7.25 (m, 5H), 7.29-7.35 (m, 3H), 7.40-7.41 (m, 3H), 7.46-7.47 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 48.6, 55.9, 114.6, 115.6, 121.7, 126.4, 127.0, 127.1, 128.0, 128.9, 129.4, 129.74, 129.78, 130.5, 131.1, 131.4, 131.7, 132.8, 135.4, 137.7, 138.2, 147.7, 160.0.

1-Benzyl-2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (1n). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ: 3.77 (s, 3H), 5.13 (s, 2H), 6.76 (d, J = 7.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 7.11-7.21 (m, 6H), 7.26-7.28 (m, 2H), 7.38-7.39 (m, 3H), 7.46 (d, J = 7.0 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d$_6$) δ: 48.5, 56.0, 114.9, 124.0, 126.4, 126.9, 127.0, 128.0, 128.9, 129.3, 129.6, 129.7, 130.6, 130.8, 131.6, 131.7, 135.5, 137.5, 138.3, 147.9, 160.5.

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