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ORIGINAL ARTICLE

Highly efficient and metal-free synthesis of tri- and tetrasubstituted imidazole catalyzed by 3-picolinic acid

Abu Zafar Al Munsur [a,b,*], **Harendra Nath Roy** [a], **Mohinuddin Khan Imon** [a]

[a] *Department of Chemistry, University of Rajshahi, Rajshahi 6205, Bangladesh*
[b] *Organic Material Synthesis Division, Kayrbat Research Institute (KRI), Bogra 5810, Bangladesh*

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KEYWORDS

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Abstract 3-Picolinic acid is an efficient organo-catalyst for a one-pot three-component synthesis of 2,4,5-triaryl substituted imidazole. Moreover, the utility of this catalyst has been extended to the four-component synthesis of 1,2,4,5-tetra-substituted imidazole. The pivotal advantages of this process are easy purification, cost-effectiveness, and high yielding, above all environmentally benign protocol.

1. Introduction

Today the synthesis, reactions, and biological properties of substituted imidazole cover a wide area of modern heterocyclic chemistry (Grimmett, 1984). Notably, compounds with imidazole core units have many pharmacological properties and play a vital role in varying biochemical processes (Liverton et al., 1999; Lombardino and Wiseman, 1974). Recent research has uncovered that highly substituted imidazole derivatives endow good photo-physical properties which result in their potential application in materials chemistry (Kulkarni et al., 2004). Moreover, appropriately substituted imidazole are extensively used as glucagon receptors (Black et al., 1974; Khanna et al., 1997), CB1 cannabinoid receptor antagonists (Lee et al., 1994), and in some cases antibacterial (Antolini et al., 1999), antitumor (Wang et al., 2002), and pesticides (Sharma et al., 2020). In the last decade, the advancement of green chemistry and organometallic catalysis have exploited the utility of imidazole as ionic liquids (Tao et al., 2016) and N-heterocyclic carbenes (Kühl, 2007; Kureja et al., 2019). Based on the above facts, lots of synthetic routes are available in the literature to synthesize imidazole analogs including ionic liquids (Akbari, 2016), [Hmim]TFA (MaGee et al., 2013), NH_4OAc (Wu et al., 2010), iodine (Kidwai et al., 2006), tons of metal-based heterogeneous catalyst (Daraji et al., 2019; Kerru et al., 2019), and microwave irradiation (Zhou et al., 2010) are most notable. Recently, a metal-free method carried out by pivalic acid (Raj and Singh, 2009) has attracted a lot in condensing three or four components to imidazole instead of benzil with excellent yields.

* Corresponding author at: Organic Material Synthesis Division, Kayrbat Research Institute (KRI), Bogra 5810, Bangladesh.
E-mail address: mazamsarker@gmail.com (A.Z. Al Munsur).
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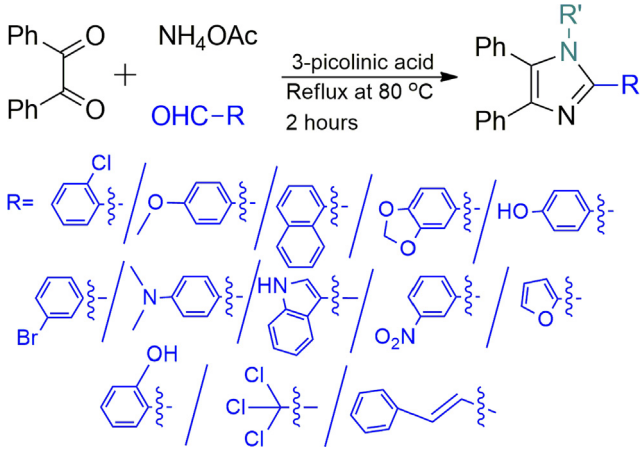
However, most of these methods are challenged by one or more limitations such as harsh reaction conditions, tedious isolation technique, unsatisfactory yield, limited examples, expensive and detrimental metal catalysts, which limit their use due to the heavy impact on environmentally benign processes. Therefore, the development of mild, economically convenient, and complementary approaches for 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives are highly recommendable.

3-Picolinic acid is an important building block of coenzymes (NAD and NADP) which are essential by all living cells. It has widely used in the fields of medicine, agriculture, and the food industry (Alkayeva et al., 2015).

Nowadays, organocatalysts (D'Souza and Müller, 2007; Dömling, 2006) have drawn much attention in different organic transformations owing to its experimental simplicity, facile handling, cost-effectiveness, and above all excellent solubility in organic solvents or water. Despite that, there are not too many organocatalysts mediated multicomponent reactions for imidazole synthesis being reported to date. By considering the current demands of different tri- and tetrasubstituted imidazole in many aspects, to explore a new organo-catalyst and to forestall possible difficulty of the typical procedures, we herein, reported a convenient multicomponent route (Scheme 1) to condense benzil or benzoin, aldehydes, ammonium acetate, benzylamine, aniline or aniline derivatives mediated by 3-picolinic acid (niacin).

2. Result and discussion

This is an extension (Roy et al., 2016) of our earlier attempts in synthesizing biologically active molecules by screening organocatalyst via a multicomponent scaffold. During flame heating, we observed the charring of the starting materials and the products. To minimize the spoilage of the starting materials and products in this present work we wished to use a little amount of ethanol. Also, our objective was to find a new catalyst with higher efficacy than the earlier catalyst. To this end, we attempted to synthesize substituted imidazoles from benzil, benzaldehyde, and ammonium acetate in ethanol mediated by some small bifunctional molecules (o- & p-aminophenol, 2-picolinic acid, and aspartic acid; Table 1). To carry out the



Scheme 1 Reaction for three substituted imidazole synthesis.

reaction, reacting components were mixed thoroughly with the mentioned small molecules (5–20 mol%) and heated gently over an oil bath at different temperatures with constant speed. But TLC monitoring indicated a tiny conversion of the starting materials, with the exception observed for 2-picolinic acid. The use of 2-picolinic acid afforded the product Entry I 1–50% yield despite the sincere alteration of catalyst, catalyst loading, solvents, and temperatures. Subsequently, by changing the catalyst from 2- to 3-picolinic acid to the same reaction and our delight, full conversions of the starting components were observed in TLC after 2 h reflux at 80 °C into ethanol solvent. Therefore, the feasibility of the reaction was investigated by the changes of catalyst loading and found 10 mol% catalysts are suitable for the desired conversion (Table 1).

With the optimized condition, herein, we have explored the scope and limitations with other benzaldehydes and observed aryl chloride & aryl bromide (Entry I and VI in Table 2) were the compatible substrates with the yield of 90% and 88% respectively. Moreover, these two entities could provide convenient access to other products by metal-catalyzed cross-coupling reactions. Heterocyclic aldehydes (Entry IV, VIII, and X in Table 2) were endured under similar reaction conditions to obtain compound 4, 8, and 10 in 94%, 85%, and 87% yield, respectively. A few aldehydes like salicylaldehyde, chloralhydrate, and cinnamaldehyde were reacted but did not produce the expected imidazole. The presence of excess electron pushing functionalities in the benzene ring, accumulation of $-v_e$ charge by resonance in cinnamaldehyde, and the presence of three hydrolyzable $-Cl$ atom in chloralhydrate possibly caused such failures (Roy et al., 2013). With the success of a three-component reaction, we wish to extend this methodology to other various substituted imidazole scaffolds by utilizing four-component strategies (Scheme 2).

Under identical reaction conditions, and a stoichiometric amount of different substituted aniline derivatives as the fourth component, the reaction underwent an elegant transformation to various products in good to excellent yield. Moreover, heterocyclic amines (Entry, XXI) or other substituted amines did not create any problems during the product formation shown in Table 3. The reaction mechanism may follow a similar pattern as reported in the literature (Damavandi and Sandaroos, 2016), but in our case, *3*-picolinic acid is donating its proton to aldehyde for necessary activation and on the other hand N-atom in pyridine ring abstracts protons to complete the reaction where it is necessary (shown in Fig. 1). In this manner, *3*-picolinic acid is assisting the reaction in a dual way both by the rates and the yield of the products. With the same catalyst, twenty-three different tri- (Table 2) and tetrasubstituted imidazole (Table 3) were synthesized successfully without any sophisticated column chromatographic purification techniques.

Interestingly, benzoin also reacted in the same fashion and afforded imidazole with high yield and thereby making the reaction path shorter. Besides, the efficiency and reusability of the catalyst activity were verified for the three consecutive reactions, by drying the filtrate solutions and subsequent purifications by column chromatography, whereas two reactions were going on smoothly without any loss of catalyst activity Table 4.

Table 5 compares our results for the synthesis of 2-(4-Chlor ophenyl)-1,4,5-triphenyl-1H-imidazole (11). with the results of

Table 1 Tunning of the reaction conditions to synthesize imidazole derivatives.

Entry	Catalyst	Catalyst Concentration (mol%)	Solvent	Temperature/°C	Time (hour)	Yield (%)[a]
1	Without catalyst	–	Ethanol	RT	48	19
2	Without catalyst	–	Ethanol	40	48	21
3	Without catalyst	–	Ethanol	50	48	23
4	Without catalyst	–	Ethanol	60	48	24
5	Without catalyst	–	Ethanol	70	48	25
6	Without catalyst	–	Ethanol	Refluxes	48	25
7	Without catalyst	–	Ethanol	80	48	25
8	o-Aminophenol	5	Ethanol	40	48	18
9	o-Aminophenol	5	Ethanol	50	48	20
10	o-Aminophenol	5	Ethanol	60	48	21
11	o-Aminophenol	5	Ethanol	70	48	22
12	o-Aminophenol	5	Ethanol	Reflux	48	23
13	o-Aminophenol	5	Ethanol	80	48	23
14	o-Aminophenol	10	Ethanol	40	48	21
15	o-Aminophenol	10	Ethanol	50	48	23
16	o-Aminophenol	10	Ethanol	60	48	25
17	o-Aminophenol	10	Ethanol	70	48	27
18	o-Aminophenol	10	Ethanol	Reflux	48	26
19	o-Aminophenol	10	Ethanol	80	48	27
20	o-Aminophenol	15	Ethanol	40	48	15
21	o-Aminophenol	15	Ethanol	50	48	17
22	o-Aminophenol	15	Ethanol	60	48	22
23	o-Aminophenol	15	Ethanol	70	48	21
24	o-Aminophenol	15	Ethanol	Reflux	48	23
25	o-Aminophenol	15	Ethanol	80	48	26
26	o-Aminophenol	20	Ethanol	40	48	20
27	o-Aminophenol	20	Ethanol	50	48	21
28	o-Aminophenolo-Aminophenol	20	Ethanol	60	48	22
29	o-Aminophenol	20	Ethanol	70	48	25
30	o-Aminophenol	20	Ethanol	Reflux	48	27
31	o-Aminophenol	20	Ethanol	80	48	26
32	p-Aminophenol	5	Methanol:water (1:1)	40	48	24
33	p-Aminophenol	5	Methanol:water (1:1)	50	48	26
34	p-Aminophenol	5	Methanol:water (1:1)	60	48	28
35	p-Aminophenol	5	Methanol:water (1:1)	Reflux	48	30
36	p-Aminophenol	10	Methanol:water (1:1)	40	48	26
37	p-Aminophenol	10	Methanol:water (1:1)	50	48	28
38	p-Aminophenol	10	Methanol:water (1:1)	60	48	31
39	p-Aminophenol	10	Methanol:water (1:1)	Reflux	48	35
40	p-Aminophenol	15	Methanol:water (1:1)	40	48	23
41	p-Aminophenol	15	Methanol:water (1:1)	50	48	31
42	p-Aminophenol	15	Methanol:water (1:1)	60	48	36
43	p-Aminophenol	15	Methanol:water (1:1)	Reflux	48	43
45	p-Aminophenol	20	Methanol:water (1:1)	40	48	25
46	p-Aminophenol	20	Methanol:water (1:1)	50	48	27
47	p-Aminophenol	20	Methanol:water (1:1)	60	48	30
48	p-Aminophenol	20	Methanol:water (1:1)	Reflux	48	41
49	Aspartic acid	5	Methanol	40	48	20
50	Aspartic acid	5	Methanol	Reflux	48	25
51	Aspartic acid	10	Methanol	40	48	23
52	Aspartic acid	10	Methanol	Reflux	48	28
53	Aspartic acid	15	Methanol	40	48	21
54	Aspartic acid	15	Methanol	Reflux	48	30
55	Aspartic acid	20	Methanol	40	48	24
56	Aspartic acid	20	Methanol	Reflux	48	29
57	2-Picolinic acid	5	Ethanol:water (1:1)	35	12	20
58	2-Picolinic acid	5	Ethanol:water (1:1)	45	12	24
59	2-Picolinic acid	5	Ethanol:water (1:1)	60	12	23
60	2-Picolinic acid	5	Ethanol:water (1:1)	75	12	25
61	2-Picolinic acid	5	Ethanol:water (1:1)	Reflux	12	29
62	2-Picolinic acid	10	Ethanol:water (1:1)	35	12	35
63	2-Picolinic acid	10	Ethanol:water (1:1)	45	12	39

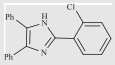
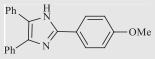
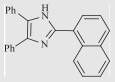
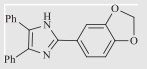
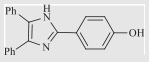
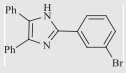
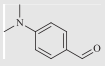
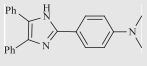
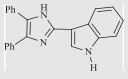
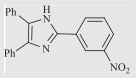
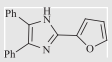
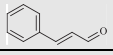
(*continued on next page*)

Table 1 (*continued*)

Entry	Catalyst	Catalyst Concentration (mol%)	Solvent	Temperature/°C	Time (hour)	Yield (%)[a]
64	2-Picolinic acid	10	Ethanol:water (1:1)	60	12	43
65	2-Picolinic acid	10	Ethanol:water (1:1)	75	12	45
66	2-Picolinic acid	10	Ethanol:water (1:1)	Reflux	12	50
67	2-Picolinic acid	15	Ethanol:water (1:1)	35	12	29
68	2-Picolinic acid	15	Ethanol:water (1:1)	45	12	35
69	2-Picolinic acid	15	Ethanol:water (1:1)	60	12	41
70	2-Picolinic acid	15	Ethanol:water (1:1)	75	12	40
71	2-Picolinic acid	15	Ethanol:water (1:1)	Reflux	12	45
72	2-Picolinic acid	20	Ethanol:water (1:1)	35	12	31
73	2-Picolinic acid	20	Ethanol:water (1:1)	45	12	35
74	2-Picolinic acid	20	Ethanol:water (1:1)	60	12	38
75	2-Picolinic acid	20	Ethanol:water (1:1)	75	12	42
76	2-Picolinic acid	20	Ethanol:water (1:1)	Reflux	12	48
78	3-Picolinic acid	5	Ethanol	Reflux at 80	12	70
79	3-Picolinic acid	10	Ethanol	Reflux at 80	2	93
80	3-Picolinic acid	15	Ethanol	Reflux at 80	12	80
81	3-Picolinic acid	20	Ethanol	Reflux at 80	12	80

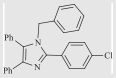
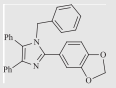
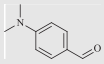
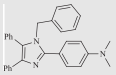
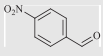
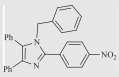
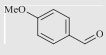
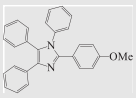
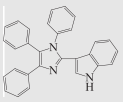
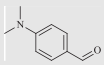
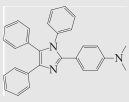
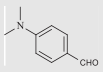
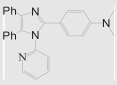
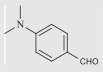
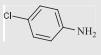
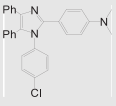
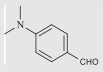
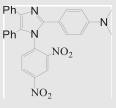
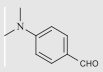
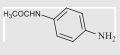
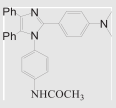
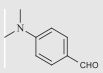
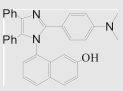
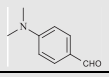
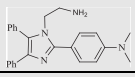
[a] Isolated yield.

Table 2 Data table for yield, melting points to the synthesis of trisubstituted imidazole derivatives.

Entry	Aldehydes	Products	Time (hour)	Yield (%)[a]	M.p (°C)	Reported M.p (°C)	Reference
I			2.15	90	195–197	196–198	Maleki et al. (2015)
II			2.10	92	229–231	234	Zhou et al. (2010)
III			2	92	215–217	215	Roy et al. (2013)
IV			2	94	295–297	300	Zhou et al. (2010)
V			2.15	92	269–270	260–261	Kidwai et al. (2006)
VI			2	88	200–201	199–200	Roy et al. (2013)
VII			2	97	259–261	259–260	Zhou et al. (2010)
VIII			1.5	85	181–182		This Work
IX			1.5	97	300	298–301	Maleki et al. (2015)
X			2	87	200–202	199–201	Maleki et al. (2015)
XI		No result	48	–	–	–	
XII		No result	47	–	–	–	
XIII		No result	48	–	–	–	

[a] Isolated yield.

Table 3 Data table for yield, melting points to the synthesis of tetrasubstituted imidazole derivatives.

Entry	Aldehydes	Amines	Products	Time (hour)	Yield (%)[a]	Calculated M.p (°C)	Reported M.p (°C)	Reference
XIV				2	96	162–163	162–165	Kantevari et al. (2007)
XV				2	98	130–132	–	This Work
XVI				2	97	180–182	–	This Work
XVII				2	98	170–172	–	This Work
XVIII				2	96	174–176	177–180	Safari and Zarnegar (2013)
XIX				2	97	247–249	–	This Work
XX				2	95	238–240	220–223	Hosseini et al. (2019)
XXI				2	90	254–256	–	This Work
XXII				2	92	168–170	–	This Work
XXIII				2	95	218–220	–	This Work
XXIV				2	91	157–158	–	This Work
XXV				2	89	247–249	–	This Work
XXVI				2	92	233–235	–	This Work

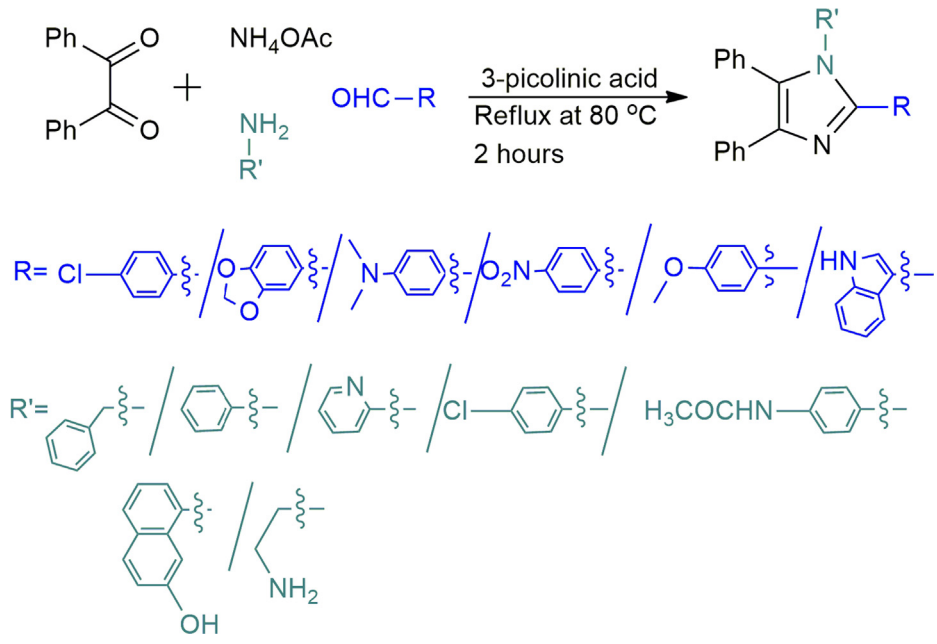
[a] Isolated yield.

different catalysts and reaction conditions obtained by other groups.

Many of the synthesized products are known in the literature, and for such cases, melting points were compared with the literature values.

3. Conclusion

In conclusion, the study delineates a rapid, efficient, and convenient synthesis of tri- and tetrasubstituted imidazole in a one-pot, three, and four-components condensation strategy using inexpensive, less toxic, and readily available *3*-picolinic acid as an organocatalyst in ethanol. Although *3*-picolinic acid is not a familiar organocatalyst in the organic transformation but this report, we have exploited it the first time in an elegant way to construct various substituted imidazole with great ease and in high yield. Some of the products are known in the literature, so far, such cases only melting points were compared with the literature values. We strongly believe that this methodology will be a great strategy annexed to the remaining



Scheme 2 Reaction for four substituted imidazole synthesis.

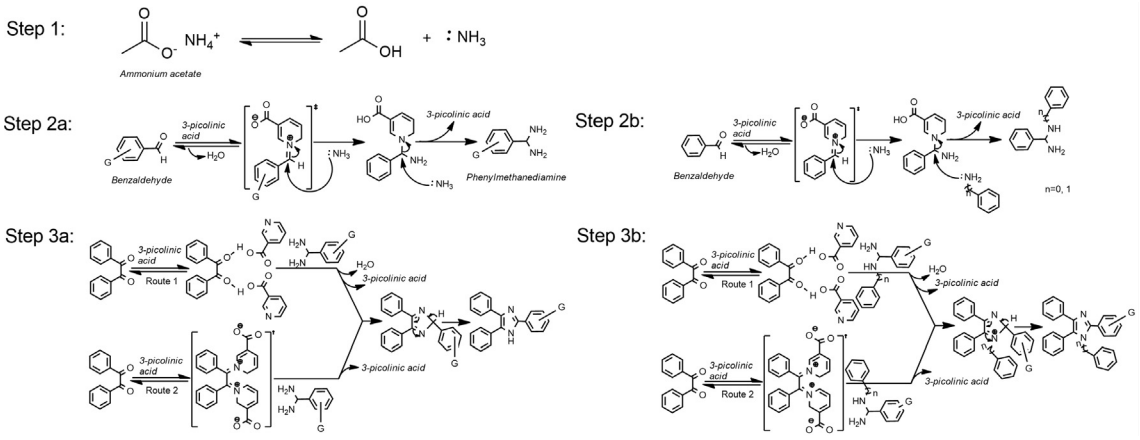


Fig. 1 The stepwise mechanistic pathway for the multi-substituted imidazole synthesis via one-pot, three, and four components condensation reaction mediated by 3-picolinic acid.

methods for the synthesis of tri- and tetrasubstituted imidazole.

4. Experimental

4.1. Materials and method

The melting points of the compound were measured on an electrothermal melting point apparatus (Gallenkamp) and the melting points incorporated are uncorrected. Infrared spectra (IR) were recorded on KBr pellets for solids and neat for liquids by FT-IR 8400 PerkinElmer 883 grating spectrometer. 1H NMR spectra were recorded on AC-Bruker 500 MHz spectrometer in D_6-DMSO or $CDCl_3$, containing TMS as an internal standard. All 'J' values are given in Hz and chemical shifts δ- in ppm units. Reactions were monitored by thin-layer chromatographic (TLC) plates over silica gel (60 GF254. E. Merck).

Table 4 Reusability of catalyst 3-Picolinic acid.

Cycle	Yield (%)	Catalyst recovered (%)
Native	95	86
1st	95	83
2nd	95	85
3rd	94	82

4.2. General procedure for the synthesis of 2,4,5-triaryl-1H-imidazoles

A mixture of benzyl/benzoin (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol), and *3*-picolinic acid (12 mg, 10 mol%) in ethanol (2 mL) was stirred at reflux temperature for 2–3 hr. The reaction was monitored by thin-layer chro-

Table 5 Comparison of the efficiency of various catalysts in the synthesis of 2-(4-Chlorophenyl)-1,4,5-triphenyl-1H-imidazole (11).

Catalyst	Conditions	Time (min)	Yield (%)	Reference
SBA-15/TFE	TFE/90 °C	180	90	Rostamnia and Zabardasti (2012)
[Poly(AMPS-co-AA)]	Solvent-free/110 °C	30	90	Mohammadi et al. (2012)
TFA	Glycerol (5 mL) MW(300)/120 °C	10	90	Khalafi-Nezhad et al. (2016)
$HClO_4$–SiO_2	Solvent-free/140 °C	8	94	Kantevari et al. (2007)
$[bmim]_3[GdCl_6]$	Solvent free/120 °C	120	94	Akbari (2016)
3-Picolinic acid	Ethanol/80 °C	120	96	This work

matography (TLC), the eluent was a mixture of solvent (Hexane & Ethyl acetate). After completion of the reaction, the mixture was cooled to room temperature, neutralized with 5% $NaHCO_3$ solution, diluted with water, and poured on crushed ice. The obtained crude solid product was filtered, dried, and recrystallized from ethanol.

4.2.1. Spectral data for imidazole derivatives

Entry I: 2-(2-Chlorophenyl)-4,5-diphenyl-1H-imidazole (1). Mp: 195–197 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 10.48 (*br.s*, 1H, NH), 8.38 (*dd, J* = 2.5, 8 Hz, 2H, Ar—H), 7.68–7.29 (*m,* 11H, Ar—H), 2.08 (*s,* 1H); ^{13}C NMR (300 MHz, DMSO d_6): 143.3, 130.4, 128.9, 128.5, 128.3, 128.3, 127.8, 127.4, 127, 100; HRMS: calcd. for $C_{21}H_{15}ClN_2$, 330.8123; found: 330.8121.

4.2.2. General procedure for the synthesis of 1,2,4,5-tetra-substituted imidazole:

A mixture of benzyl/benzoin (1 mmol), aldehyde (1 mmol), ammonium acetate (2.5 mmol), amine (1 mmol), and 3-Picolinic acid (12 mg, 10 mol%) in ethanol (2 mL) was stirred at reflux temperature for 2–3 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, neutralized with 5% $NaHCO_3$ solution, diluted with water, and poured on crushed ice. The obtained crude solid product was filtered, dried, and recrystallized from ethanol.

Entry XIV: 2-(4-Chlorophenyl)-1,4,5-triphenyl-1H-imida zole (11): Mp: 162–163 °C. ^{1}H NMR (500 MHz, DMSO d_6): 7.63–7.57 (*m,* 4H, Ar—H), 7.38–7.35 (*m,* 5H, Ar—H), 7.29–7.16 (*m,* 8H Ar—H), 6.84 (*dd, J* = 1.5, 8 Hz, 2H), 5.12 (*s,* 2H) ppm; ^{13}C NMR (300 MHz, DMSO d_6): 146.9, 138.3, 137.3, 135, 134.3, 131, 130.8, 130.4, 130.3, 129.4, 128.8, 128.8, 128.8, 128.7, 128.1, 127.5, 126.8, 126.5, 125.9, 48.3; HRMS: calcd. for $C_{28}H_{21}ClN_2$, 420.9347; found: 420.93451429.

The rest of the spectral data and spectrum are included in the supporting information file.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2020.10.010.

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